

International Normalized Ratio for monitoring therapy with vitamin K antagonists

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Subjects

- ISI model and International Standards
- Uncertainty of INR
- Local calibration and commutability
- Point-of-care INR monitors
- Biological variation and precision
- External Quality Assessment

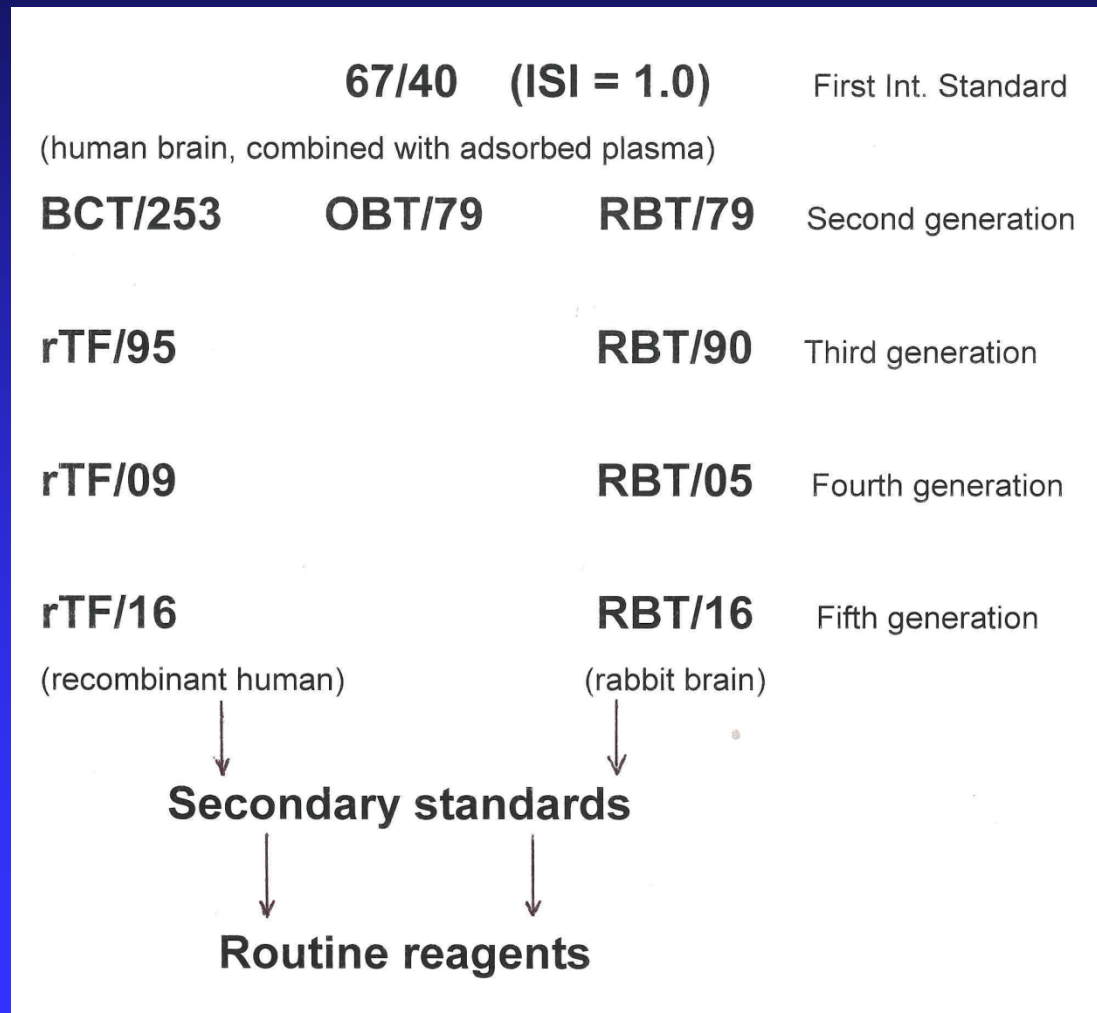
Transform PT results to INR

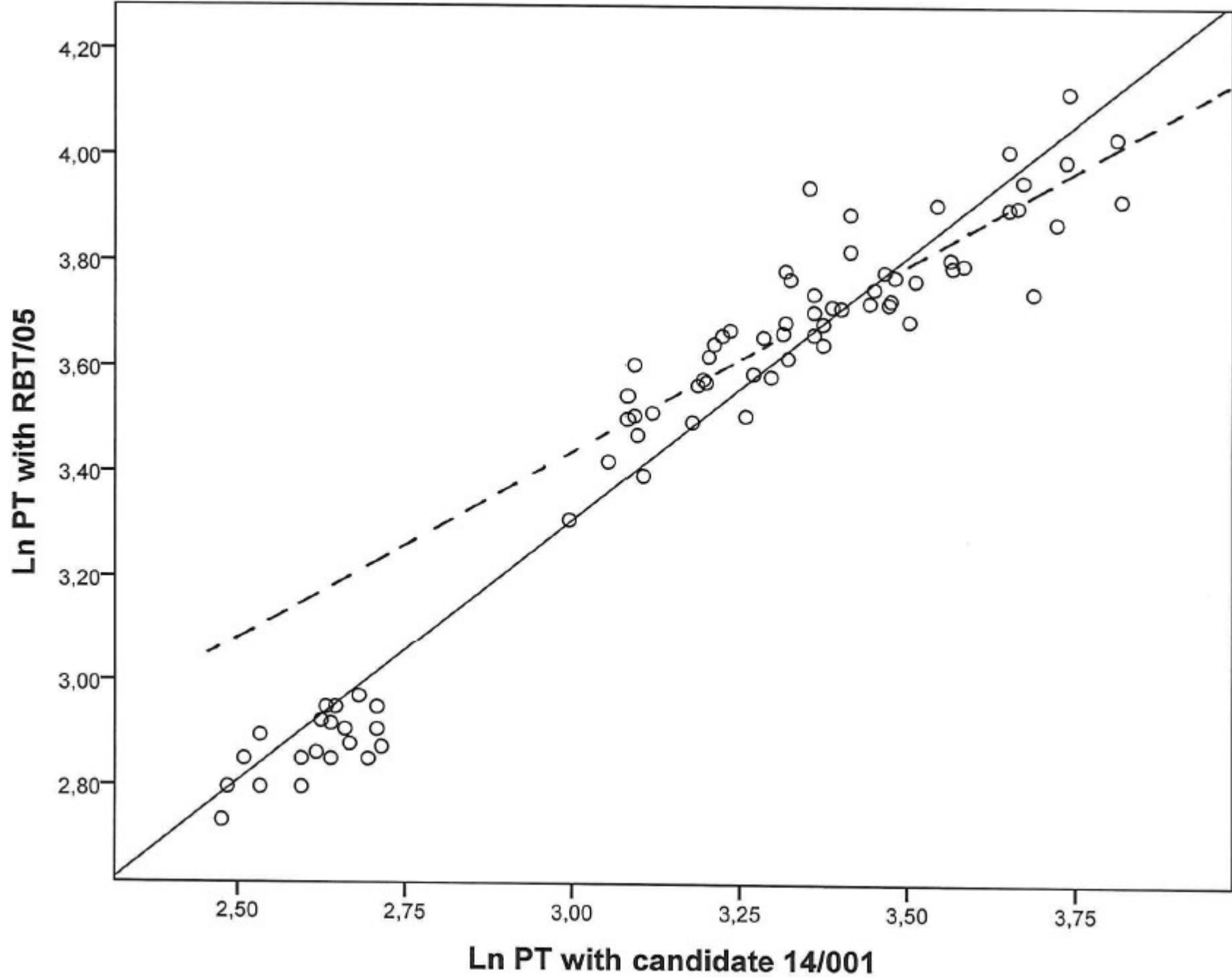
$$\text{INR} = (\text{PT}/\text{MNPT})^{\text{ISI}}$$

MNPT: Mean Normal PT (geometric mean of healthy individuals' Prothrombin Times)

ISI: International Sensitivity Index

Hierarchy of Thromboplastin calibration





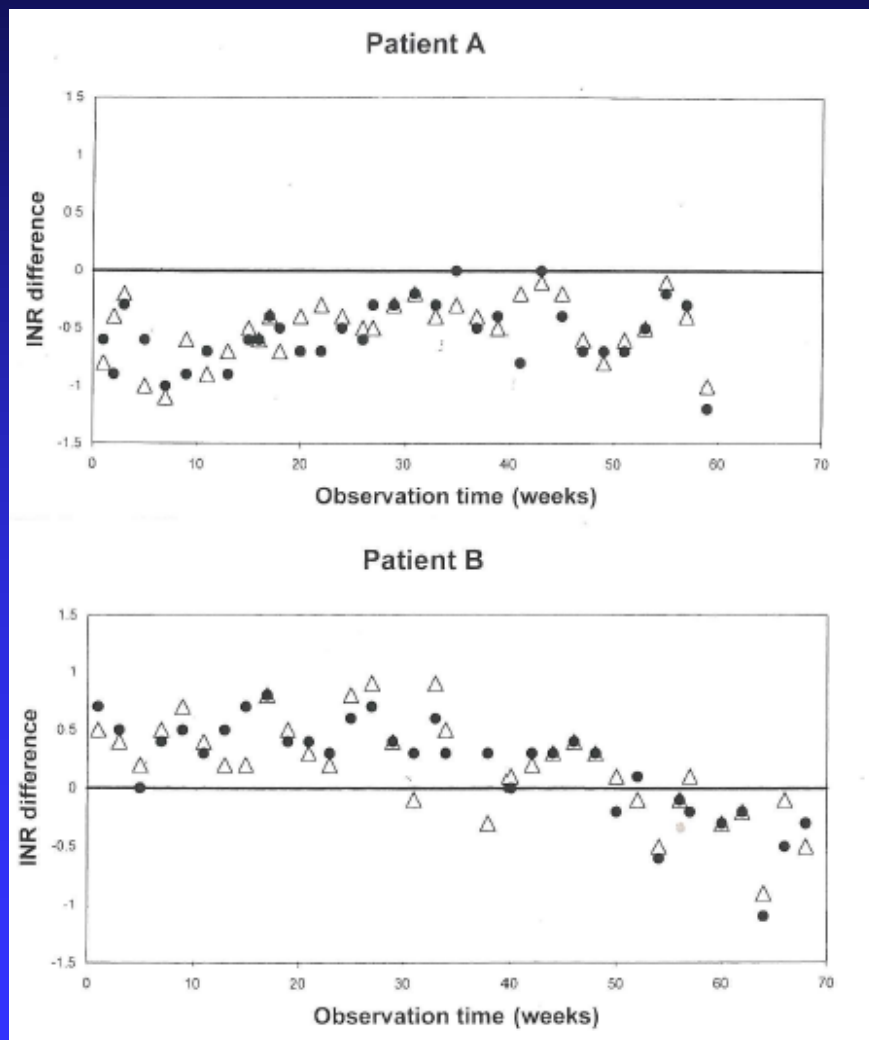
Mean ISI for new International Standards after exclusion of non-valid assessments

| | rTF/16 (recombinant, human) | | RBT/16 (rabbit brain) | |
|-----------------------|--------------------------------|----------------------|---------------------------|----------------------|
| | Reference: rTF/09 | Reference: RBT/05 | Reference: rTF/09 | Reference: RBT/05 |
| Mean ISI | 1.092 (n = 20) | 1.138 (n = 13) | 1.201 (n = 11) | 1.212 (n = 18) |
| Between-lab CV (%) | 2.1 | 8.0 | 4.6 | 4.6 |
| Overall mean ISI | 1.11 | | 1.21 | |
| Between-lab CV (%) | 5.7 | | 4.6 | |

Uncertainty of INR

- PT test is influenced by multiple factors
- Thromboplastin reagents have different sensitivities to individual factors
- Between-laboratory error of ISI
- Imprecision of PT and MNPT

INR difference between Point-of-care and laboratory

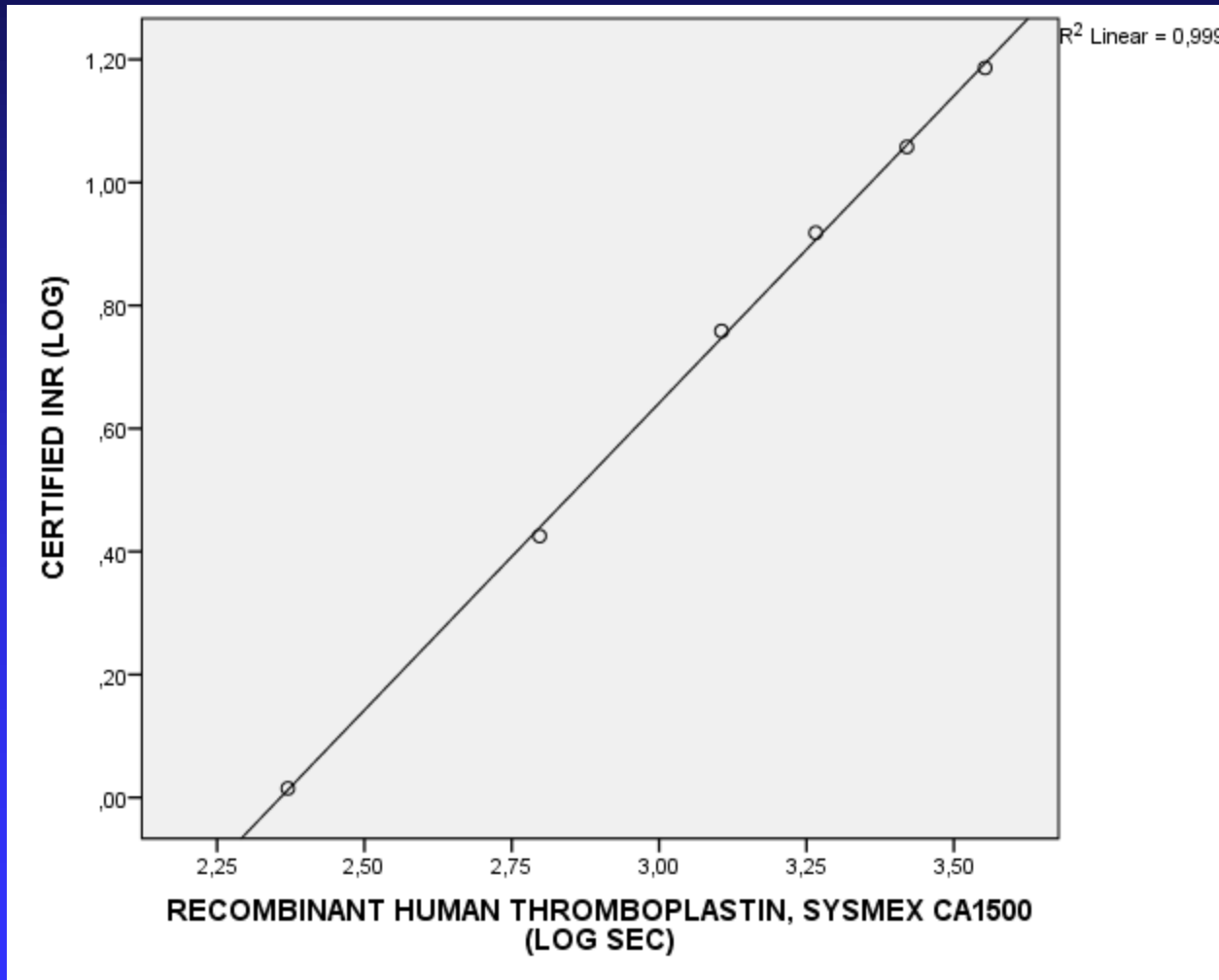


From: Tripodi A et al. Semin Vasc Med 2003;3:243-254

“Direct INR” method for local calibration

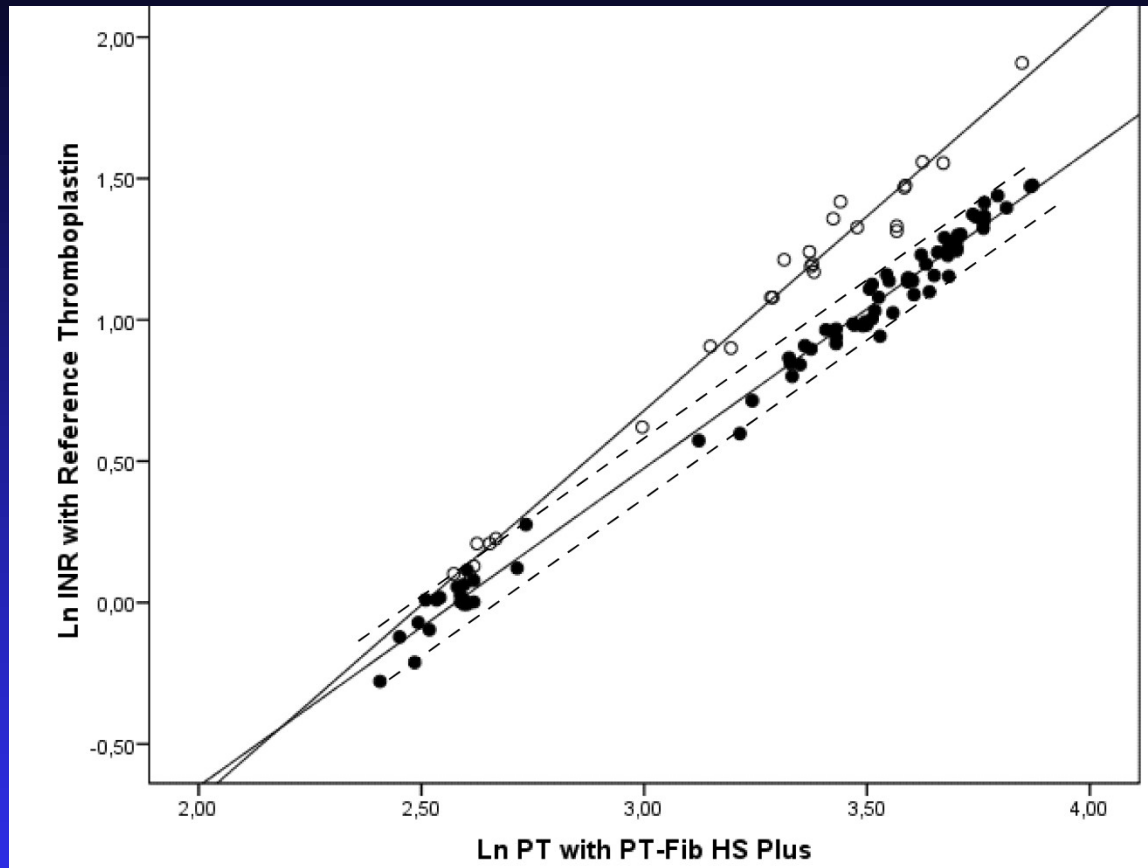
- Set of lyophilized or deep-frozen plasmas with certified INR values
- No need for MNPT determination with many (≥ 20) fresh normal plasma samples.
- INR can be calculated from regression line:
$$\text{Log INR (patient)} = a + b \times \log \text{PT (patient)}$$
- Be careful: commutability of certified plasma

'Direct' INR method for local calibration



Commutability

- Commutability is defined as the equivalence of the mathematical relationships between the results of different procedures for a ‘reference material’ and for representative samples from healthy and diseased individuals.
- For INR procedures, the ‘reference material’ is the set of certified plasmas.



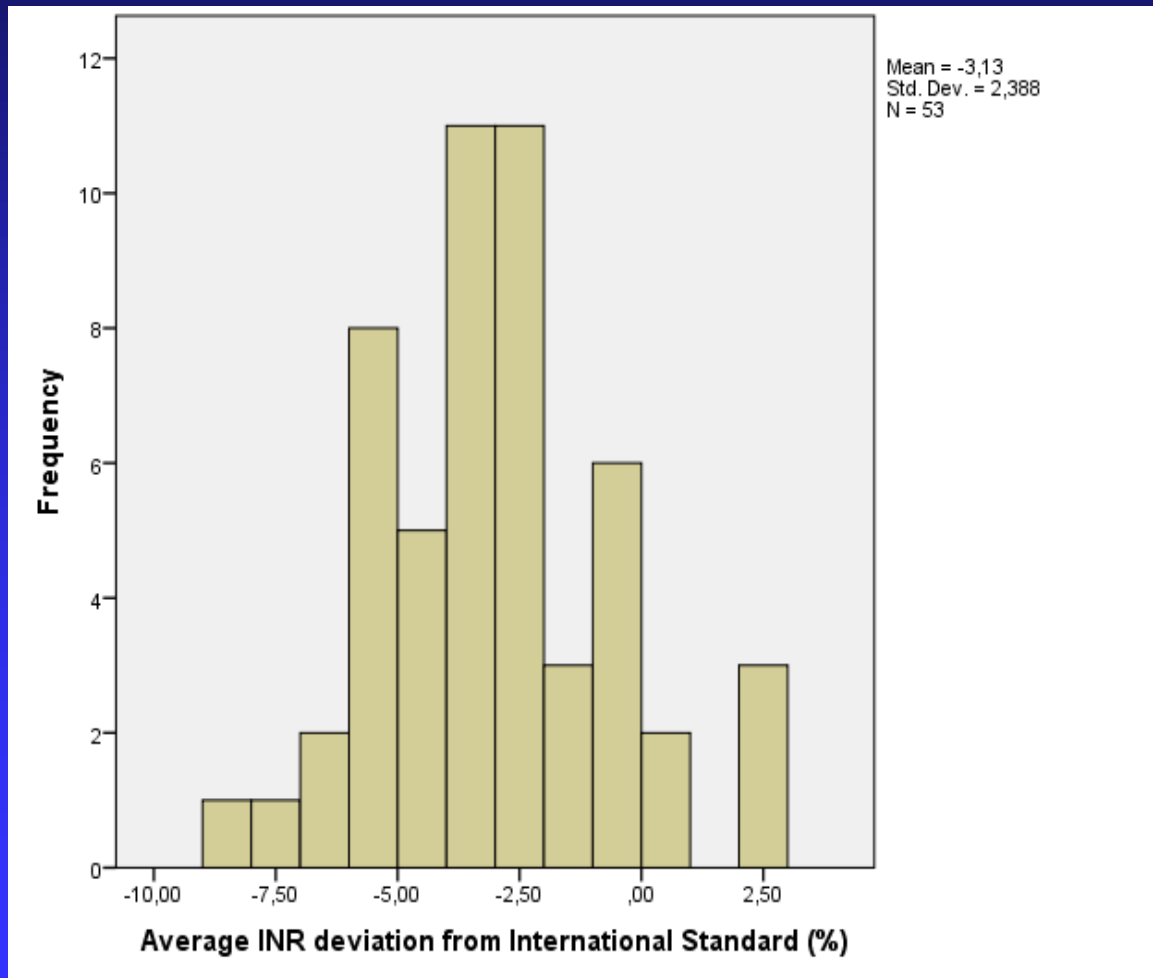
Non-commutability of Freeze-dried Artificial Plasmas (J Thromb Haemost 2012;10:303)

Filled symbols: fresh native plasma samples of 20 normal and 60 VKA patients. Open symbols: 7 freeze-dried normal samples and 20 freeze-dried artificially depleted plasmas. Dotted lines: 95% prediction interval.

Point-of-Care (POC) INR monitors

- POC systems are calibrated by the manufacturer using split-sample procedure.
- Calibration equation is fixed and cannot be changed by the user.
- In the Netherlands each lot of test strips is validated by a Coagulation Reference Laboratory (CRL) collaborating with a group of Thrombosis Services.

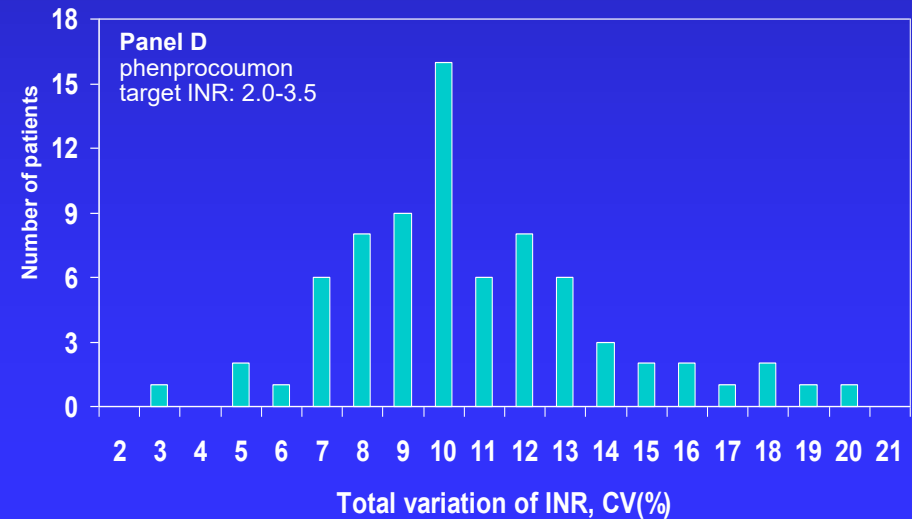
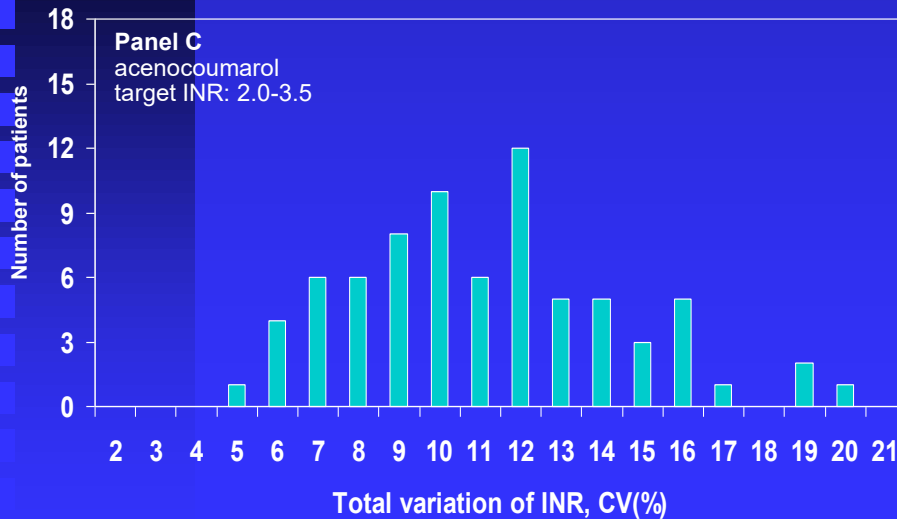
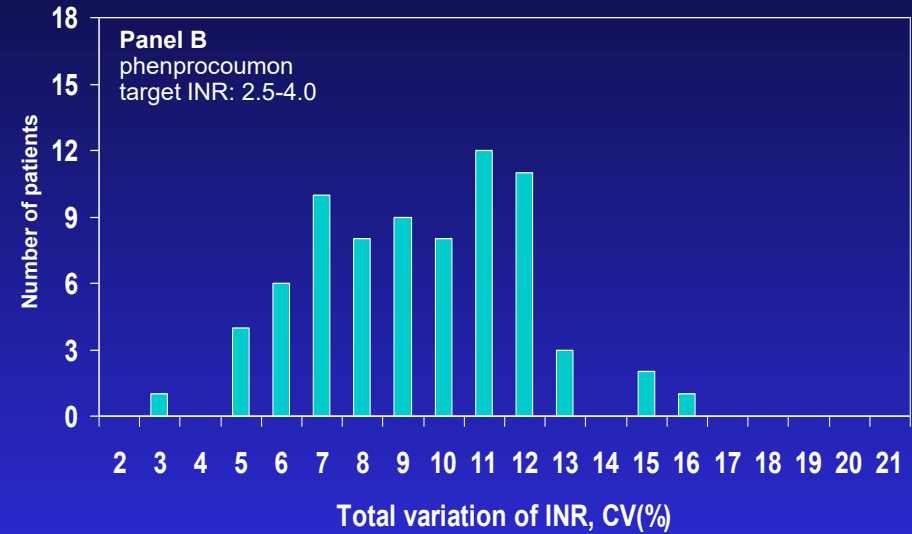
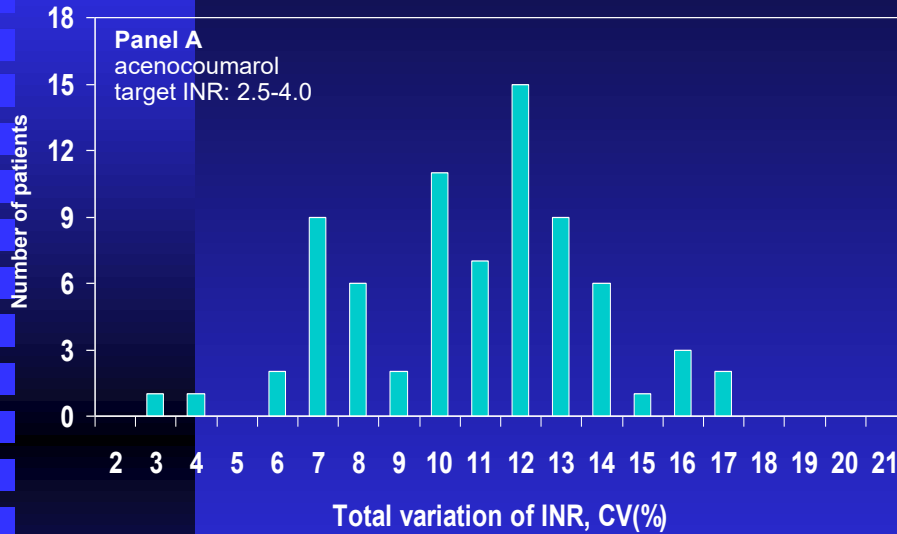
Average INR deviation of 53 consecutive lots of test strips for CoaguChek XS



Biological variation and precision

- Analytical performance goals should be based on biological variation.
- Biological variation: within-subject and between-subject.
- Biological variation of INR in healthy population should not be used.
- Within-subject variation in long-term patients with constant VKA dose.

Total within-patient variation (CV_T) of INR



Average within-subject variation (CV, %) in long-term patients receiving a constant dose of vitamin K antagonist

| | Acenocoumarol | | Phenprocoumon | |
|----------------|---------------|--------------|----------------|----------------|
| | INR: 2.0-3.5 | INR: 2.5-4.0 | INR: 2.0 - 3.5 | INR: 2.5 – 4.0 |
| Hepato Quick* | 10.9 | 10.5 | 10.4 | 9.1 |
| CoaguChek XS** | 10.4 | 10.2 | 8.8 | 8.1 |

* Van Geest-Daalderop et al. *Thromb Haemost* 2009;102:588-592

** Van den Besselaar et al. *Thromb Haemost* 2015;114:1260-7

Desirable INR precision goals (CV, %) according to Fraser et al. (*Ann Clin Biochem* 1997;**34**:8-12)

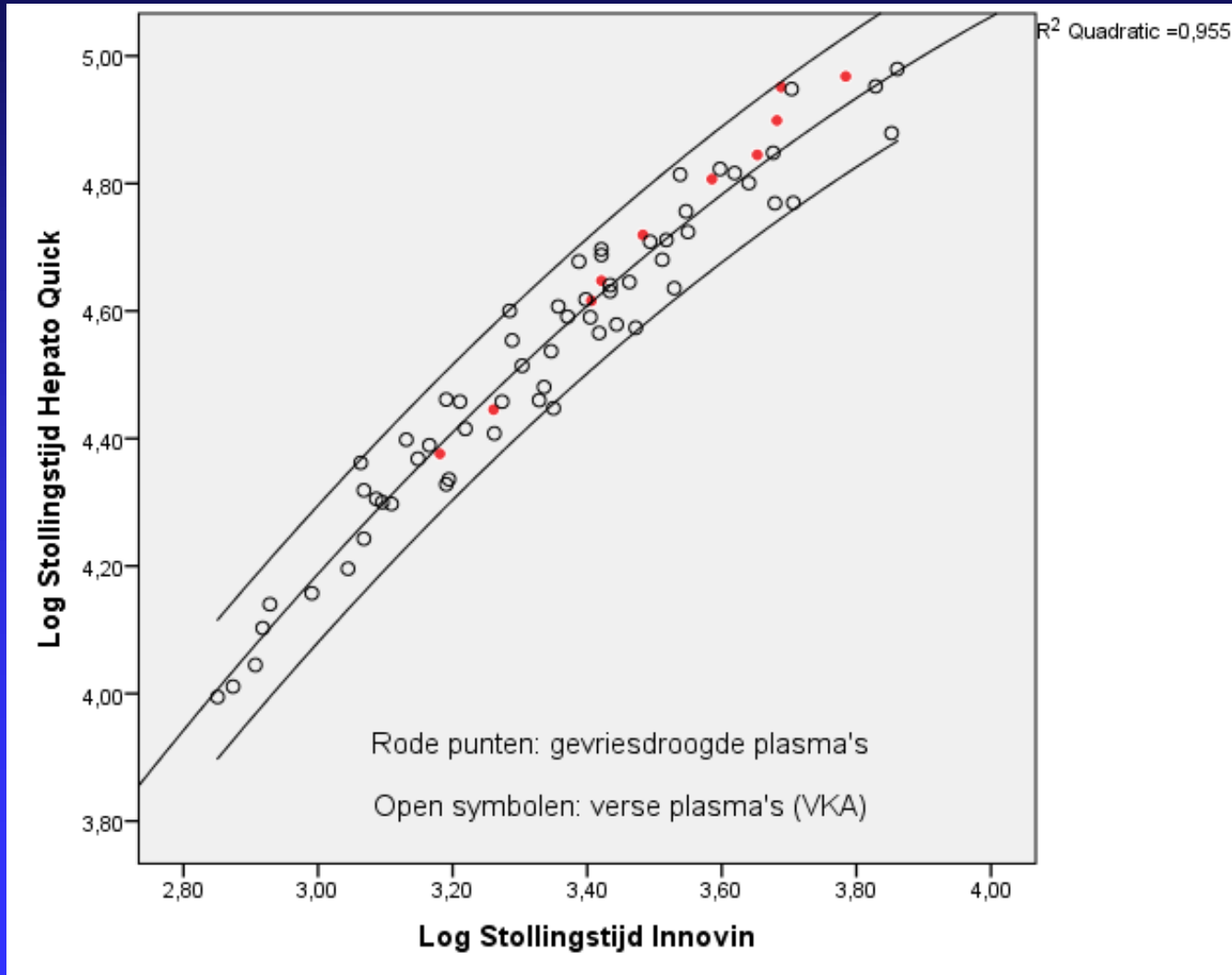
| | Acenocoumarol | | Phenprocoumon | |
|--------------|----------------|----------------|----------------|----------------|
| | INR: 2.0 - 3.5 | INR: 2.5 - 4.0 | INR: 2.0 - 3.5 | INR: 2.5 - 4.0 |
| Hepato Quick | 5.4 | 5.2 | 5.2 | 4.5 |
| CoaguChek XS | 5.2 | 5.1 | 4.4 | 4.0 |

Desirable precision = 0.5 x average within-subject CV

External Quality Assessment (EQA)

- Control samples: lyophilized plasma
- Are lyophilized samples commutable for all laboratory methods?
- Are lyophilized samples commutable for laboratory methods and POC systems?

Scatterplot fresh VKA samples and lyophilized samples



Further work

- Assess commutability of lyophilized plasma samples (local calibration and EQA).
- Standardize the manual technique for International Standards and submit for establishment by SSC/ISTH.
- Develop an international network of reference laboratories for calibration of secondary standards.

Participants of multicenter study for replacement of International Standards

| | | |
|---------------------|-----------|-----------|
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| ■ A. van den Besselaar | Leiden | Pays-Bas |
| ■ R. Zerback | Mannheim | Germany |

Acknowledgements

- Charmane Abdoel
- Christa Cobbaert
- Piëtte Deutz
- Carla van Dyk
- Mandy Quinten
- Claudia van Rijn