

NOAC: Future perspectives: academic perspective

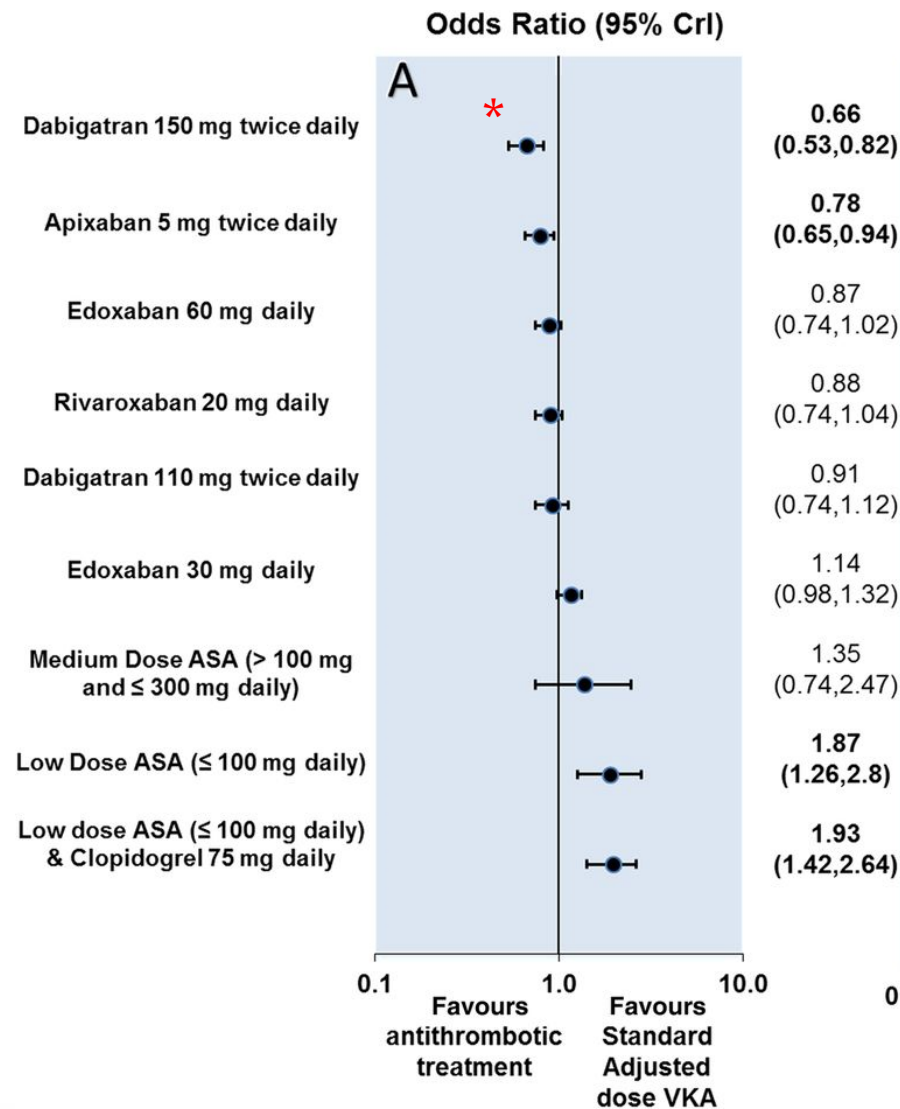
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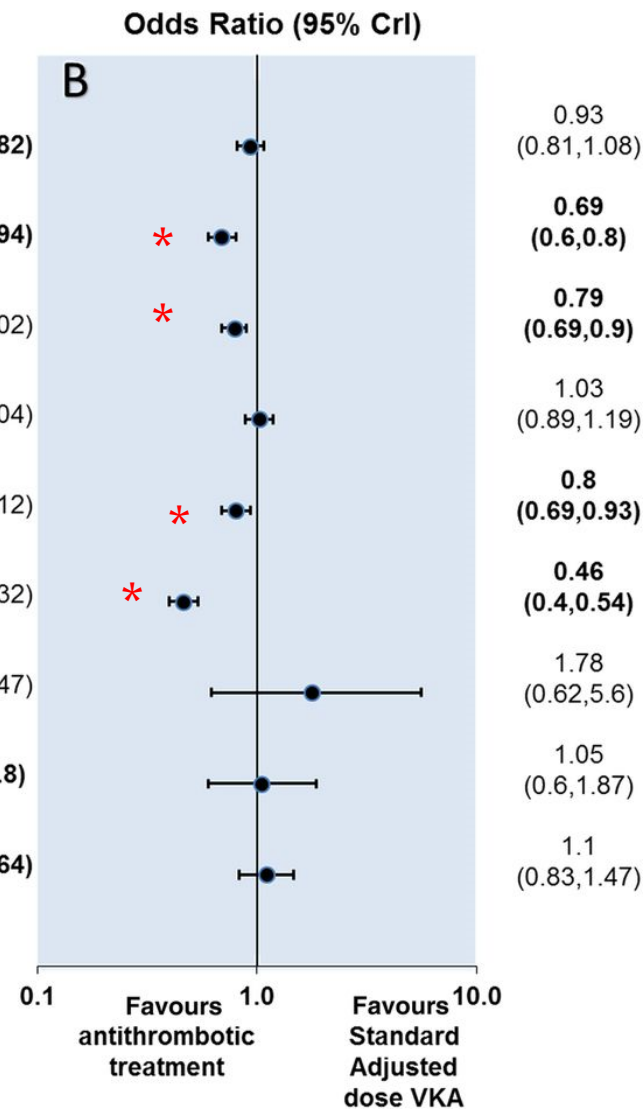
To discuss

- Lessons from the NOAC-VKA studies and optimal VKA management
- How to improve the quality of NOAC?

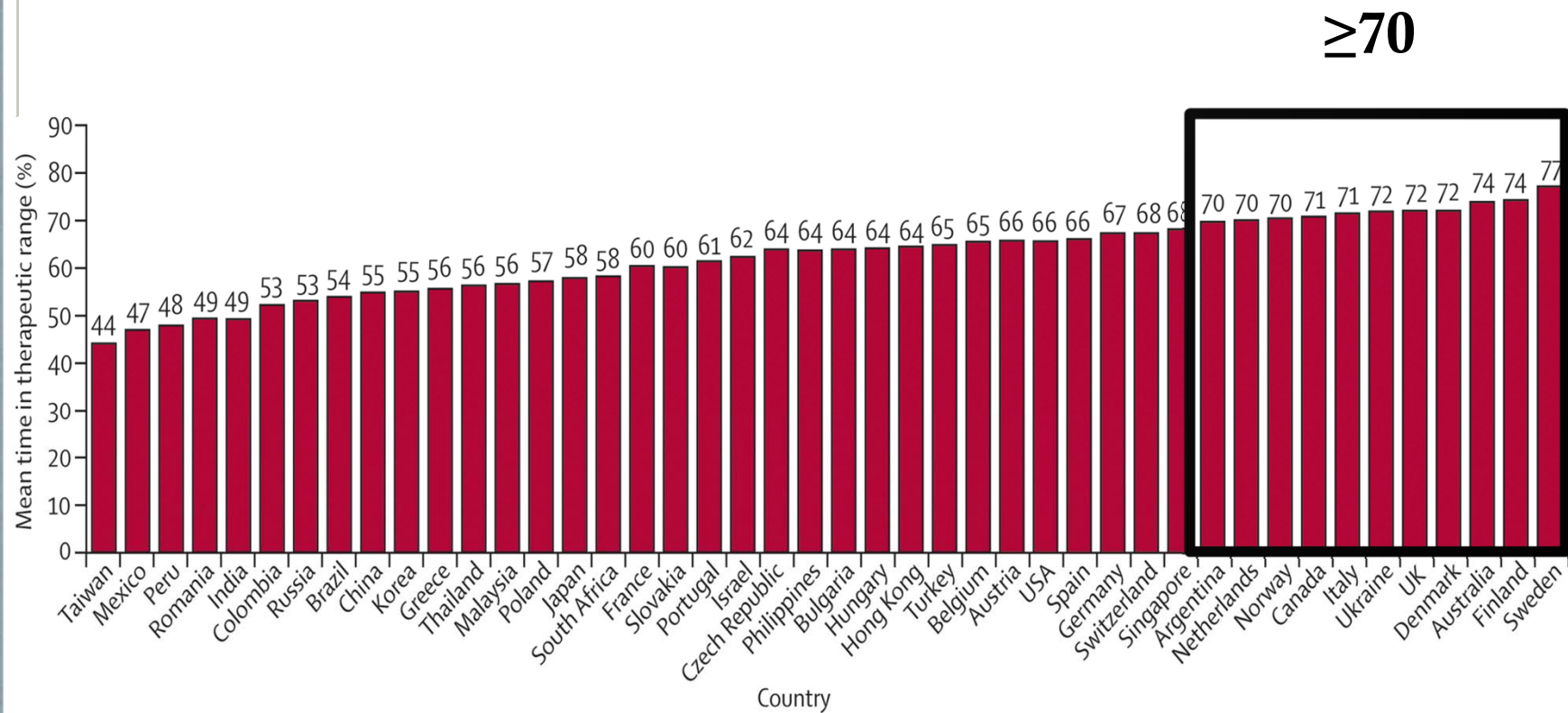
(A) stroke or systemic embolism



B) major bleeding



Mean TTR in NOAC studies



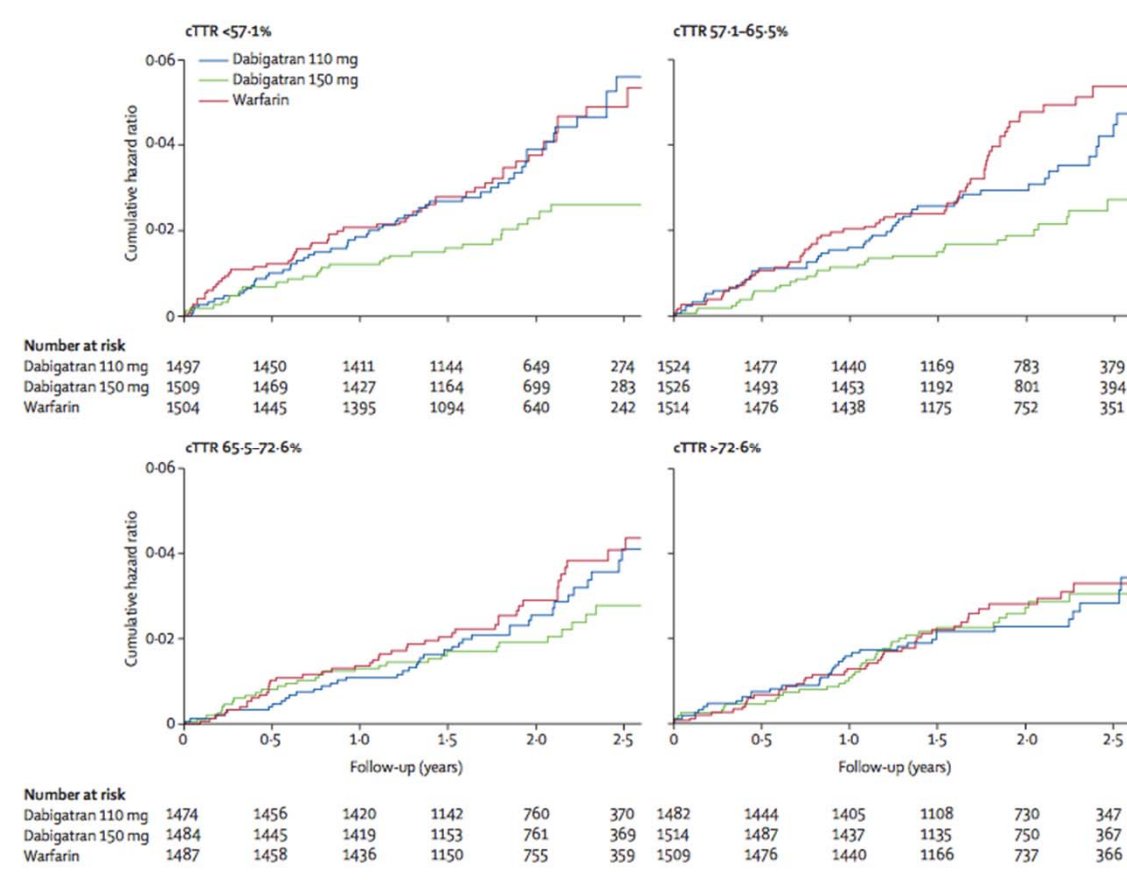
Wallentin et al. Lancet 2010, vol 376:975-83

Quality VKA

- TTR of $\geq 70\%$ is recommended in the European Society of Cardiology guidelines¹
- **Mean TTR ranged from 55–65% in the warfarin arm of key trials of non-VKA oral anticoagulants²⁻⁴**

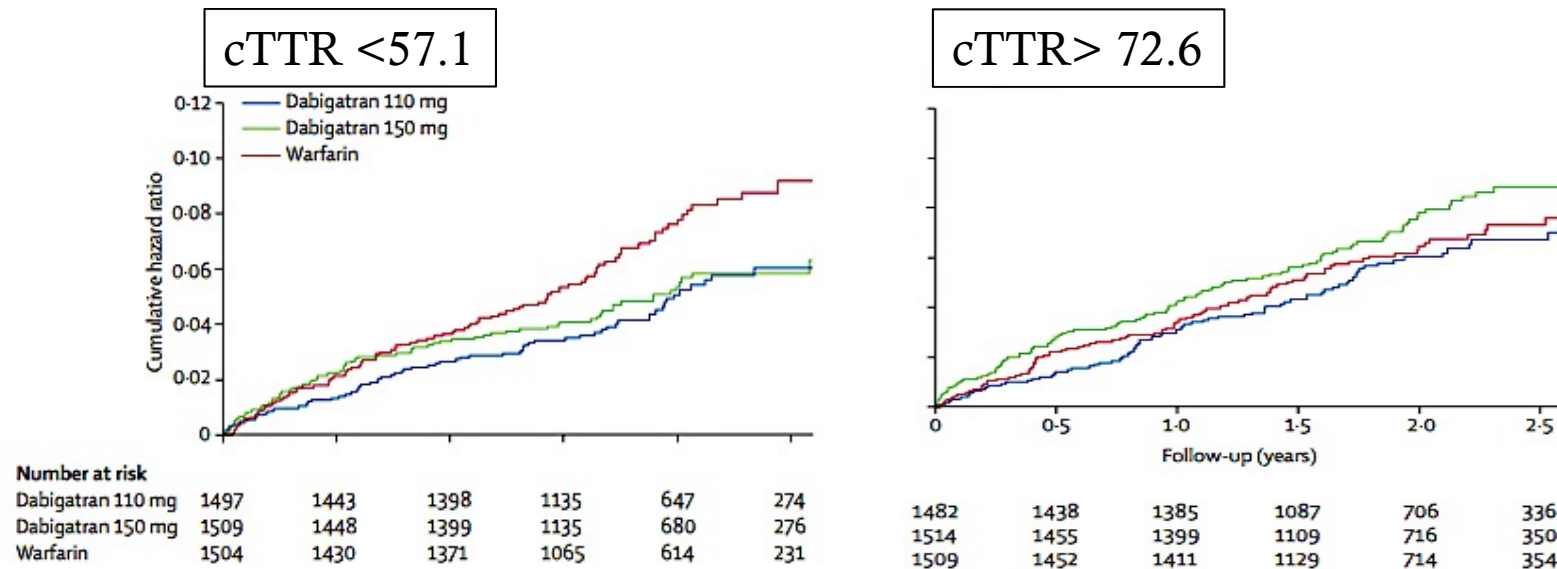
1. Camm AJ et al. Eur Heart J. 2012. 2. Patel MR et al. N Engl J Med. 2011.
3. Connolly SJ et al. N Engl J Med. 2009 4. Granger CB et al. N Engl J Med. 2011.

TTR and effectiveness



Wallentin et al. Lancet 2010, vol 376:975-83

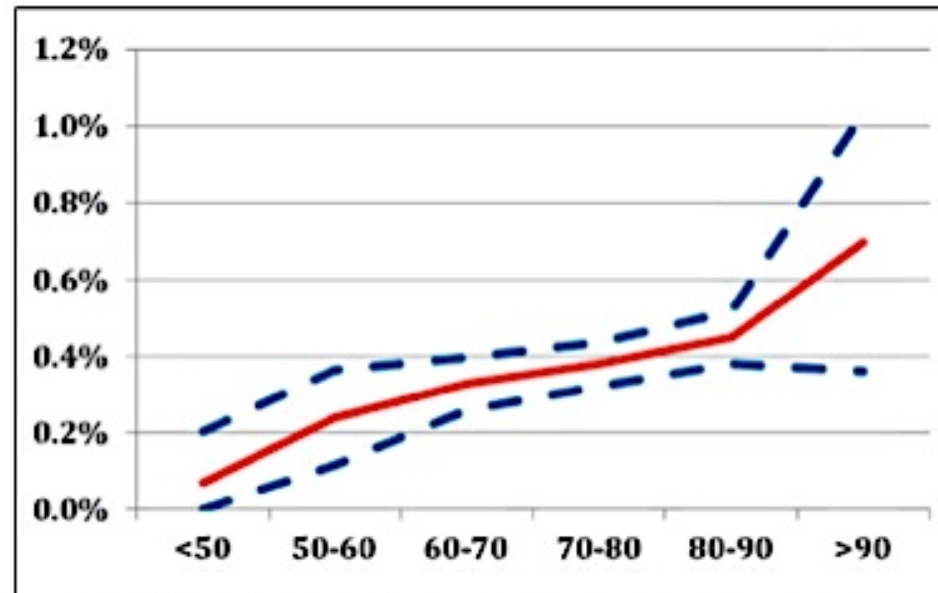
TTR and Bleeding



Wallentin et al. Lancet 2010, vol 376:975-83

Intracranial hemorrhage

	Bleeding Intracranial
All	0.37 (0.36–0.38)
Men	0.39 (0.38–0.41)
Women	0.34 (0.32–0.36)
Atrial fibrillation	0.38 (0.37–0.40)
Heart valve disease	0.51 (0.46–0.55)
VTE	0.30 (0.27–0.33)
Other indications	0.32 (0.28–0.36)



(n=68.797)

Risk ICH red: per treatment year,
blue: age groups

Lessons from VKA

- TTR > 70% offers greater protection against TE stroke (and mortality) than poorly controlled VKA
- At TTR > 70% bleeding complications are acceptable (in Sweden)
- In NOAC trials the average comparator (warfarin) had a rather modest TTR (55-64%)
- So, why are we satisfied with non-inferior or limited superiority of NOAC as compared to suboptimal warfarin.
- **Implication is that NOAC therapy should be improved!**

To tackle with NOAC

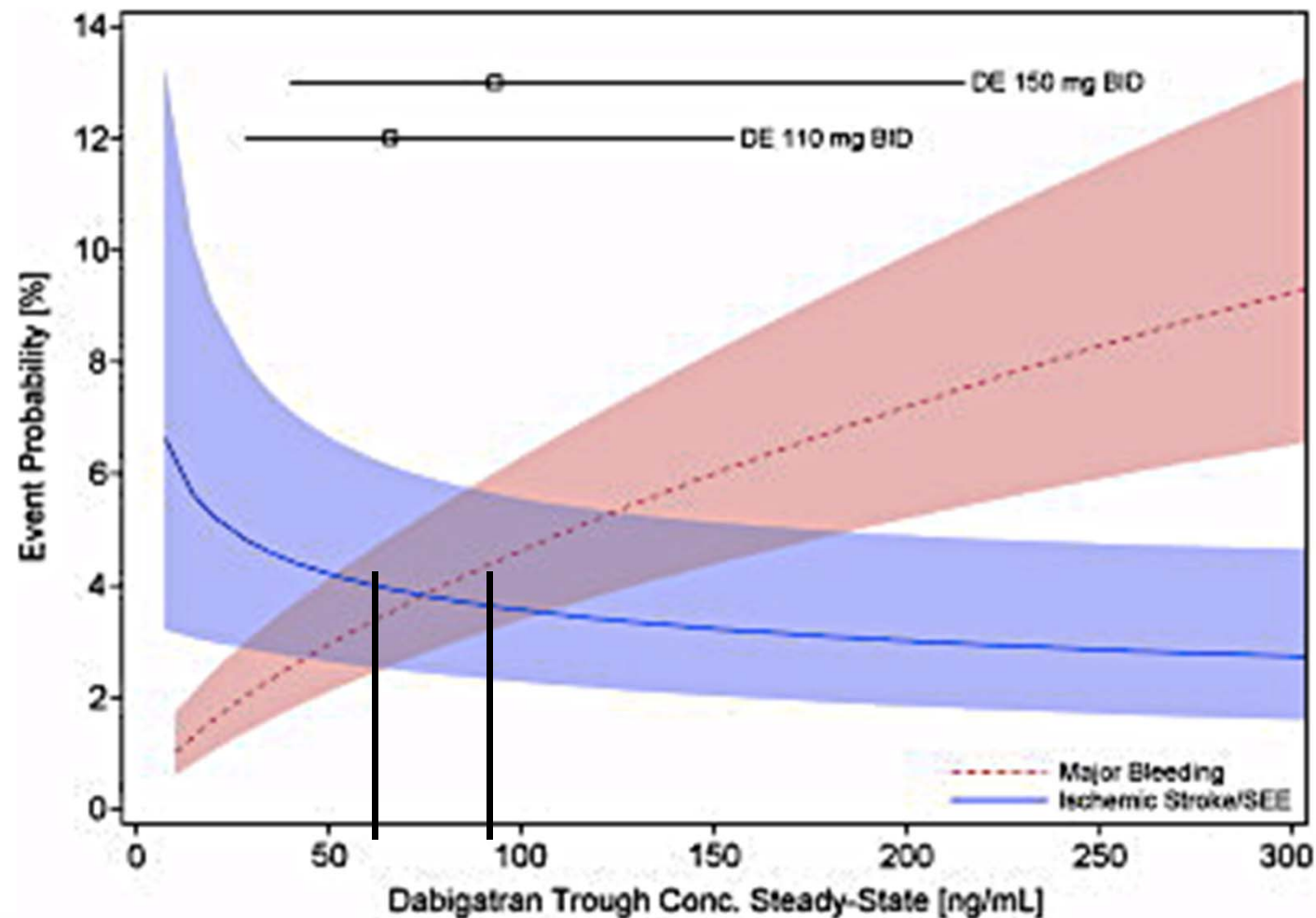
- Fixed dose; why not assess individual's response and suitability for specific NOAC?
- Improve adherence
- How to monitor, reversal, thrombolysis, after recent stroke; when to resume; after ICH, in multi-morbid geriatric patients, during episodes of intercurrent disease..

ten Cate H. Thromb J. 2013 Jun 28;11(1):8. ten Cate H. Thromb Haemost. 2012 May;107(5):803-5. Hankey. Thromb Haemost 2014; 111: 808

Does one size fit all?



Dabigatran trough & outcomes

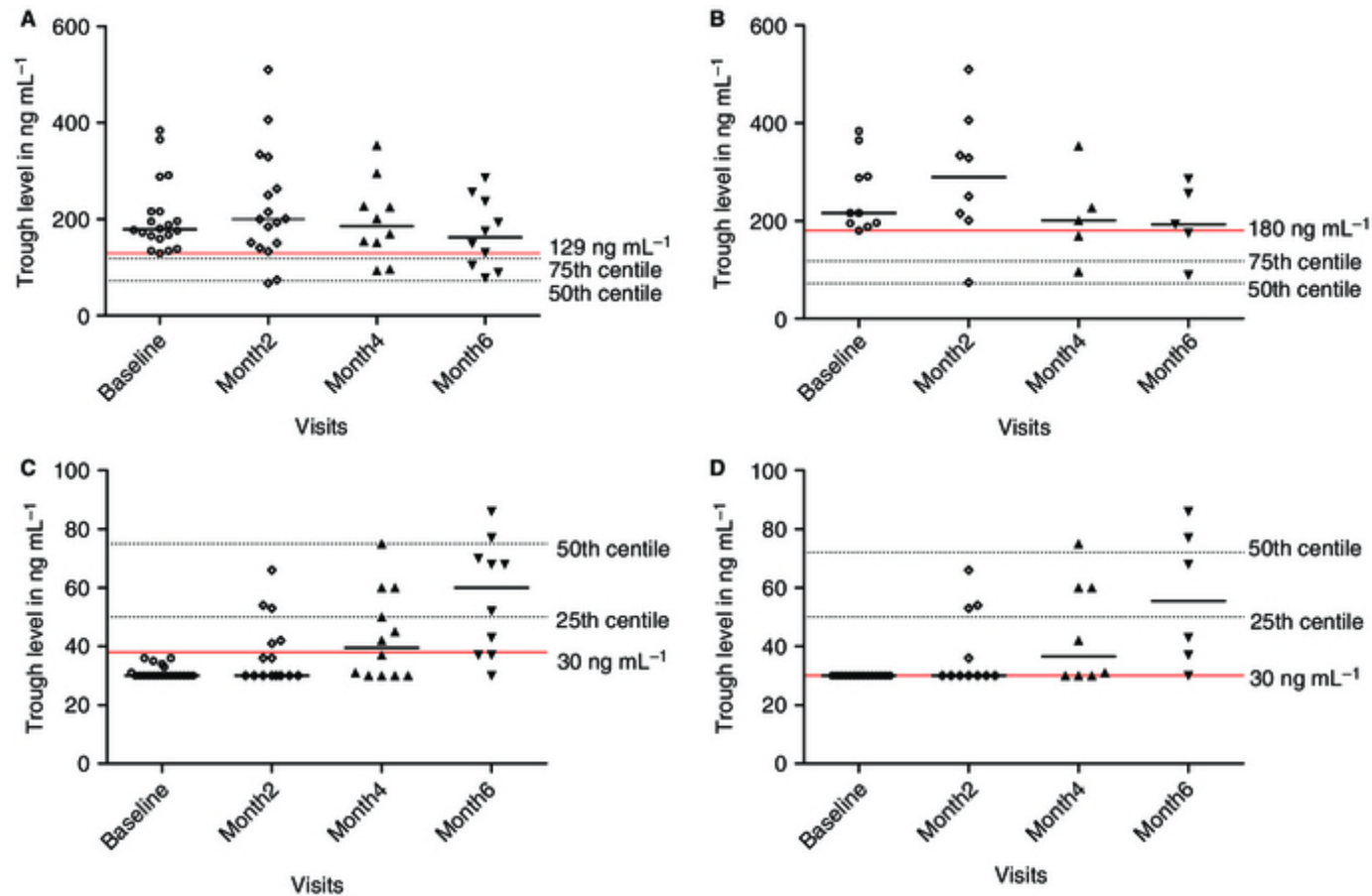


Reilly et al, J Am Coll Cardiol, 63 (4) 2014: 321 - 328

Levels & Patient characteristics

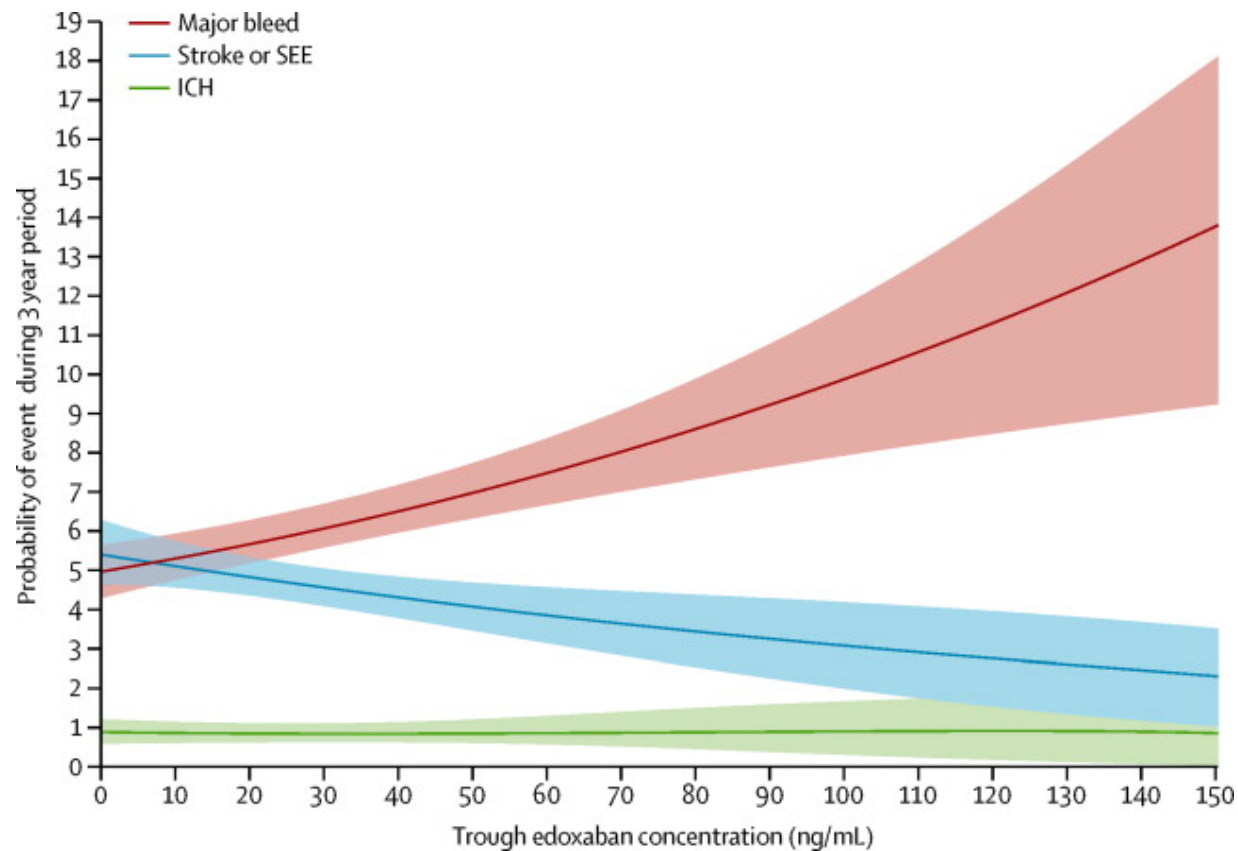
- Long-term FU RE-LY, 9183 pt, 112 isch. stroke (1.3%), 323 major bleed (3.8%)
- **IS** inversely related to trough ($p=0.045$), age and previous stroke ($p<0.0001$)
- **Major bleed** related to dabigatran overexposure ($p<0.0001$), age ($p<0.0001$), ASA use ($p<0.003$) and diabetes ($p<0.018$)

Variability Dabigatran levels

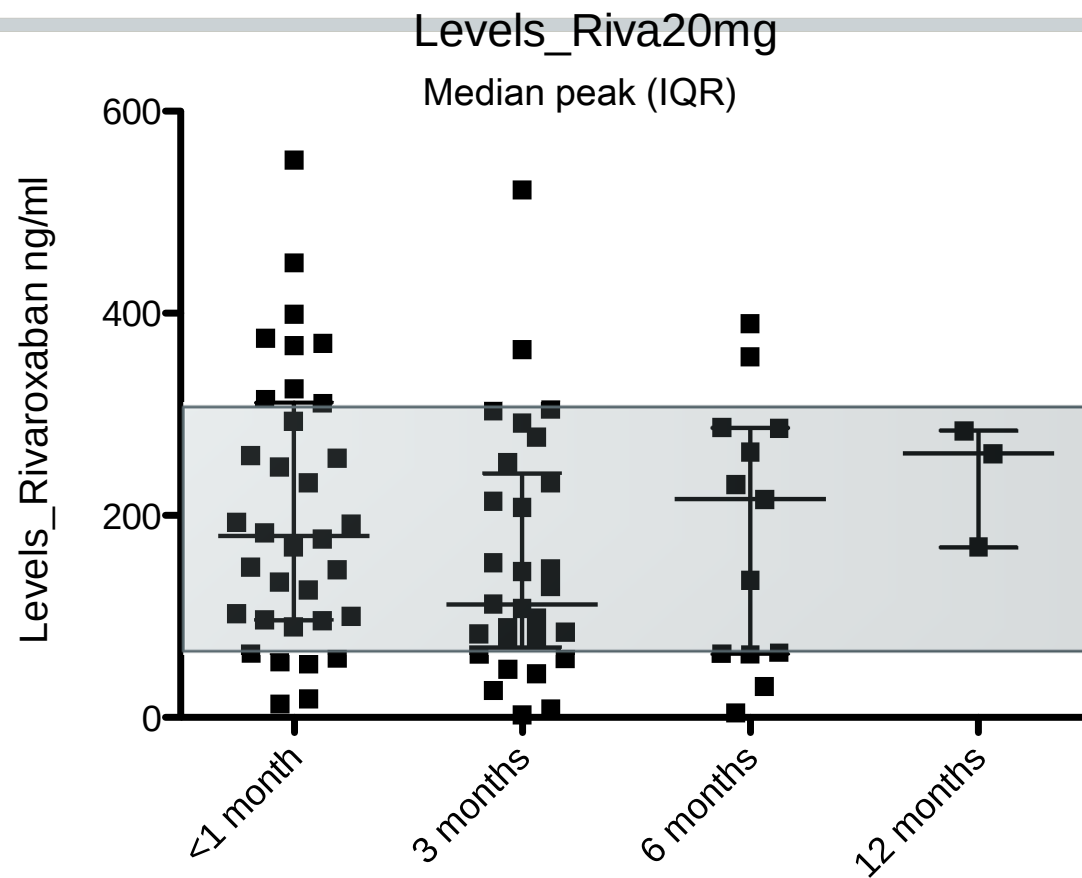


Chan et al, Thromb Haemostas 2015: [13\(3\)](#), 353-359

Edoxaban trough & outcomes

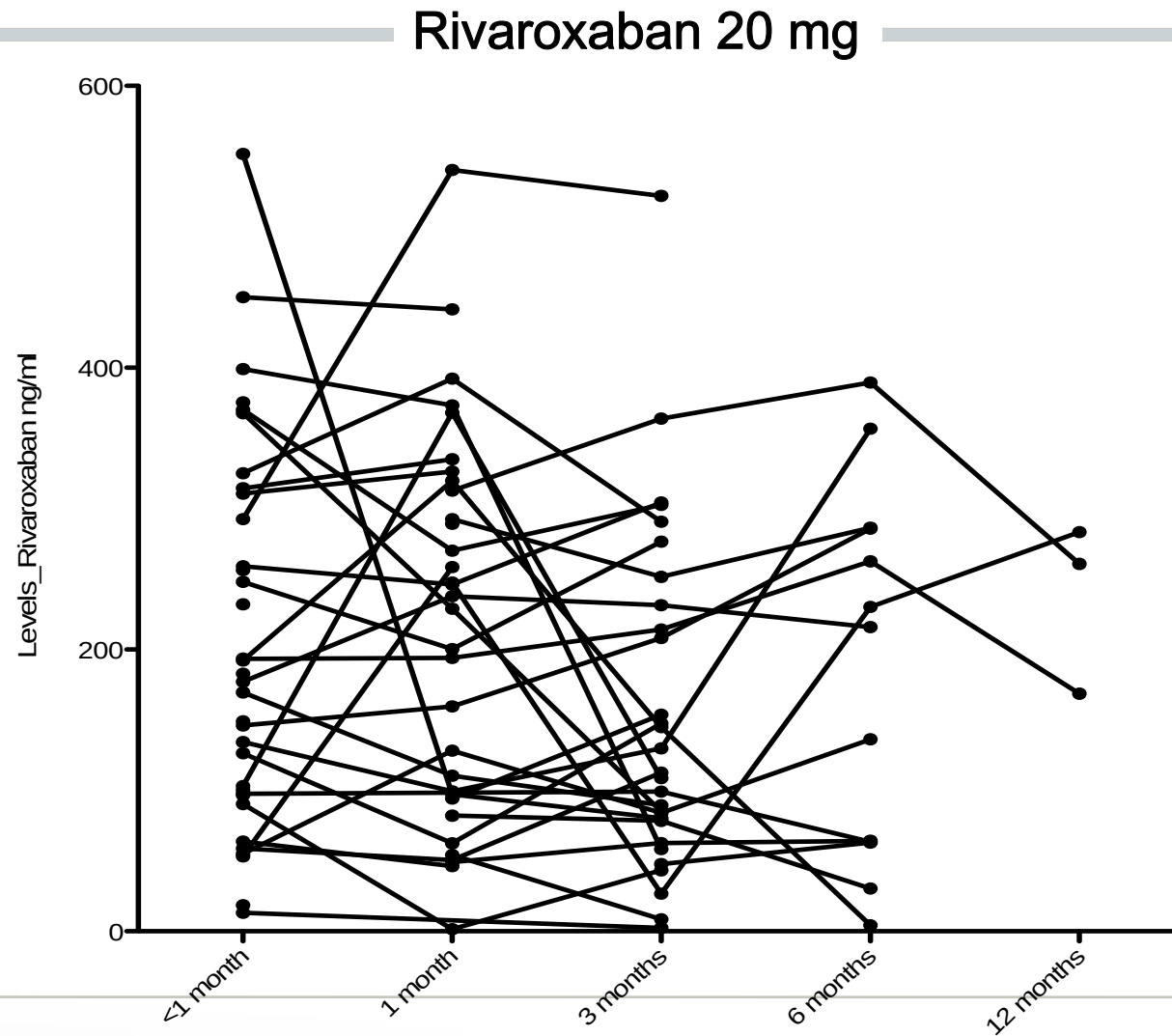


Rivaroxaban



Ten Cate-Hoek et al, unpublished

Levels per patient over time



Conclusion from PK analyses

- Data suggest that at least for dabigatran we should check dose-responses in individuals
- Data are sufficiently robust to merit assessing individual trough levels
- Instead of concentrations, quantitative assays may be used
- This cannot lead to individual dose optimization for a single NOAC beyond registered doses

How to proceed?

- Informed decision on type of anticoagulant (VKA or NOAC)
- Assess optimal drug (and dose) response to determine whether drug X is appropriate using a quantitative assay (and/or concentration assay?).
- If trough is in extreme end (lower 10 or 20%): either tailoring to other dose or switch drug (other NOAC or VKA).
- If it is within range it provides a personal patient's bench mark for unanticipated situations

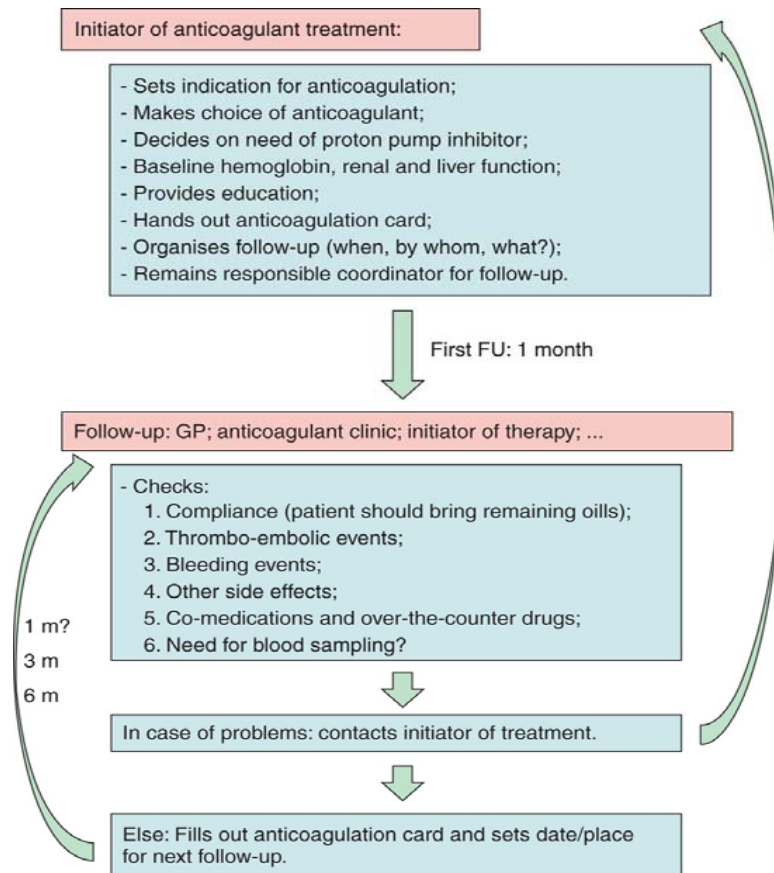
New studies: what is the basis?

- We need all available data on dose response relationships from the large trials on all NOAC, including for concentrations and activity assays (PT, TG etc); therapeutic ranges!
- Analysis of such data could provide sufficient information to decide on the necessity of PK based NOAC selection
- In practice: “PK” options may be limited: settle for trough or peak (eg in odd dosed NOAC)

New studies 2?

- For each patient benchmark data on “PK” are useful
- In case of registries such information could be linked to outcomes to obtain additional and “real life” data
- Specific problems require study of NOAC concentration/activity levels: intercurrent illness requiring hospitalization/antibiotic treatment/dehydration/ bleeding and thromboembolic complications etc.
- **Why?** To make better informed decisions on drug management!

Structured FU



**Structured follow-up
of patients on NOACs.
It is mandatory to ensure safe
and effective drug intake.**

Conclusions

- NOAC (and VKA) treatment should be improved
- Optimize drug and dose selection based on individual criteria (also including PK)
- Optimize long term follow up
- Investigate consequences of intercurrent illness on anticoagulant management (TE, bleeding, infectious diseases, congestive heart failure etc)

