For whom are the current dosages optimal? Who might benefit from alternative dosing strategies?

CSRC Meeting
Role for pharmacokinetic/pharmacodynamics guided dosing for novel anticoagulant
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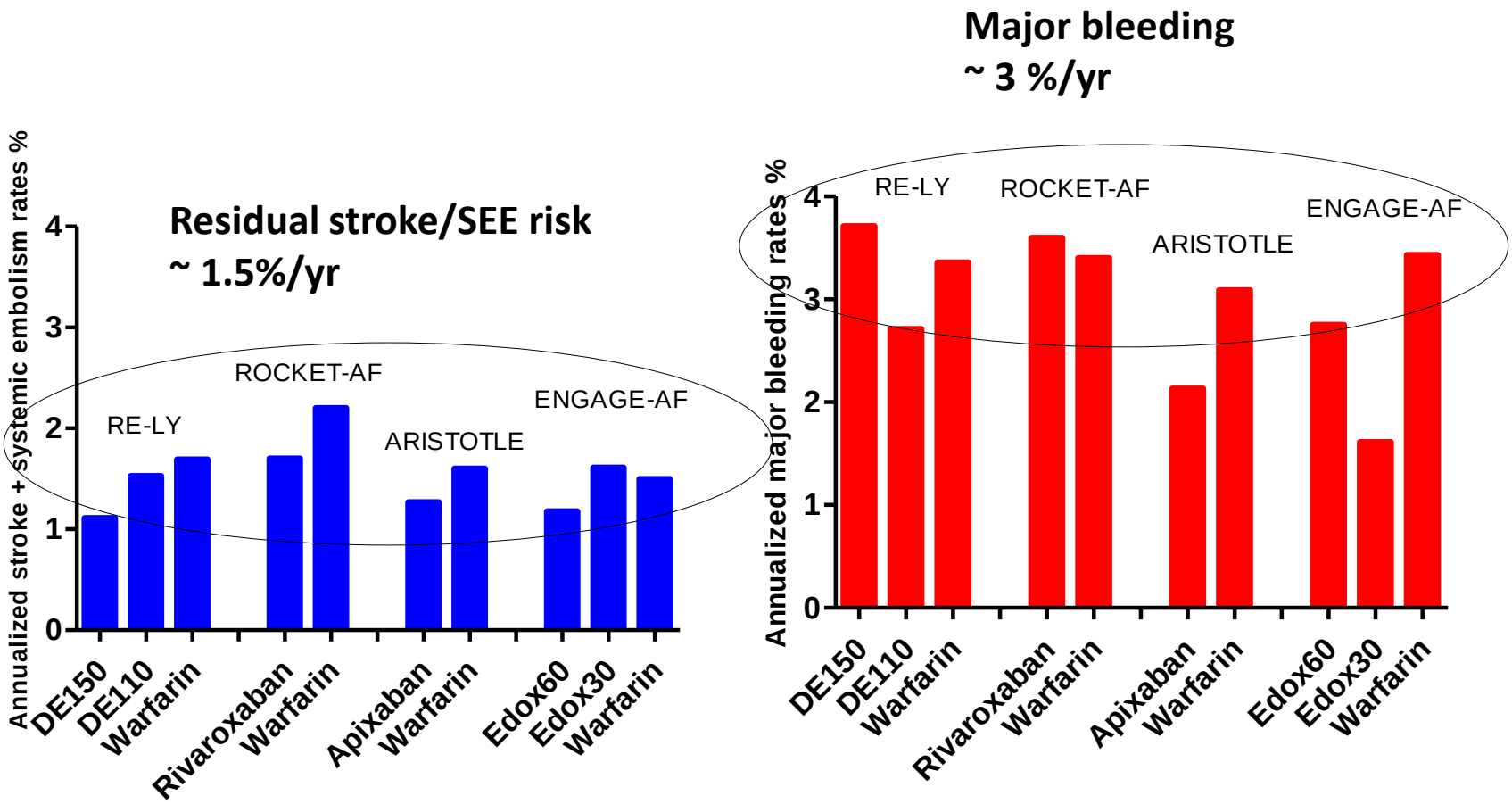
Disclosures

- Relationships with commercial interests: Bayer, Sanofi (honoraria/grants)

- Relationship with academic interests: New Investigator Fund, Hamilton Health Sciences

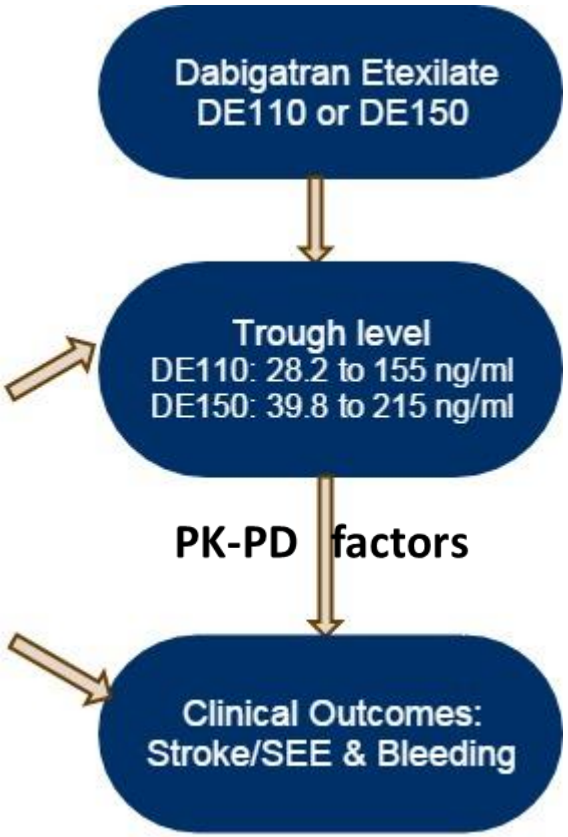
Stroke/SEE & major bleeding rates on warfarin and NOACs



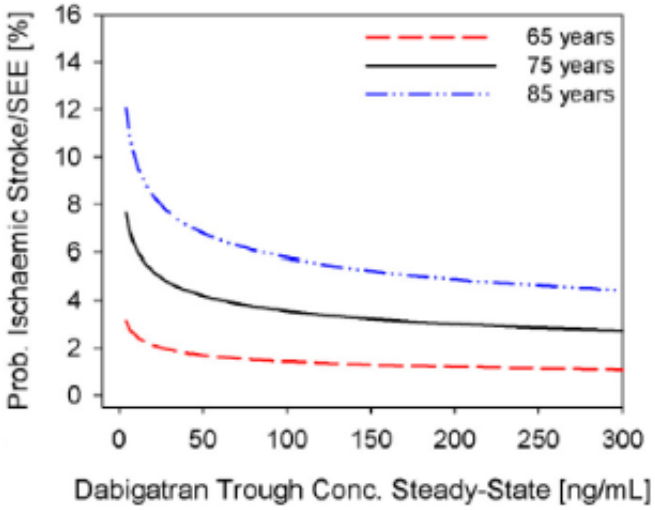
Can we do better with alternative dosing strategies?

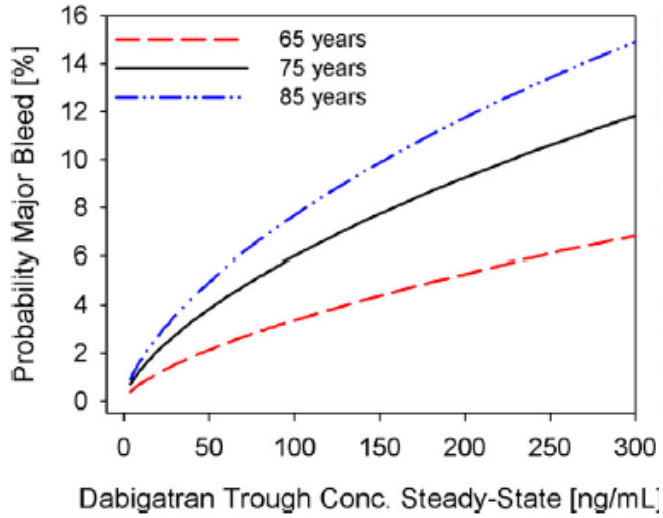
1. Connolly et al, N Engl J Med 2009; 361:1139-51
2. Granger et al, N Engl J Med 2011; 365:981-92
3. Connolly et al , N Engl J Med 2011; 364:806-17
4. Ruff et al, Am Heart J 2010; 160:635-41
5. Patel et al, N Engl J Med 2011;365:883-91

What factors affect clinical outcomes in NOAC-treated patients? E.g., dabigatran



Clinical factors
e.g., age





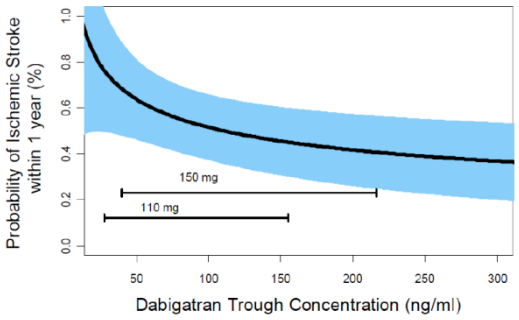
Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L; RE-LY Investigators.
The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014 Feb 4;63(4):321-8.

Possible dosing strategies:

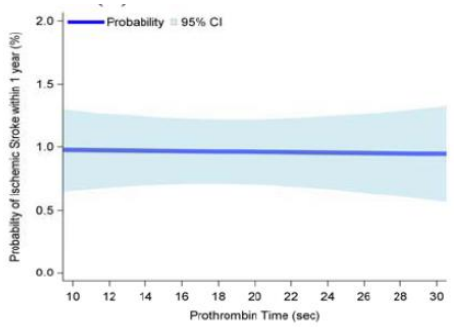
- Dose adjustment based on clinical factors
  - Age, renal function, body weight, co-medications
  - Larger (absolute reduction) effect on bleeding, modest effect on stroke/SEE
- Dose adjustment based on drug level
  - Testing strategy: test all or test selected patients
  - Effect on clinical outcome is unclear

Who might benefit the most from dose adjustment based on laboratory monitoring?

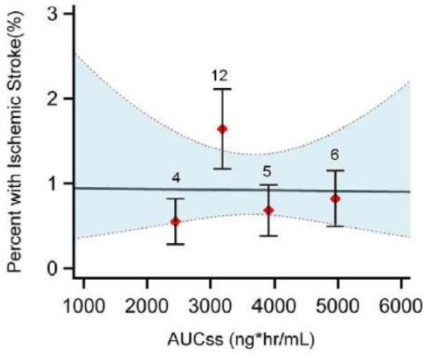
Dabigatran



Rivaroxaban



Apixaban



Edoxaban

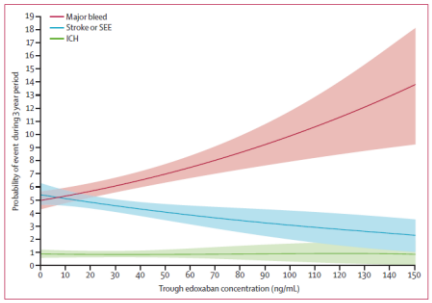
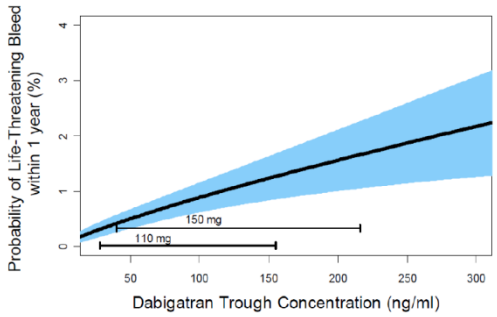


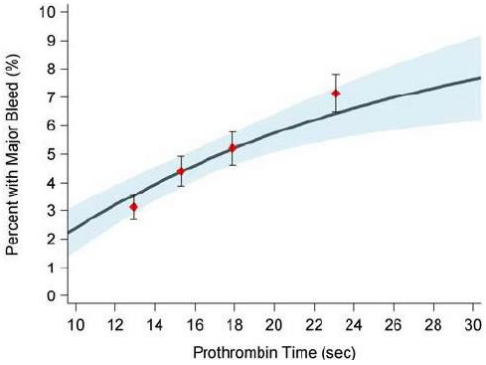
Figure 2: Probability of clinical outcomes versus edoxaban concentration
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

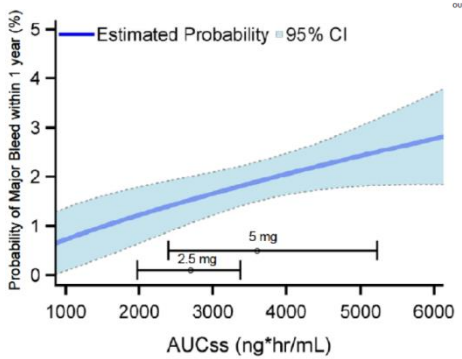
Patients at higher risk of bleeding

Steeper relationship

Higher absolute risk reduction







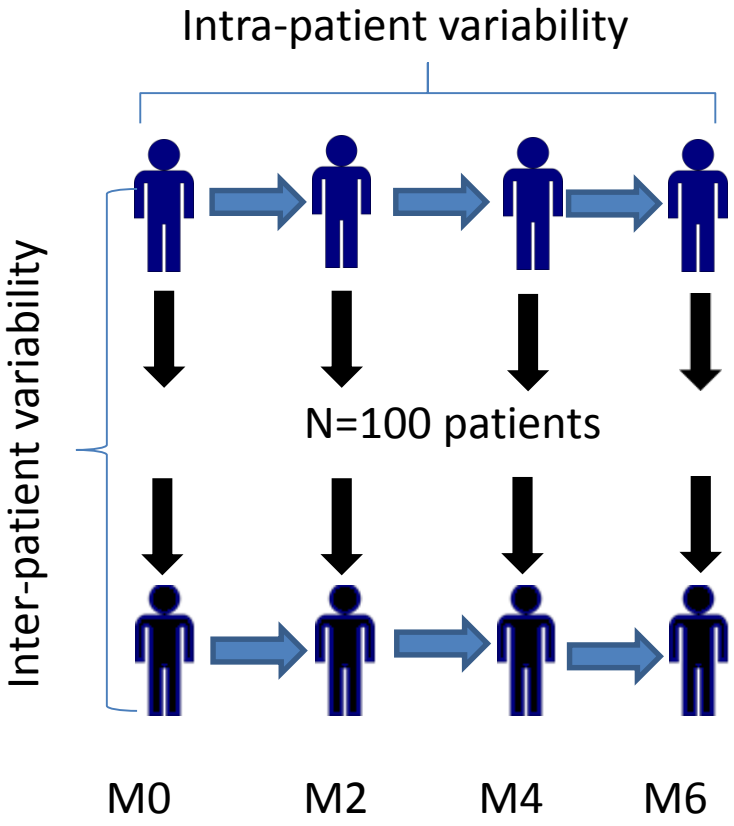
Figures obtained from :
FDA Medical Review documents & Ruff CT et al, Lancet March 2015
Note: y-axes use different scales

Factors to consider when adjusting dose based on a high drug level?

- Does “single” high drug level measurement remain consistently high?
  - can one measurement reliably identify patients with consistently high level?

- Will dose adjustment (within the constraint of dosing formulation approved) result in drug levels within the selected window?

Dabigatran variability study:



Aims:

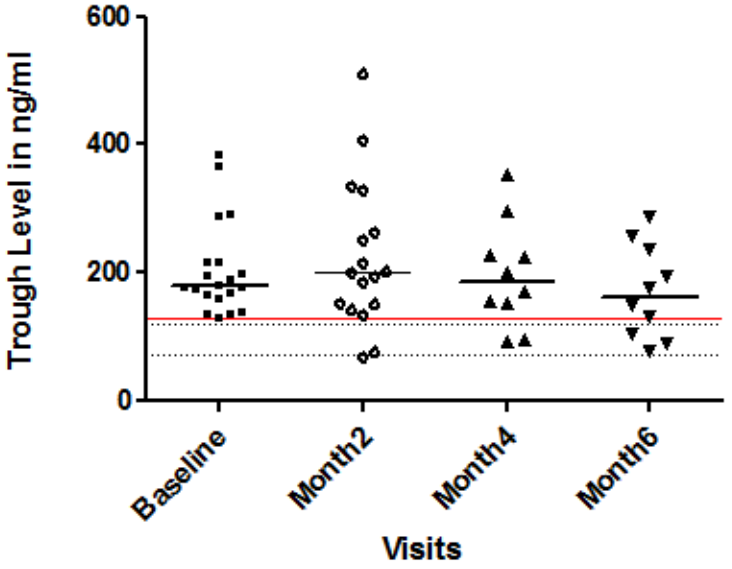
1. Estimate inter- and intra-patient variability in dabigatran level

2. Explore whether one drug level can reliably identify patients with extreme levels

Chan NC, Coppens M, Hirsh J, Ginsberg JS, Weitz JI, Vanassche T, Douketis JD, Schulman S, Eikelboom JW. Real-world variability in dabigatran levels in patients with atrial fibrillation. J Thromb Haemost. 2015 Mar;13(3):353-9.

Can a single drug level measurement reliably identify patients with consistently high level(> 80th centile)?

- Proportion of patients with levels remaining above 129 ng/ml
  - At M2: 88.2% (95% CI, 64.4–97.9%)
  - At M4: 80.0% (95% CI, 47.9–95.4%)
  - At M6: 70.0% (95% CI, 39.2–89.7%)
- Up to 30% of dabigatran-treated patients did not have subsequent levels in upper extreme



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Unknowns:

- Does single high drug level remain consistently high in subsequent measurements for the other DOACs?

- Will dose adjustment (using approved doses) result in a higher proportion of drug levels within a selected window?

- Will dose adjustment improve clinical outcomes?