New Anticoagulants: Laboratory Monitoring??

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Ideal Anticoagulant
(Hirsh et al 2004)

- High efficacy to safety ratio
- Predictable dose response (no monitoring)
- Oral and parenteral
- Rapid onset of action
- Available safe antidote
- No side effects
- Minimal drug interaction

New Oral anticoagulants Rivaroxaban and Dabigatran

	Rivaroxaban	Dabigatran
Pro-drug	No	Yes (D. etexilate)
Target	Xa	Thrombin
Half life	7 - 11 hours	14-17 hours
Renal clearance	65%	80%
Drug interactions	Protease inhibitor (Ritonavir), Antifungal (Ketoconazole)	Anti-arrhythmics (Quinidine, Amiodarone)

Rivaroxaban and Dabigatran

- Safety/efficacy data show non-inferior or superior to warfarin or LMWH
- Predictable pharmacodynamics
- Fixed doses
- No monitoring in clinical trials - so no routine monitoring for dose adjustment

JTH April 2010.

Debate
New Oral Anticoagulants: A need for laboratory monitoring?

Against: Bounameaux and Reber

- While monitoring may be needless, measuring the drug or its activity might be useful in a few situations
  - Poor renal function
  - Extreme body weights
  - Pregnancy
  - Children
  - Urgent surgery
  - overdose

For: Mismetti and Laporte

- Variability in drug response is low in highly selected (Trial) patients - no routine need to monitor

- Some inter and intra individual variability
  - Renal function
  - Hepatic function
  - Advanced age
  - Drug-drug interactions

  Laboratory monitoring should be assessed for these patients

New anticoagulants
Information on Drug Concentration?

- Compliance?

- Bleeding patients (up to 2%)
  - What effects on clotting tests?
  - How to measure concentration?

Specific tests to measure concentrations

- Specific calibrators are required

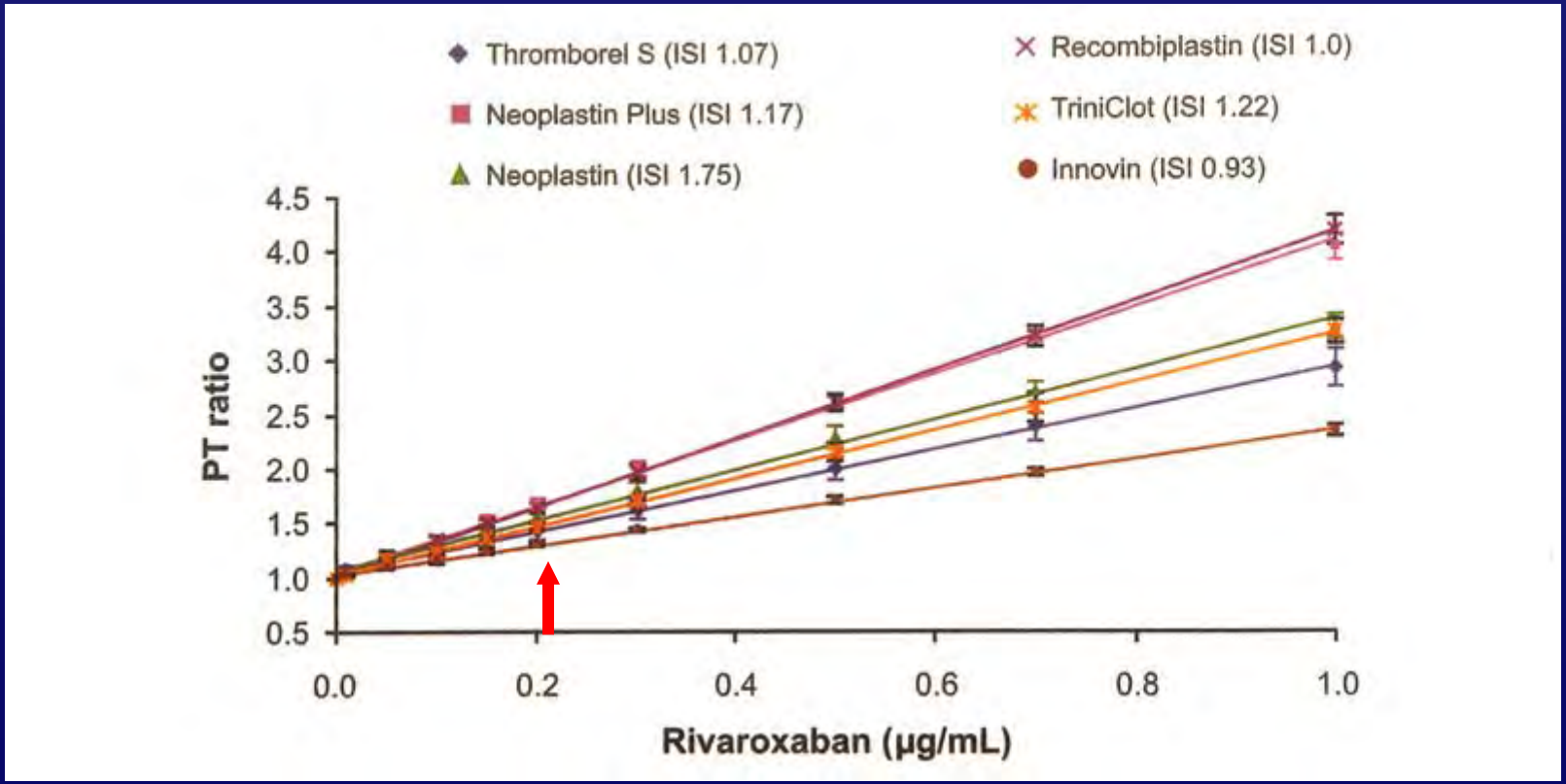
- Xa inhibitors
- Anti Xa assays

- Thrombin inhibitors
- Chromogenic anti IIa assay (Hyphen, Siemens etc)
- Clotting assays (semi specific)– eg Hemoclot (Hyphen), Ecarin

What concentrations will occur in patients? Rivaroxaban

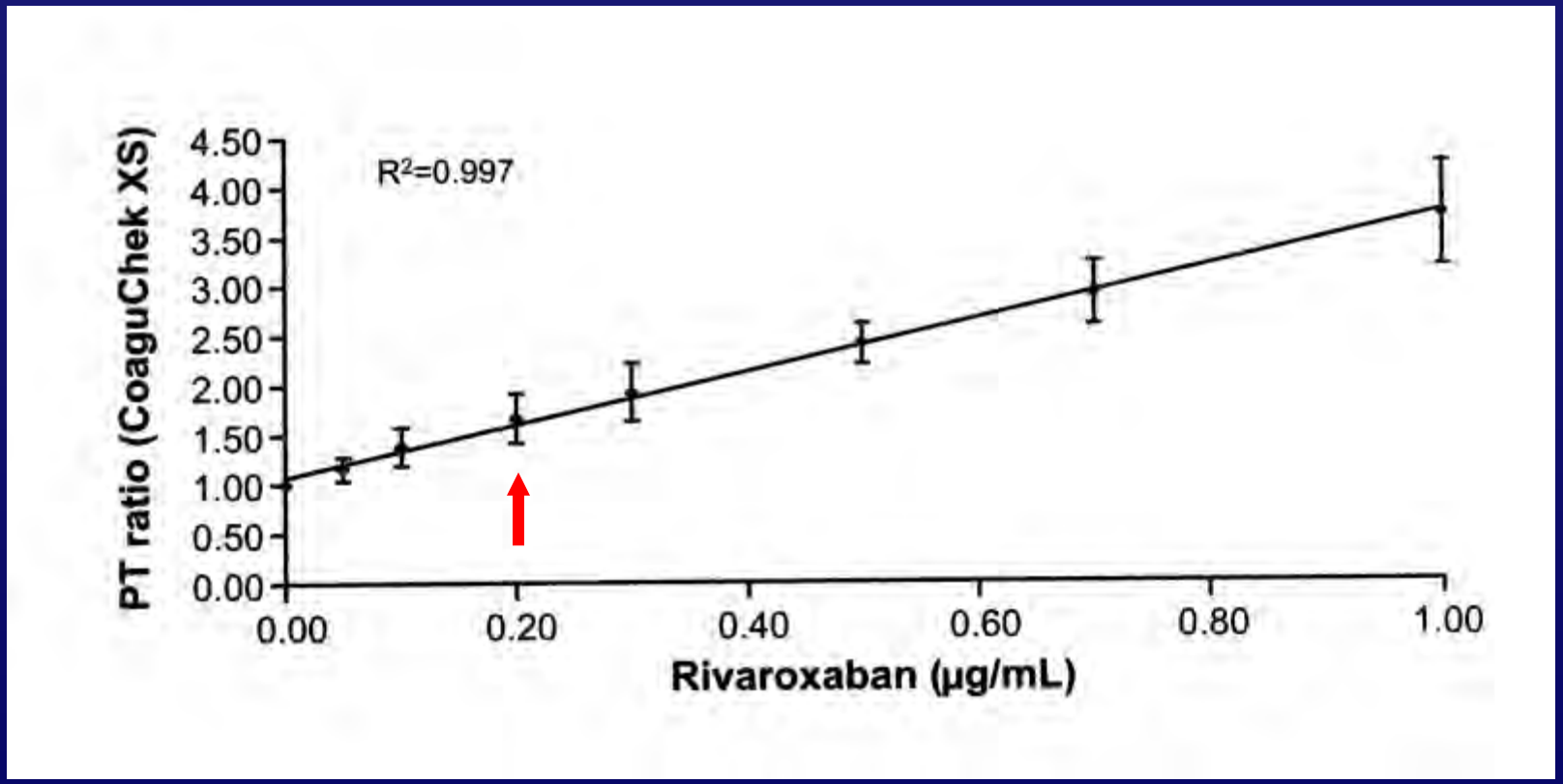
- Dose escalation study (selected cases)
- Prophylactic doses of 5-20mg /day
- Up to 0.2 µg/ml in plasma
- 10 mg /day now in use
- Plasma levels in routine use?

Effect of Rivaroxaban on PT Ratio



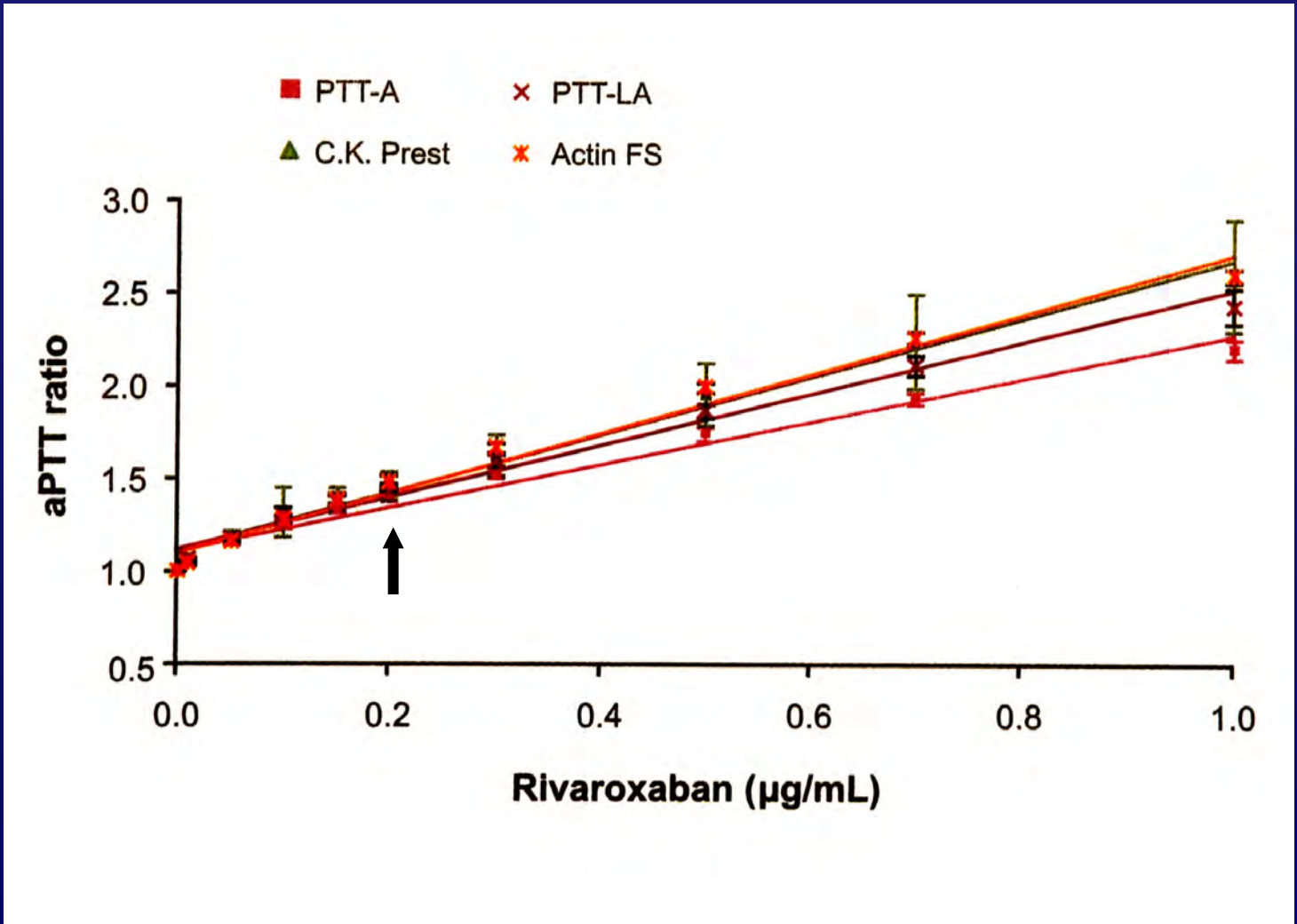
Samama et al Thromb Haem 2010

Effect of Rivaroxaban on PT/INR with CUC XS POC device



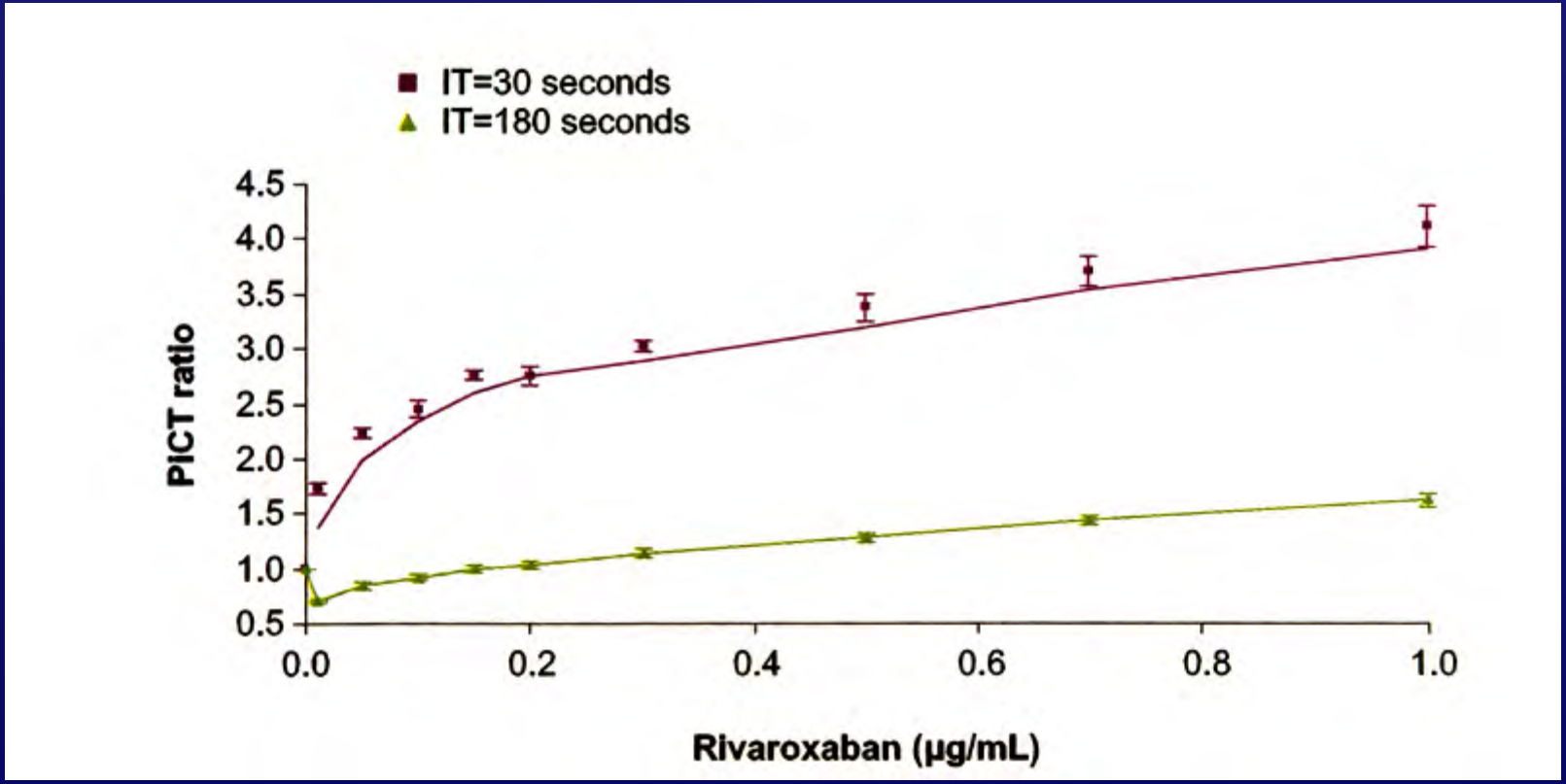
Samama et al Thromb Haem 2010

Effect of Rivaroxaban on APTT



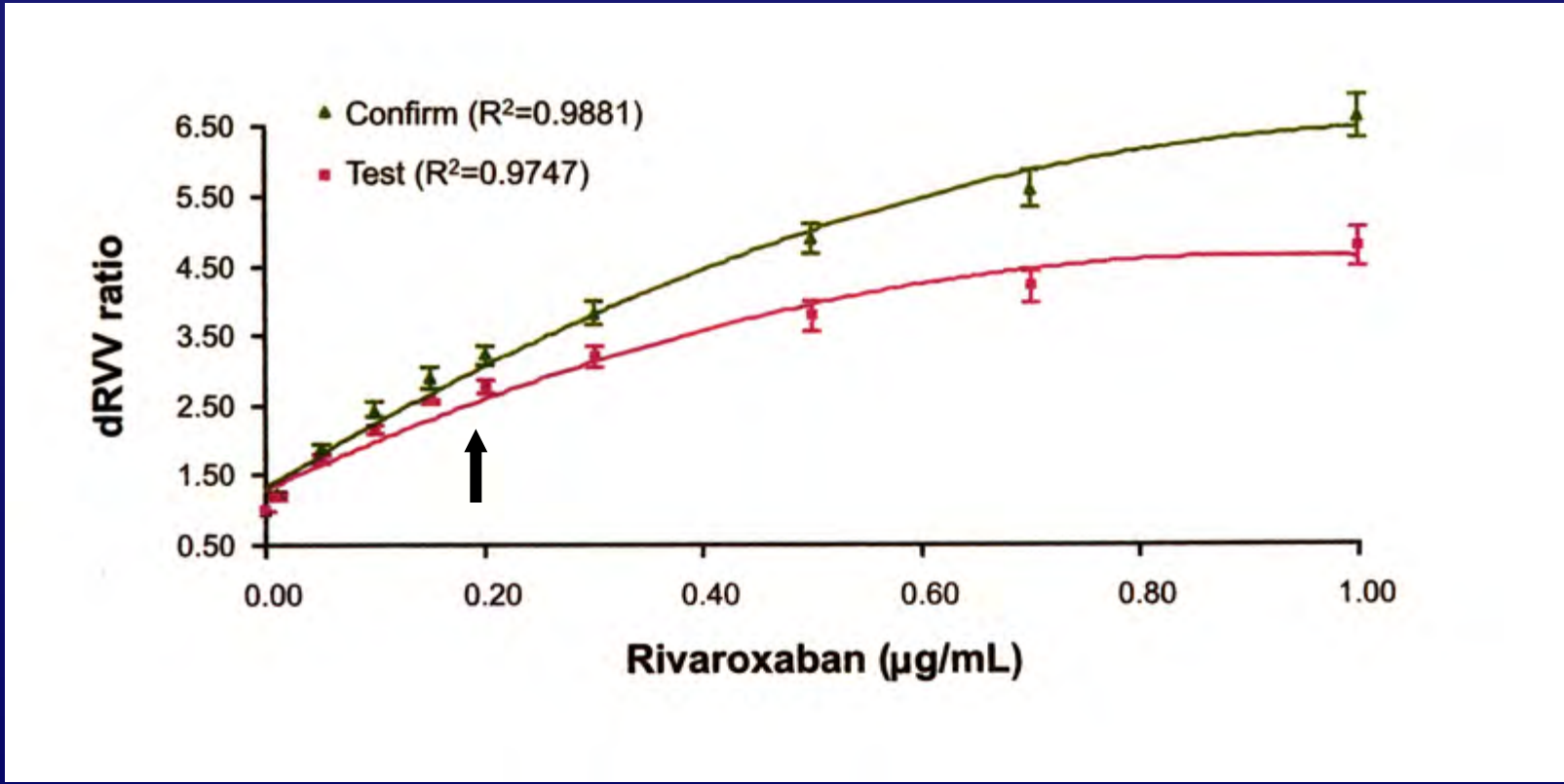
Samama et al Thromb Haem 2010

Prothrombinase Induced Clotting Time- PiCT RVV/Xa/PL to generate IIa then calcium)



Samama et al Thromb Haem 2010

Rivaroxaban prolongs DRVVT



Samama et al Thromb Haem 2010

What concentrations will occur ? Dabigatran

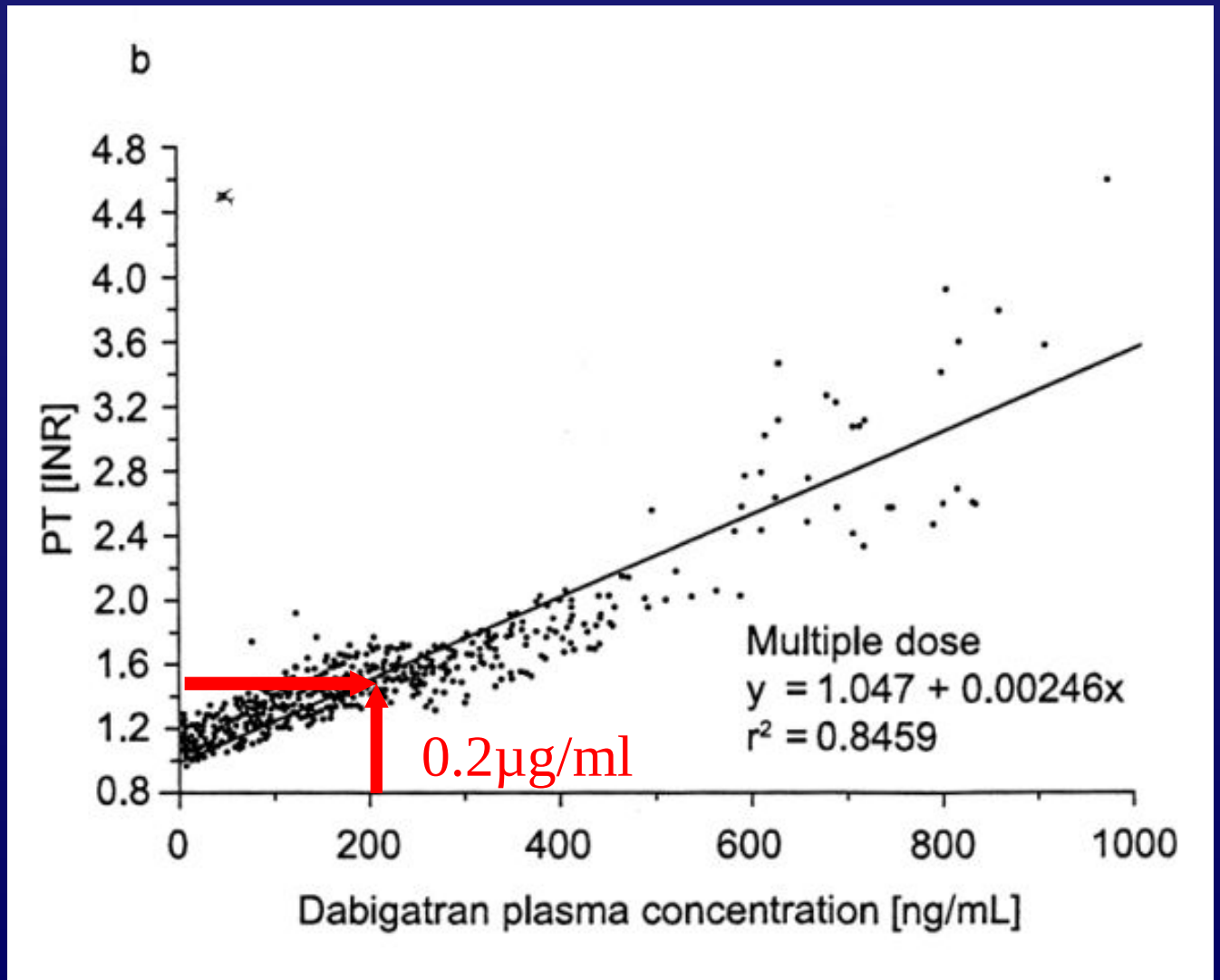
- Mean peak plasma level of 0.3 µg/ml after 300 mg bd (Eriksson et al 2004)
- After Renovate/Remodel post orthopaedic trials - 220 mg day

Peak and Trough Dabigatran
(van Ryn 2010)

Dose	Indication	Peak	Trough
220 mg od	Ortho surgery	0.183 µg/ml (95% CI 0.06 to 0.45)	0.04 µg/ml (24 hr)
150 mg bd	AF	0.184 µg/ml (95% CI 0.06 to 0.44)	0.09 µg/ml (12 hour)

Effect of Dabigatran on INR

Method not stated (van Ryn 2010)



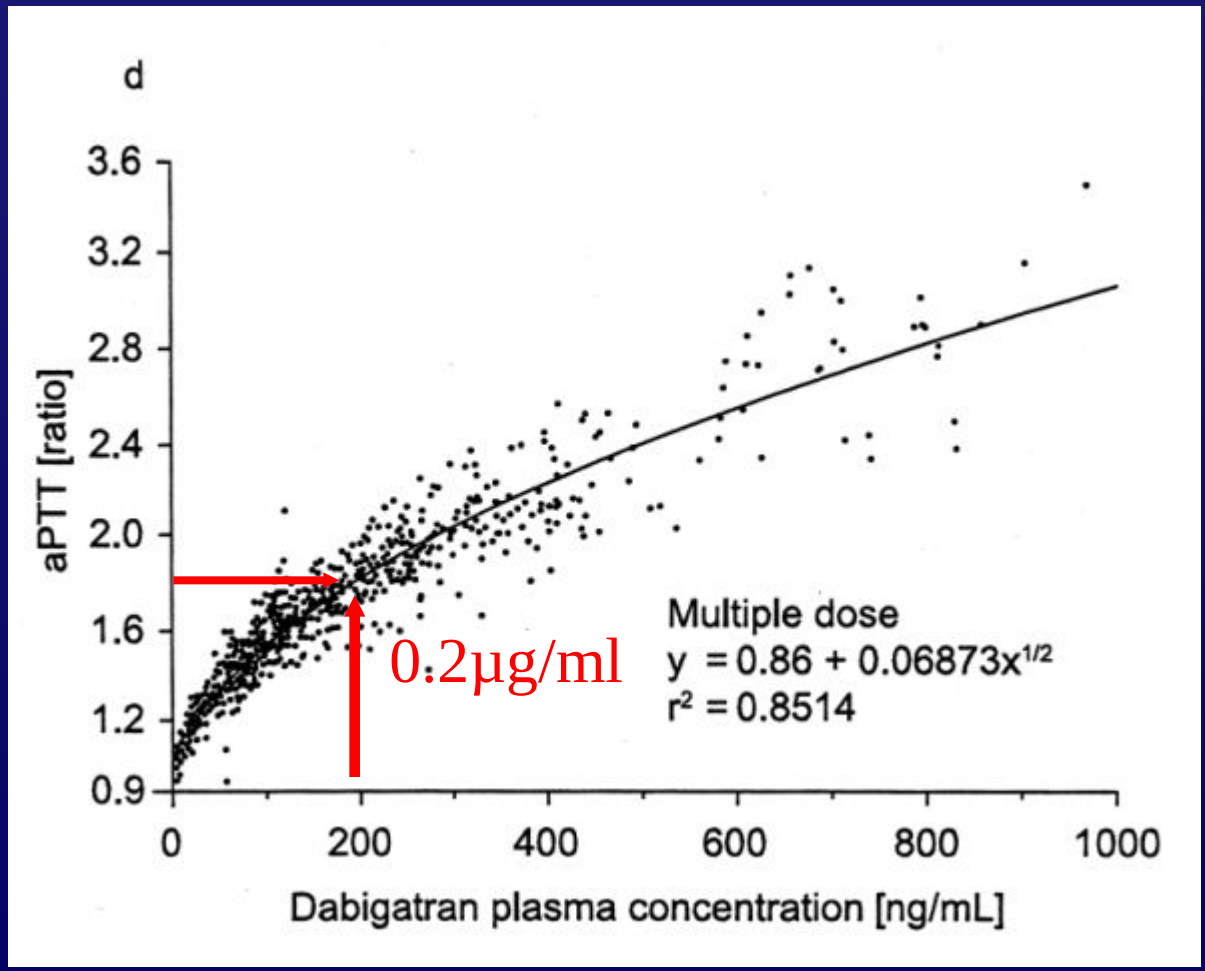
Dabigatran

- Similar prolongation PT with all reagents
- 0.5 µg/ml – PT ratio approximately 1.7 -1.9
- Innovin, Thromborel S, Simplastin, Recoimbiplastin Neoplastin, Neoplastin +

Samama personal communication

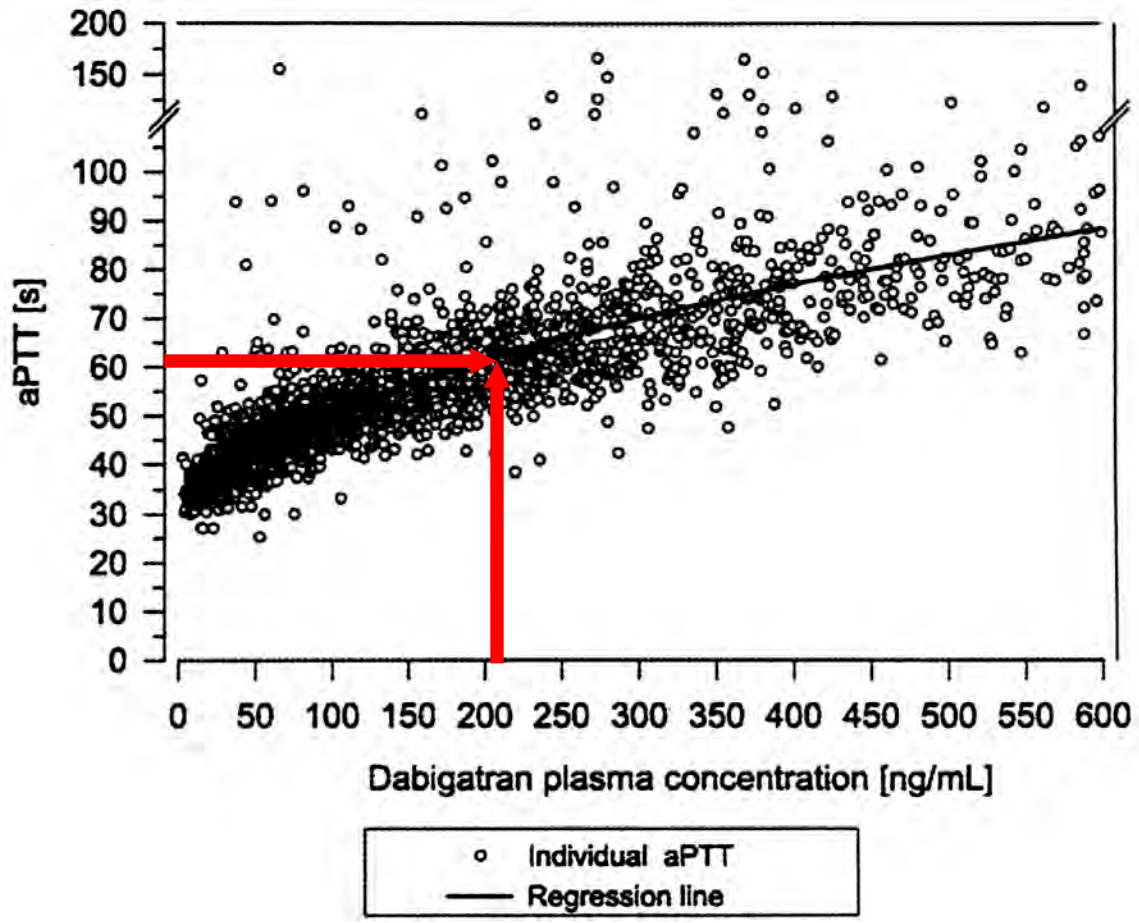
Effect of Dabigatran on APTT

Method not stated (van Ryn 2010)



Dabigatran effect on APTT

Method not stated (Eriksson et al 2004)



Dabigatran effect on APTT

- Prolongs APTT
- 150 mg bd Median peak levels 2x control
- 12 hours later (trough) Median is 1.5x control
- Method not stated

van Ryn et al 2010

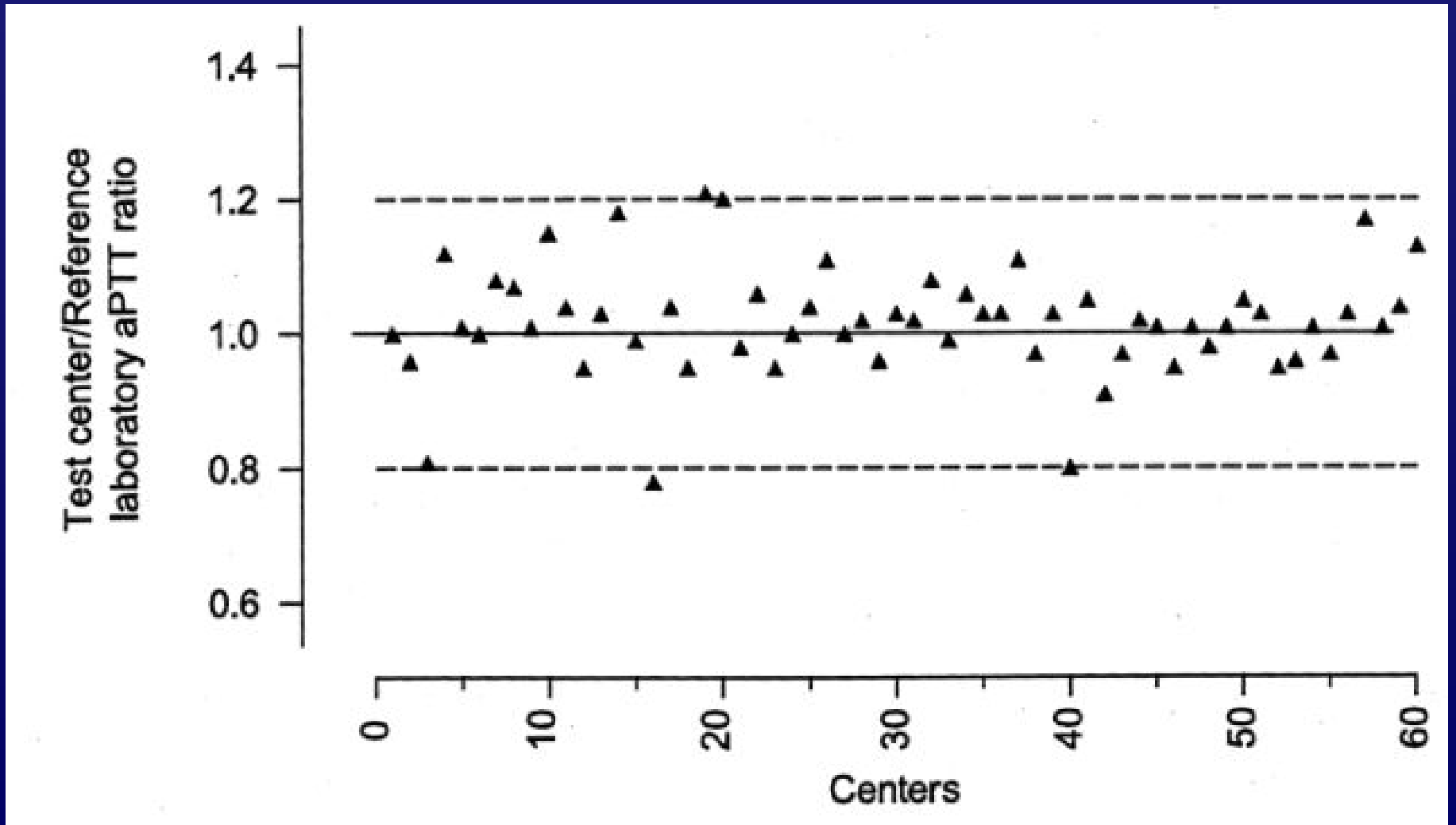
STH – case report (june 2011)

- Patient on 110 mg bd
- Sample collected 11.5 hr post ingestion
- PT 11.3 sec (n range 9.5-11.3)

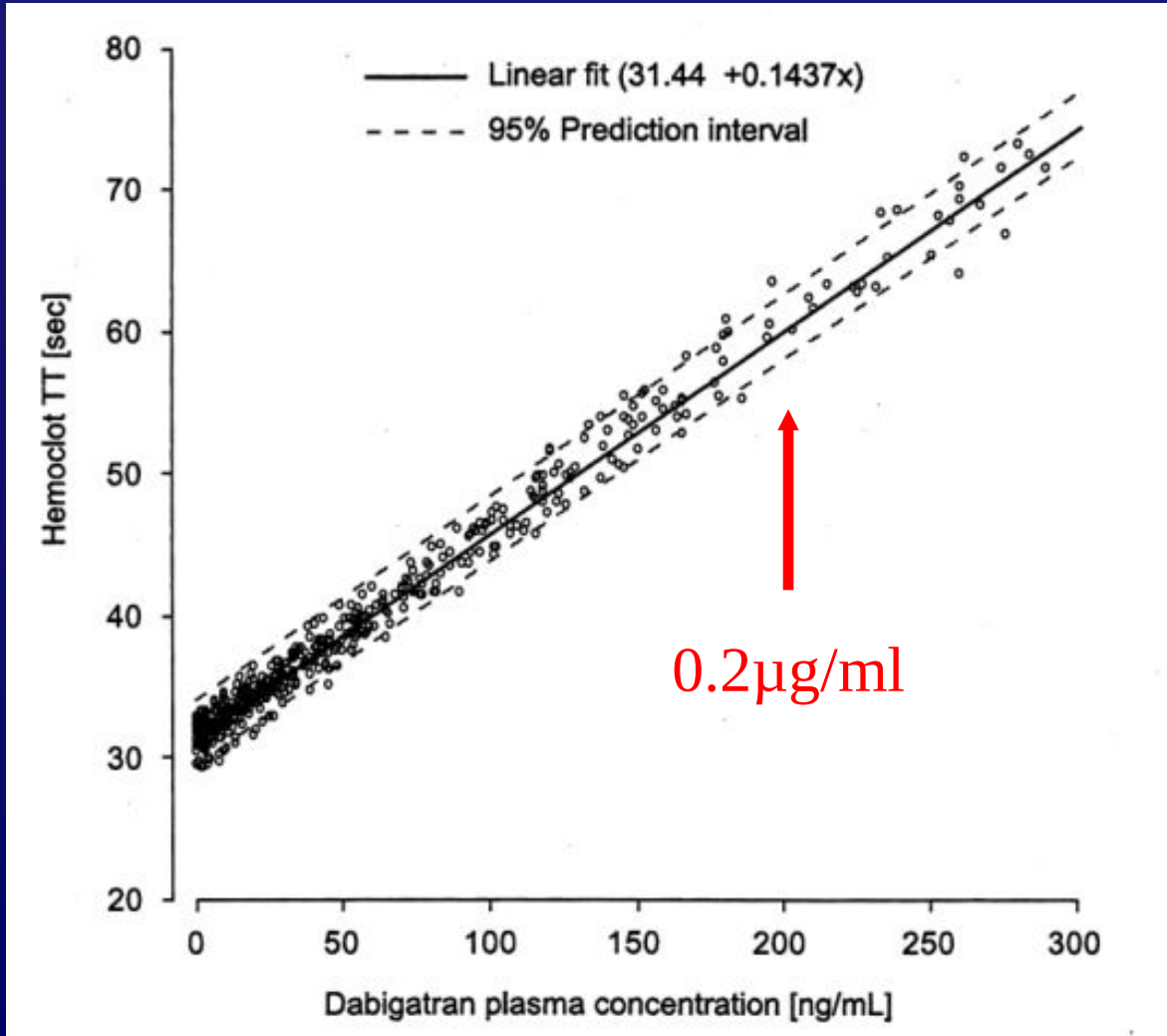
- APTT (AFS) – 39.3 sec , ratio 1.52 (N range 20.3-31.2)

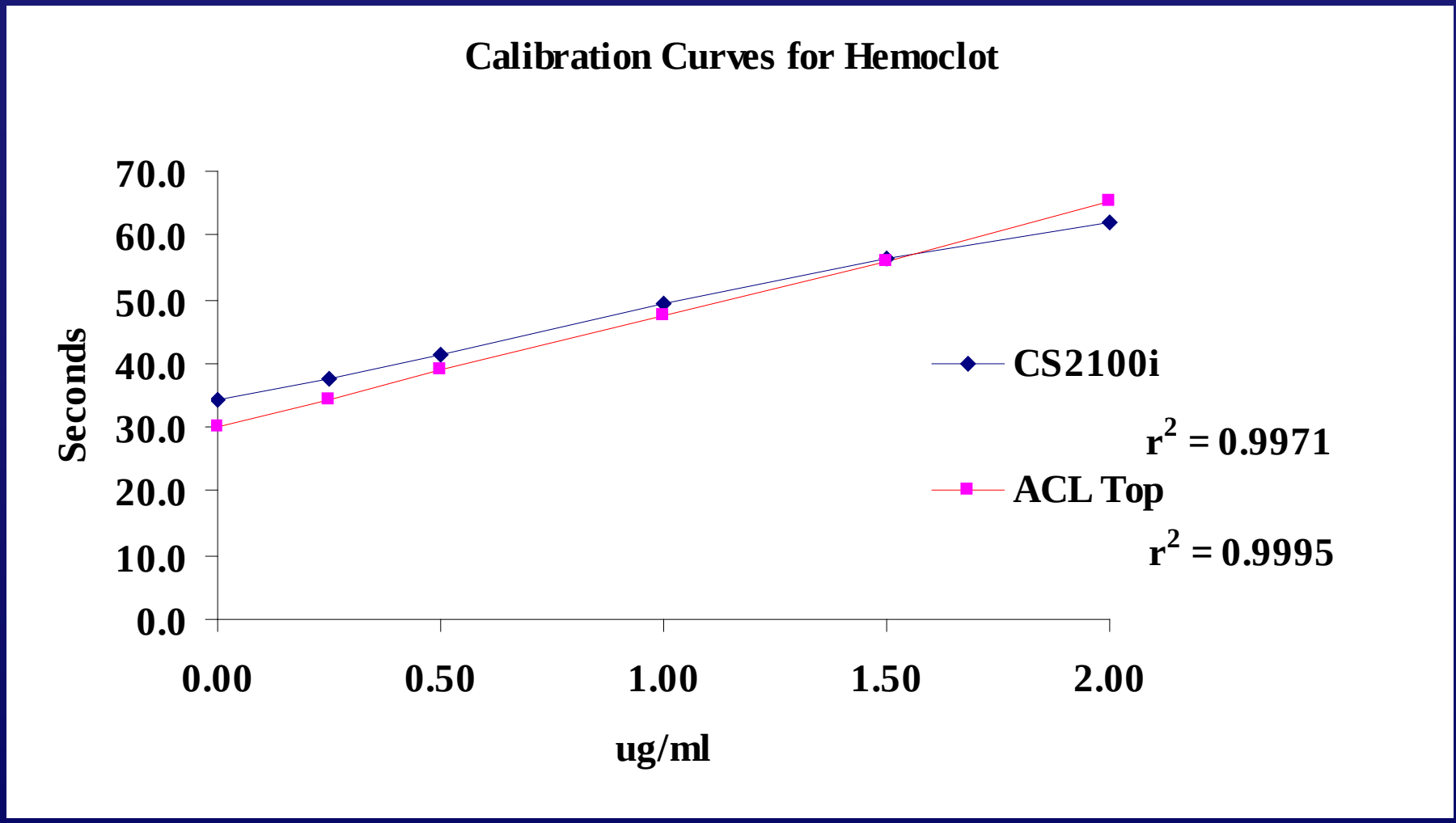
- TT >150 sec (nr 11-17)

Effect of Dabigatran on APTT
58 participant labs and core facility different methods
Dabigatran at 0.6 µg/ml (van Ryn 2010)



Effect of Dabigatran on Hemoclot Thrombin time (van Ryn 2010)





Hirudin calibrations

Dabigatran and Rivaroxaban Specific Factors/Thrombophilia investigations

- APTT based assays - Factor VIII, IX, XI assays (under estimation at low dilution)
- AT assays – Xa or IIa inhibition (overestimation)
- Interference in clot based tests – APC resistance, DRVVT (LAC)

Rivaroxaban and Dabigatran

- Clotting based tests affected – some reagent dependant effects
- Specific assays needed for drug concentration in specific patients

How fast will VKA be replaced?

- Resistance to change – clinicians, patients
- Not all indications studied
- Regulatory clearances - (Ximelagatran!)
- Costs

Costs

	Daily dose	BNF “list” price
Warfarin	5 mg	£0.04
Rivaroxaban	10 mg	£4.50 (STH pharmacy £1.86)
Dabigatran	2 x 110 mg tablets	£2.10

Where will the money come from?

- NHS lab - Reagents/instruments/staff/lab overheads - INR = £3.50
- Private laboratory INR – US - $25 UK - £15
- Phlebotomy, Anticoagulant clinics, laboratories??
- Savings from Primary care?
- Savings from Secondary care?
- WORRIED ABOUT JOB PROSPECTS?