The laboratory and new anticoagulant drugs

Andreas Hillarp
Department of Clinical Chemistry and Transfusion Medicine
Halland County Hospital, Sweden

andreas.hillarp@regionhalland.se

Disclosures for Andreas Hillarp:

No conflicts of interest to declare

8th Congress of the Croatian society of medical Biochemistry and laboratory medicin
Rijeka, Croatia, 23 September 2015

Alternatives to warfarin: NOAC/DOAC/TSOAC etc.

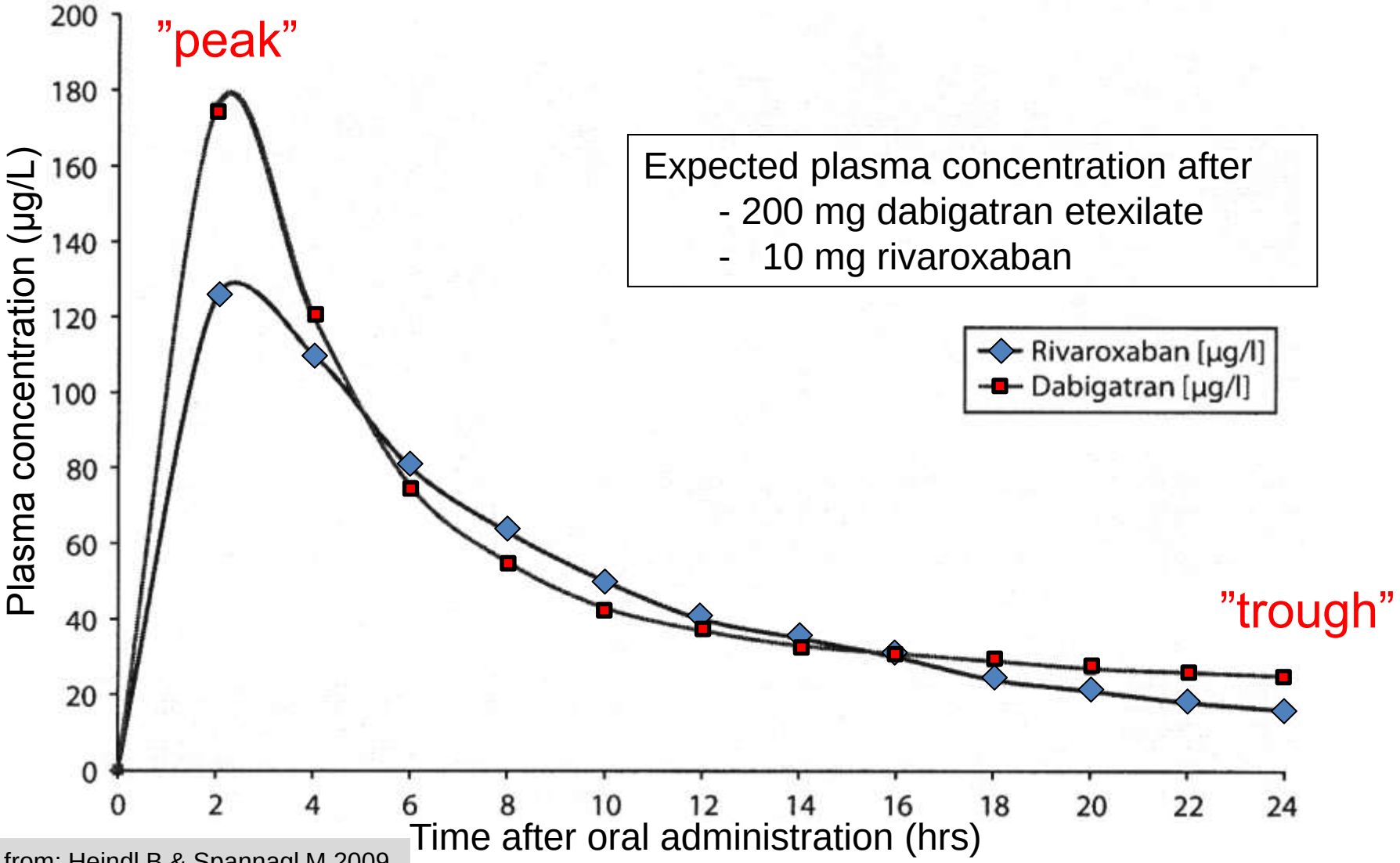
- Pradaxa® = dabigatran etexilate
- Xarelto® = rivaroxaban
- Eliquis® = apixaban
- Lixiana® = edoxaban

NOAC = non-vitamin K-dependent oral anticoagulants (ESC)
DOAC = direct oral anticoagulant (SSC-ISTH)

Key characteristics of peroral anticoagulants

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)	Warfarin (Waran)
Prodrug	yes	no	no	no	no
Factor Xa-inhibitor	no	yes	yes	yes	no
Trombin inhibitor	yes	no	no	no	no
Bioavailability (%)	6	>80	>50	45	100
Monitoring	**no**	**no**	**no**	**no**	**Yes**
Time to peak (h)	**2**	**3**	**3**	**1,5**	**120**
T½ (h)	**12-17**	**9**	**9-14**	**9-11**	**50**
Interactions	Proton pump inhibitors P-glyco-protein	CYP3A4 P-glyco-protein	CYP3A4 P-glyco-protein	CYP3A4 P-glyco-protein	Long list
Renal excretion(%)	80	33	25	35	1
Antidot (specific)	no	no	no	no	Yes

Measurements are dependent on when the last drug dose was taken!

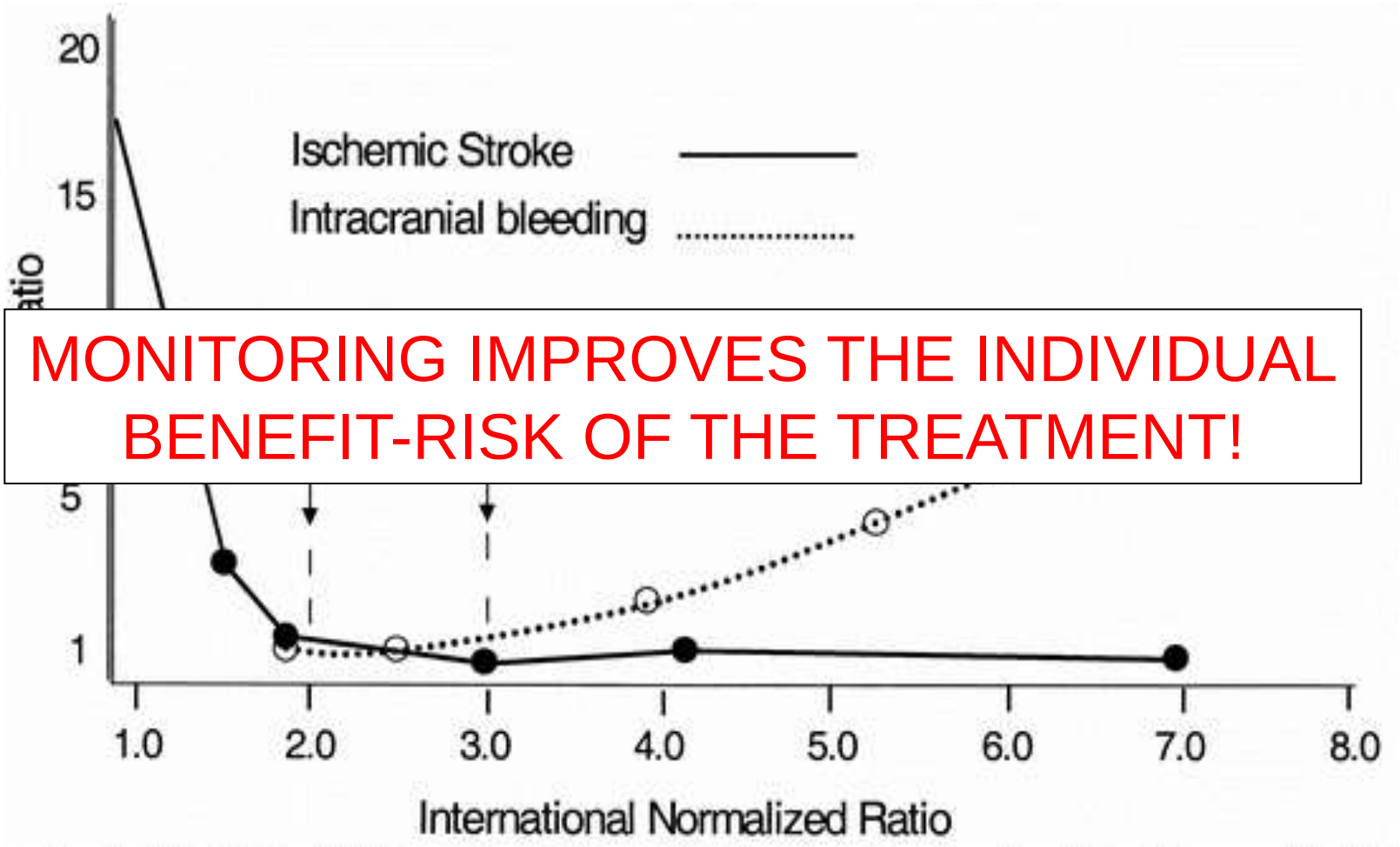


Mod. from: Heindl B & Spannagl M 2009

MEASURING AND MONITORING

What does the drug level (plasma concentration) mean?

Correlation PT(INR) and outcomes
Narrow therapeutic interval: INR 2-3



MONITORING IMPROVES THE INDIVIDUAL BENEFIT-RISK OF THE TREATMENT!

ACC/AHA/ESC 2006 guidelines, Europace 2006;8:651-745

J Am Coll Cardiol 2014; 63: 321-8

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)

Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,† Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPhil,§ John W. Eikelboom, MB BS,§ Michael D. Ezekowitz, MD, PhD,‖ Gerhard Nehmiz, PhD,† Susan Wang, PhD,* Lars Wallentin, MD, PhD,¶ on behalf of the RE-LY Investigators

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

”Individual benefit-risk might be improved by tailoring dabigatran dose”

!

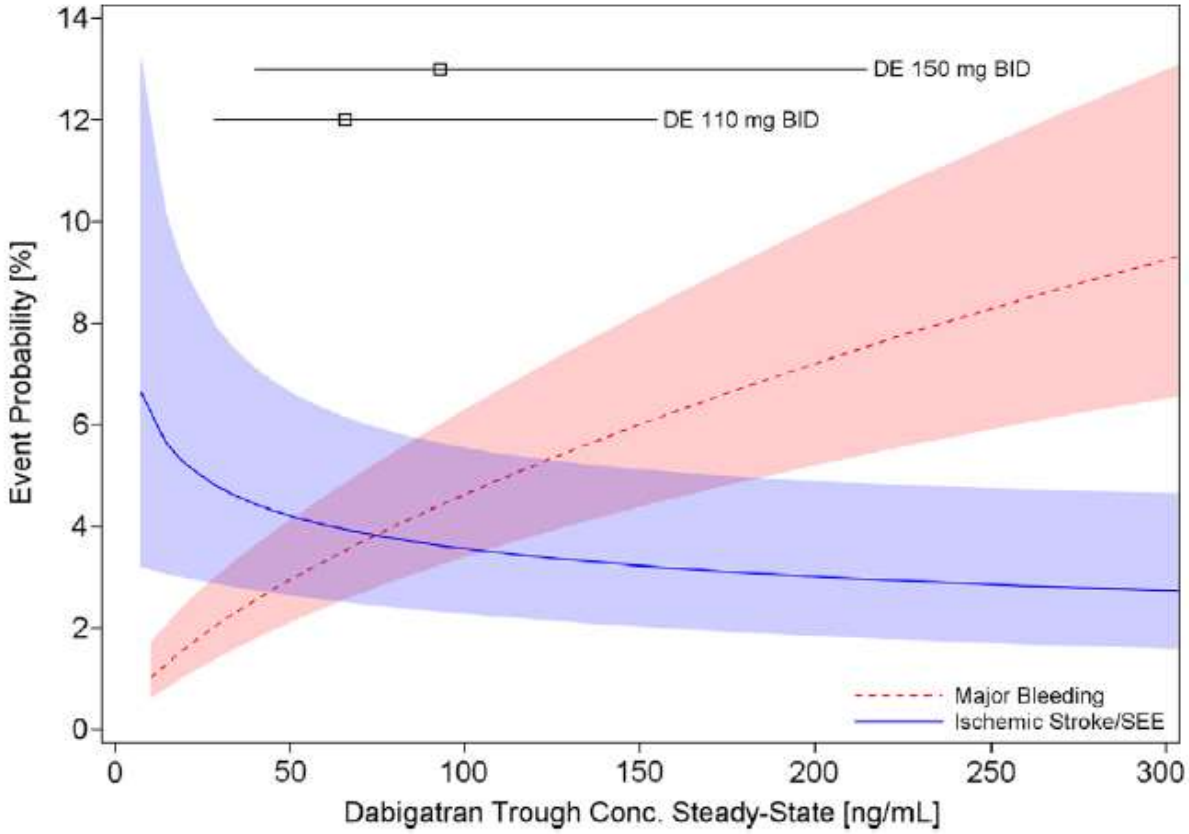


Figure 2 **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles.
Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).

Measuring NOAC – when?

Necessary in various acute situations:

- Surgery, bleeding, intoxications…

Could be useful in specific situations:

- Adverse events/failure of therapy, compliance
- Extreme body weight (high/low)
- Patients with deteriorating renal function
- Before initiation/baseline values
- At regular check-ups…

Measuring NOACs - how?

1. Qualitative tests (screening assays)

   Readily available in emergency situations.

   Indicating supra- or subtherapeutic effects.

2. Quantitative tests (specific)

   Determination of anticoagulant effects and plasma concentrations.

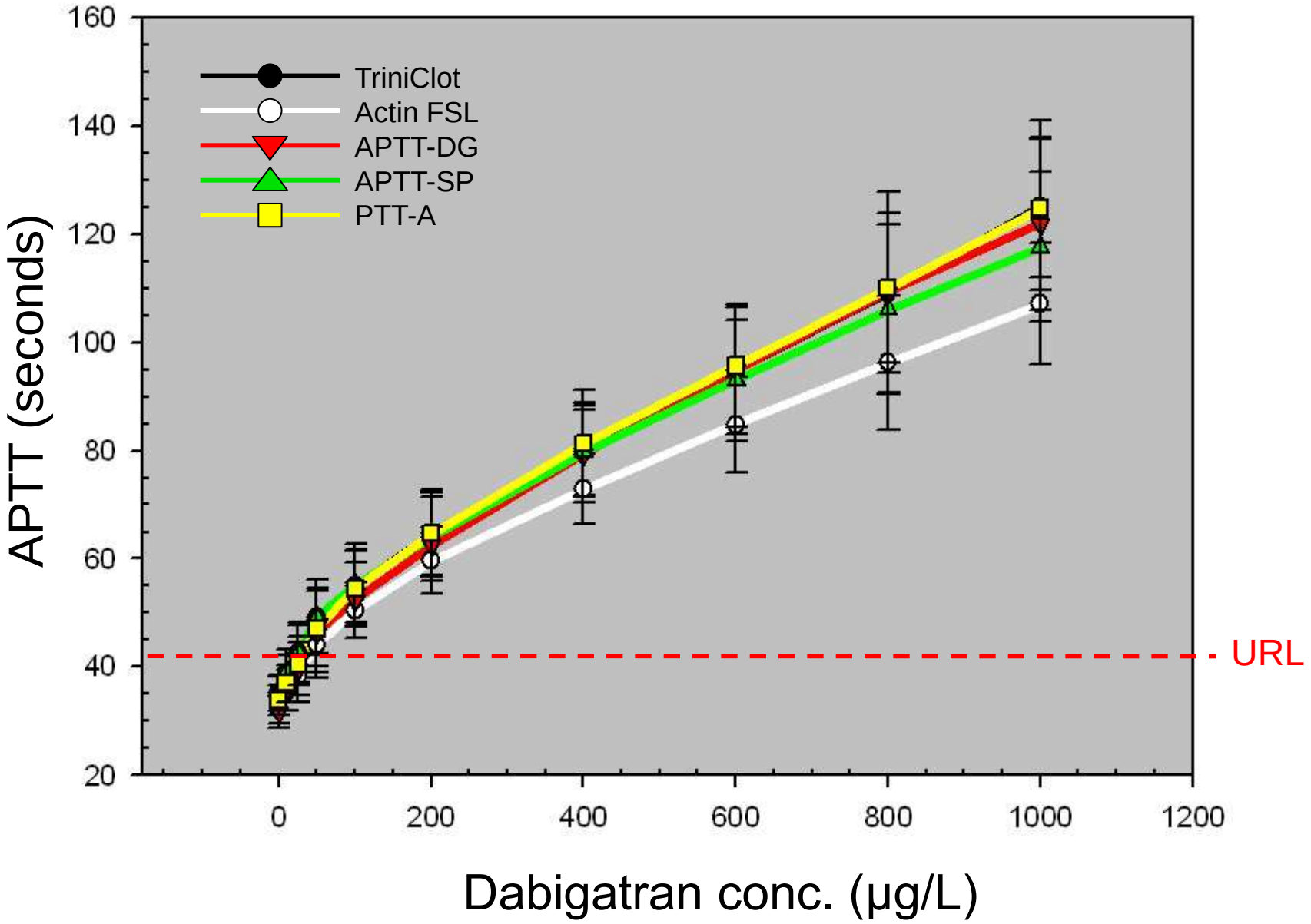
3. Reference methods

   LC-MS/MS

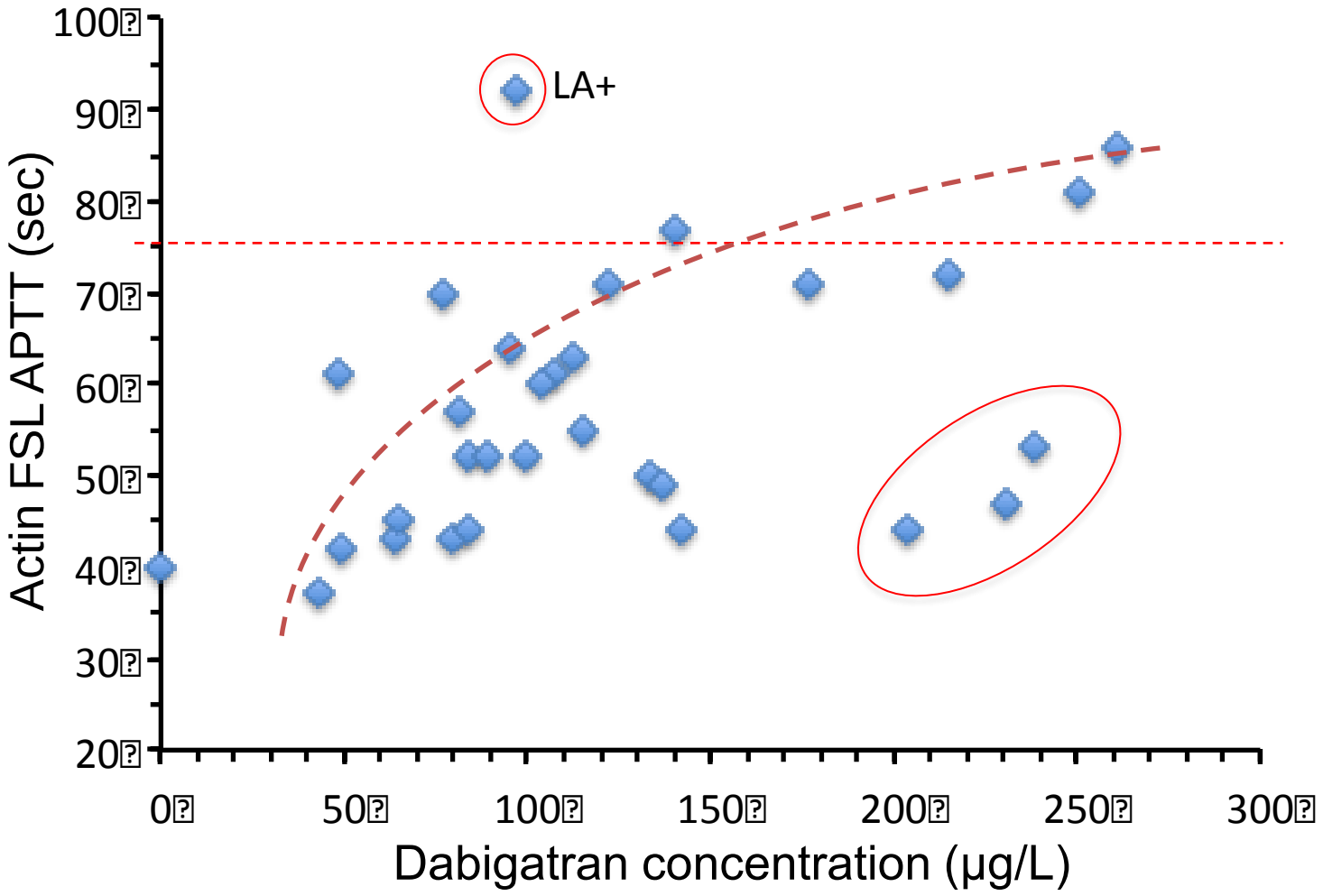
NOAC will interfere, more or less, with most coagulation-based assays!

- Screening assays: APTT, PT(INR)
- Factor assays, antithrombin, fibrinogen, protein S/C activity, lupus, etc. (thrombophilia invest.)
- Effect correlated to type of drug and concentration.
- Large differences between methods/reagents.
- Effect dependent on time since last dose due to short half-life with (”peak” and ”trough”).

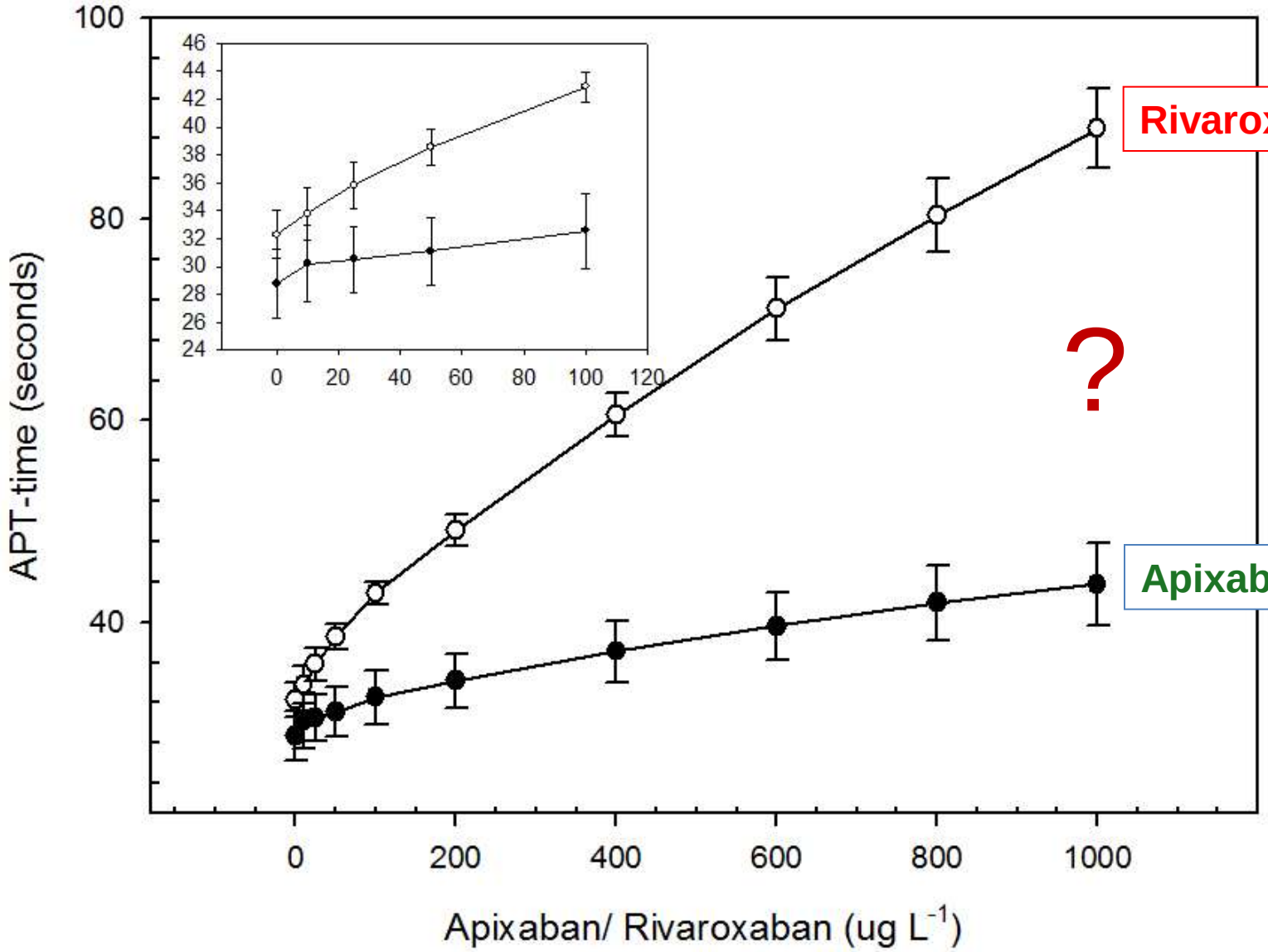
Dabigatran (spiked samples) and APTT



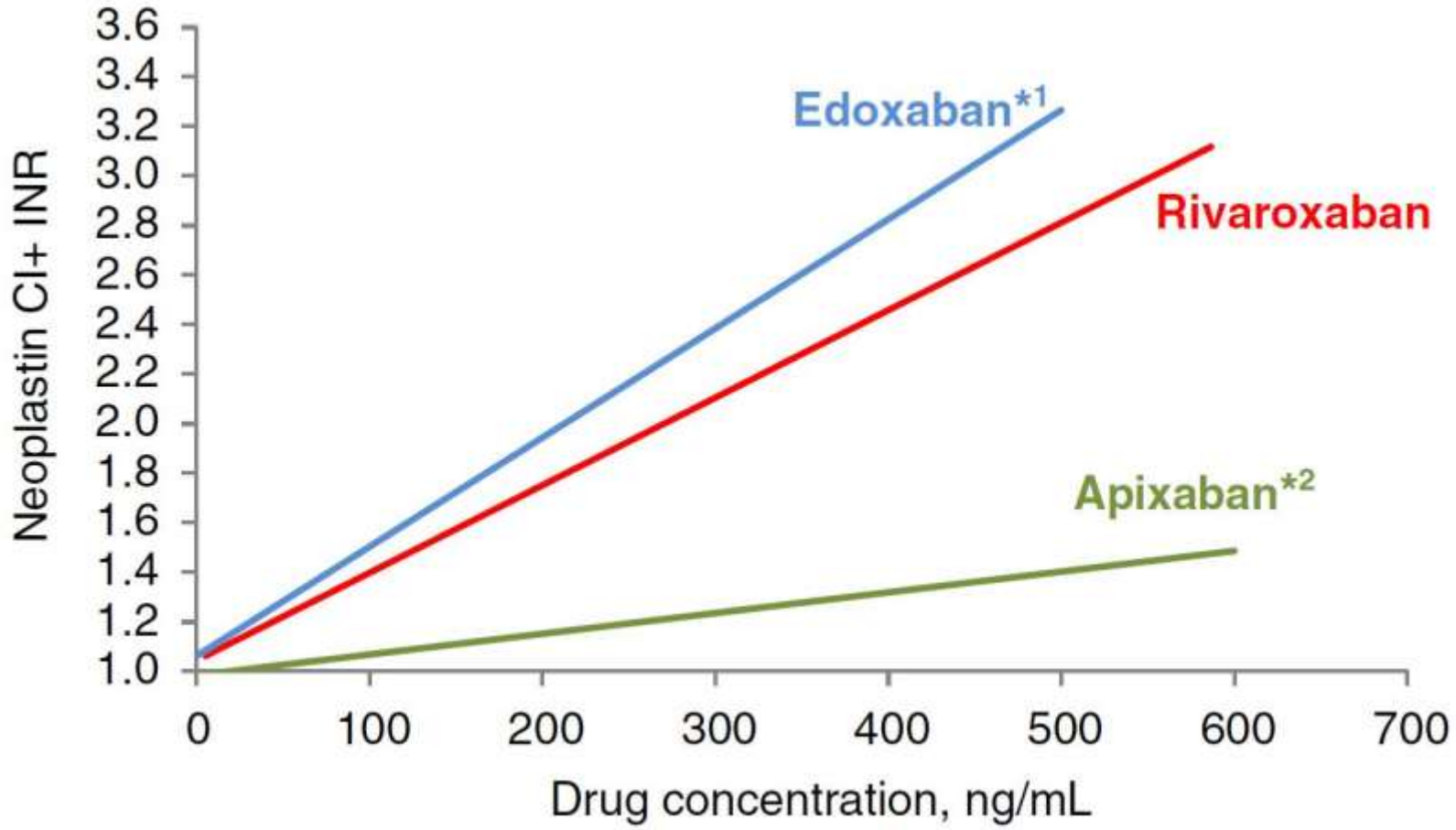
Dabigatran and APTT ”in real life”



Differences (in vitro) between rivaroxaban and apixaban!



Differences in PT(INR) responsiveness edoxaban>rivaroxaban>>apixaban



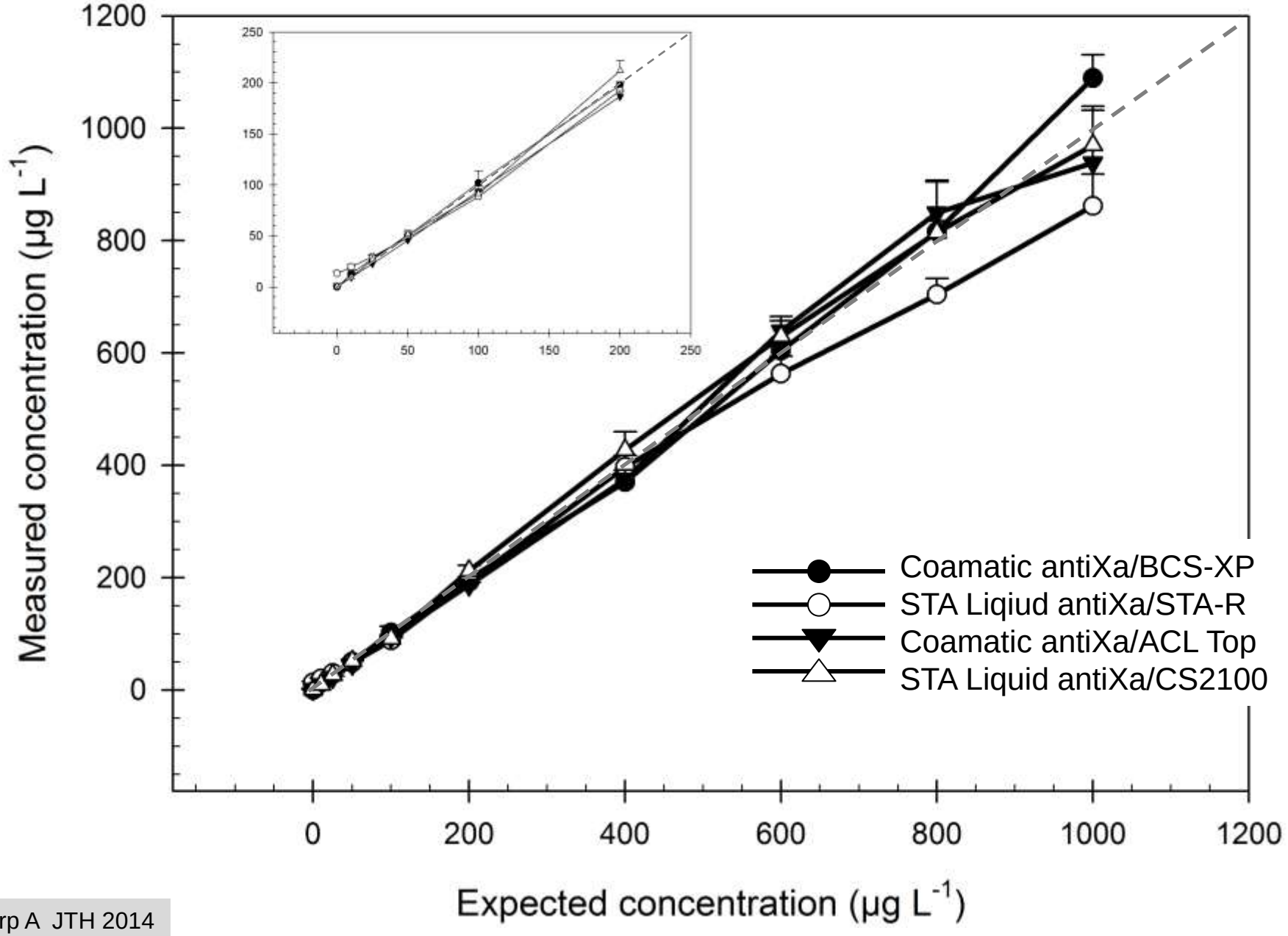
Example from: Adcock & Gosselin Thromb Res 2015; 136: 7-12.

Specific assays for measuring the effect of NOACs

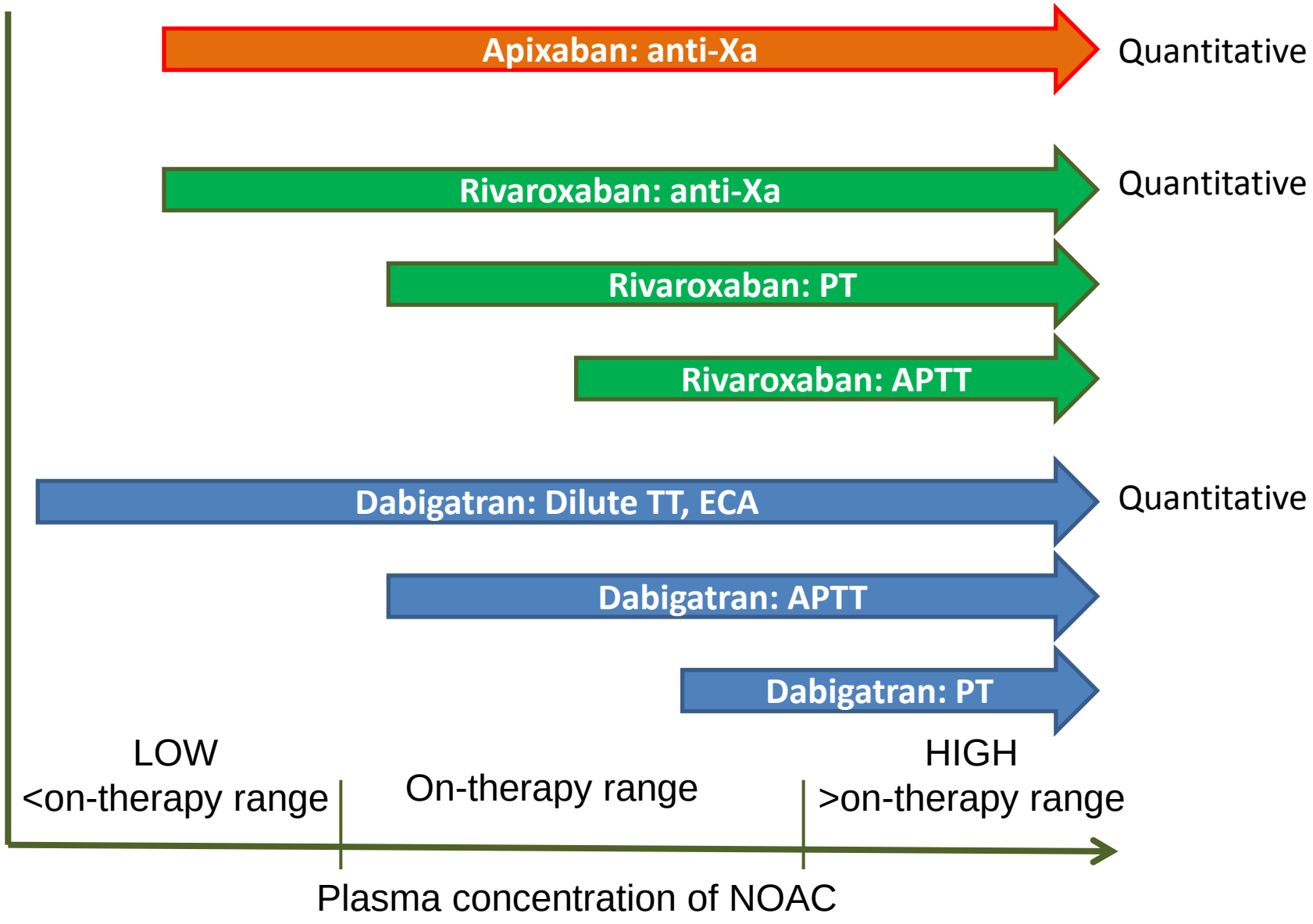
- **Thrombin inhibitor (dabigatran)**
  - *Dilute thrombin time (dTT) or ecarin-based assays*
    - Calibrated with dabigatran standard
    - Results given in mass concentration (µg/L)

- **Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)**
  - *Anti-Xa assay*
    - Calibrated with drug-specific standards
    - Results given in mass concentration (µg/L)

APIXABAN RESULTS: ANTI-XA ASSAYS



Hillarp A JTH 2014



Modified from Cuker et al. J Am Coll Cardiol 2014;64:1128

Conclusions

- Correlation between NOAC plasma concentration, effect on assays and outcome (tailoring possible?)
- Measuring is valuable at certain clinical situations.
- Dabigatran (thrombin-inhibitor) is best measured with dTT or ECA
- Xa-inhibitors (rivaroxaban, apixaban and edoxaban) are measured with anti-Xa assays
- Variable effect *in vitro* with anti-Xa NOACs

BÄSTA LIVSPLATSEN
Region Halland

LUND UNIVERSITY

Thank you for your attention