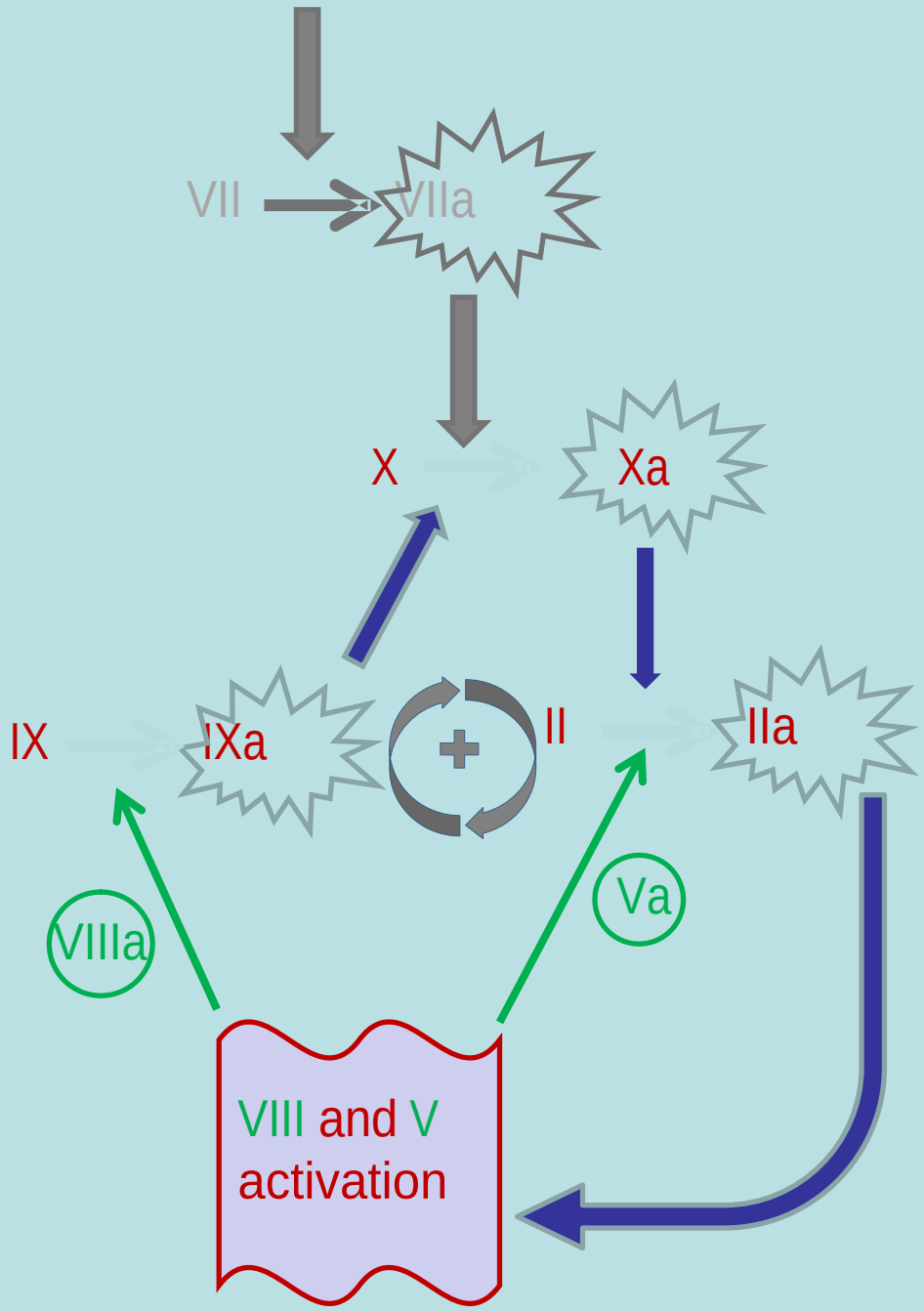
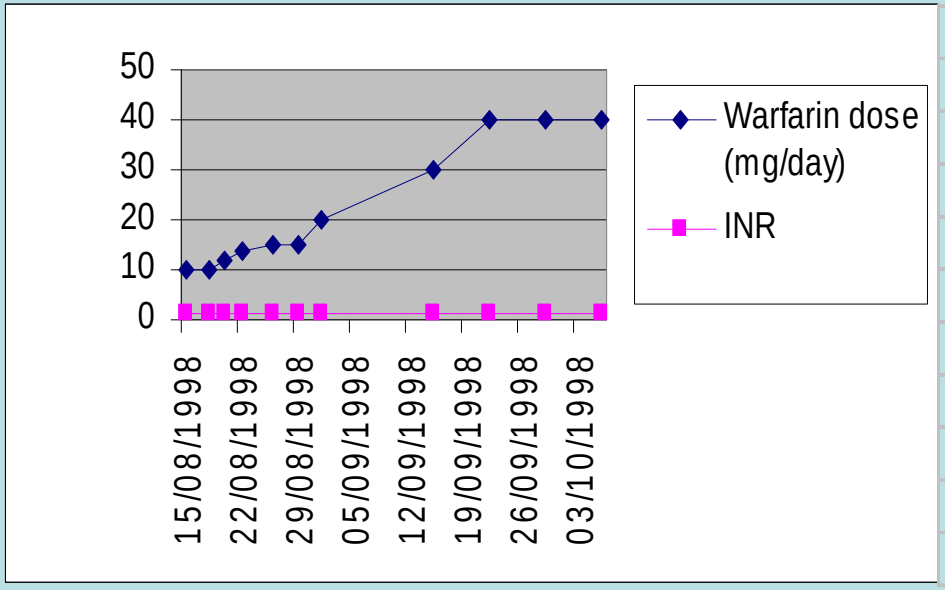


Basic Clotting - The 'Thrombin Burst'
activation of Factors VII and V by a small amount of thrombin results in the explosive generation of large amounts more thrombin *- a positive feedback loop*

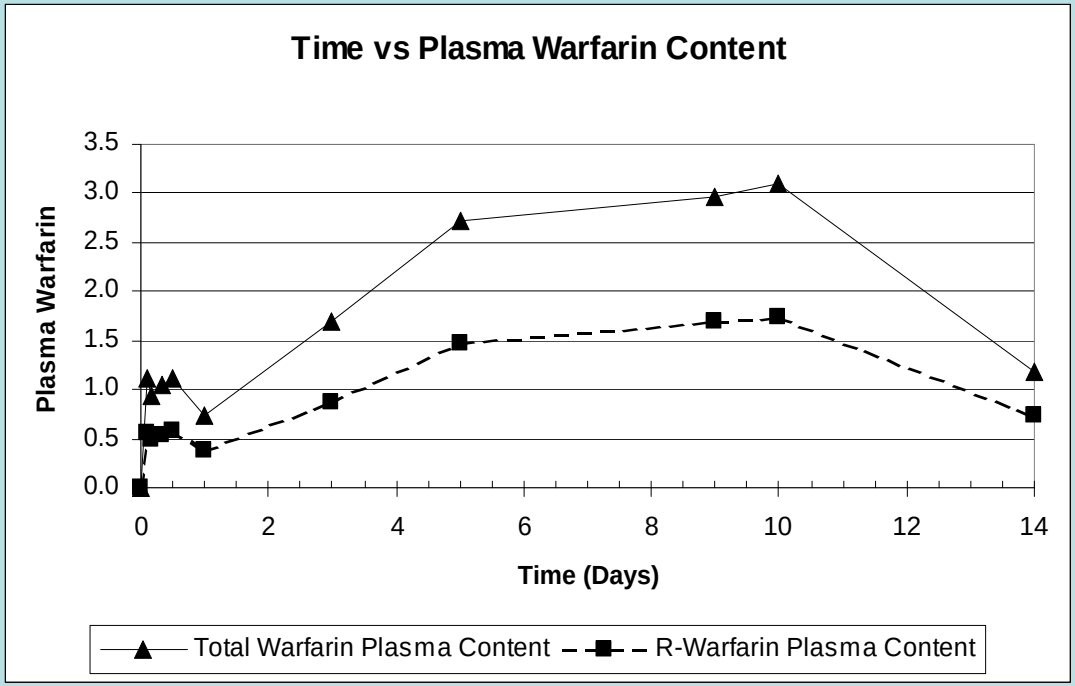
Warfarin impairs synthesis of Factors II, VII, IX and X

Monitored by INR

Genetics –an extreme example



15-Aug-98	10	1.3
18-Aug-98	10	1.3
20-Aug-98	12	1.3
22-Aug-98	14	1.3
26-Aug-98	15	1.3
29-Aug-98	15	1.2
1-Sep-98	20	1.1
15-Sep-98	30	1.1
22-Sep-98	40	1.2
29-Sep-98	40	1.5
6-Oct-98	40	1.3



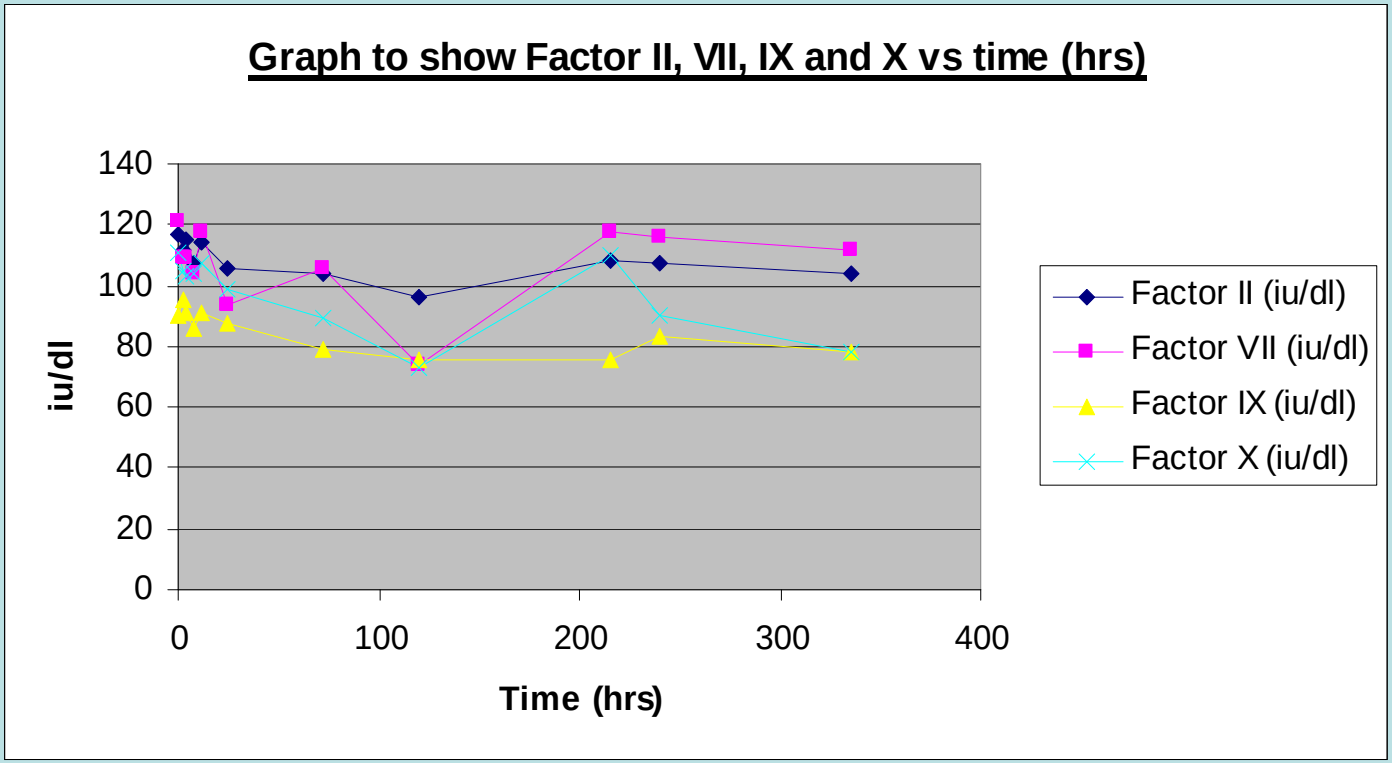
Plasma warfarin levels were performed by Dr Allan Rettie at The Washington Institute, Washington, America. The method employed was a modification of a High Pressure Liquid Chromatography (HPLC) method of Banfield and Rowland (1984) (Naidong W, Lee JW 1993; Henne KR, Gaedigk A, Gupta G, Leeder JS, Rettie AE 1998)

levels were within the therapeutic range (*i.e.* between 0.6 – 8.7 μg/mL)

Enaniomers were normal (cytochrome P450 allelic variation may cause relative resistance)

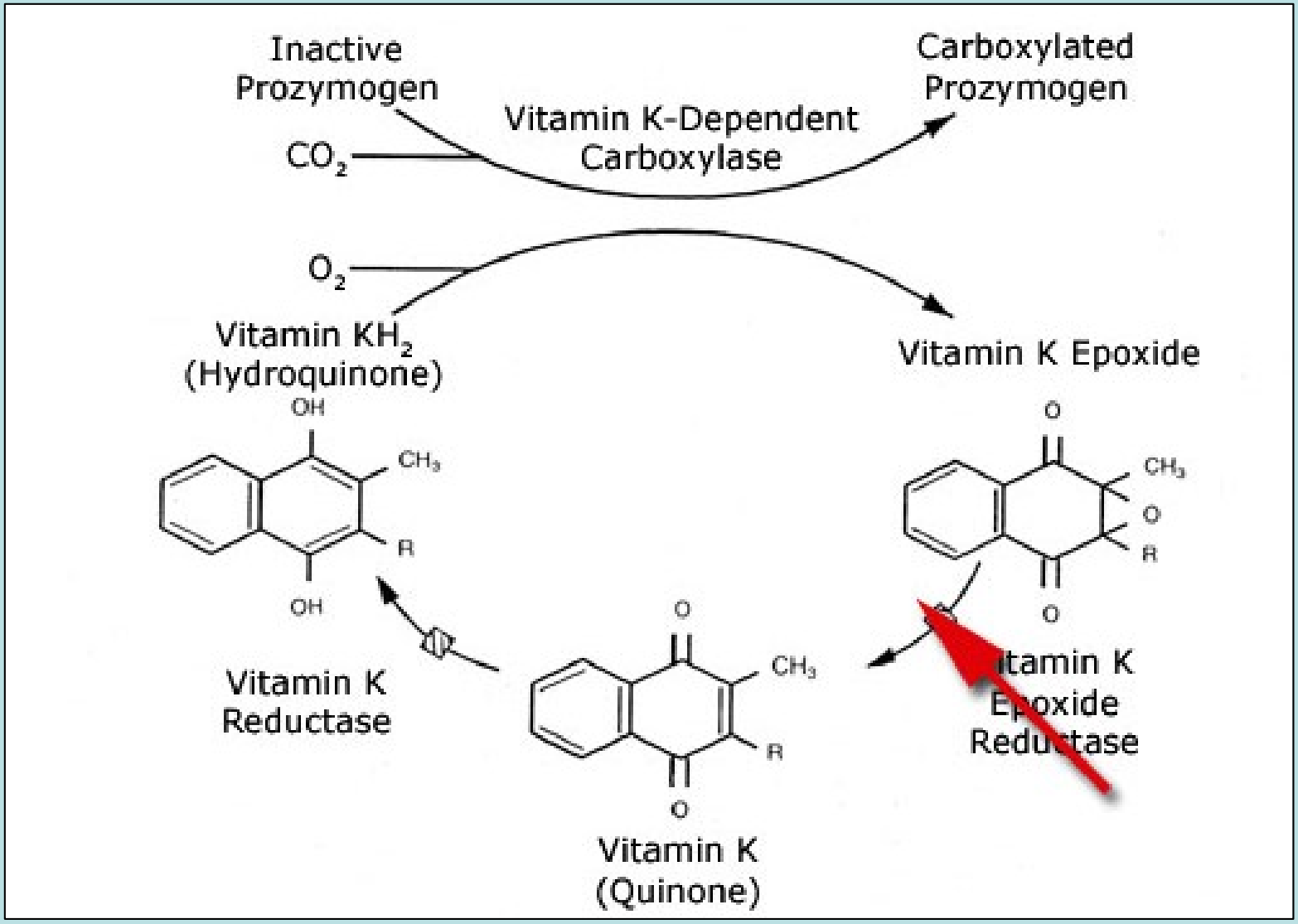
ie; patient is absorbing and metabolising the warfarin relatively normally

No effect on Gla domain clotting factors



Performed by Mrs Price with the help of the Haemophilia Centre, Oxford

(INRs taken over this period and Protein C and Protein S also remained normal, PIVKAII probably a small increase by d4 but technically unsatisfactory)


Inactive
Prozymogen
CO_2
Vitamin K-Dependent
Carboxylase
Carboxylated
Prozymogen
O_2
Vitamin KH_2
(Hydroquinone)
OH
CH_3
R
OH
Vitamin K
Reductase
O
CH_3
R
O
Vitamin K
(Quinone)
Vitamin K Epoxide
O
CH_3
O
R
O
itamin K
Epoxide
Reductase

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Stephen E. Kimmel, M.D., Benjamin French, Ph.D., Scott E. Kasner, M.D., Julie A. Johnson, Pharm.D., Jeffrey L. Anderson, M.D., Brian F. Gage, M.D., Yves D. Rosenberg, M.D., Charles S. Eby, M.D., Rosemary A. Madigan, R.N., M.P.H., Robert B. McBane, M.D., Sherif Z. Abdel-Rahman, Ph.D., Scott M. Stevens, M.D., Steven Yale, M.D., Emile R. Mohler, III, M.D., Margaret C. Fang, M.D., Vinay Shah, M.D., Richard B. Horenstein, M.D., Nita A. Limdi, Pharm.D., Ph.D., James A.S. Muldowney, III, M.D., Jaspal Gujral, M.B., B.S., Patrice Delafontaine, M.D., Robert J. Desnick, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Henny H. Billett, M.D., Robert C. Pendleton, M.D., Nancy L. Geller, Ph.D., Jonathan L. Halperin, M.D., Samuel Z. Goldhaber, M.D., Michael D. Caldwell, M.D., Ph.D., Robert M. Califf, M.D., and Jonas H. Ellenberg, Ph.D. for the COAG Investigators

N Engl J Med 2013; 369:2283-2293 | December 12, 2013 | DOI: 10.1056/NEJMoa1310669

Warfarin - Drug Interactions

Table 1: Chemotherapy Agents with Possible Interactions with Warfarin

Chemotherapy Agent	Effect on international normalized ratio	Proposed mechanism
androgens/antiandrogens	increase	unknown
capecitabine	increase	down-regulation of CYP2C9
carboplatin	increase	unknown
cyclophosphamide	increase/decrease	unknown
doxorubicin	increase	unknown
erlotinib	increase	unknown
estrogens	decrease	increased synthesis of clotting factors
etoposide	increase	unknown
fluorouracil	increase	inhibition of CYP2C9
gefitinib	increase	unknown
gemcitabine hydrochloride	increase	unknown
ifosfamide/mesna	increase	unknown
imatinib	increase	inhibition of CYP2C9, CYP3A4, CYP2D6
mechlorethamine	increase	unknown
mercaptopurine	decrease	unknown
methotrexate	increase	unknown
nilotinib	Increase	inhibition of CYP2C9 and CYP3A4
paclitaxel	increase	change in protein binding?
procarbazine	increase	unknown
sorafenib	increase	unknown
tamoxifen	increase	inhibition of CYP2C9?
toremifene	increase	unknown
trastuzumab	increase	unknown
vincristine	increase	unknown
vindesine	increase	unknown
vorinostat	increase	unknown

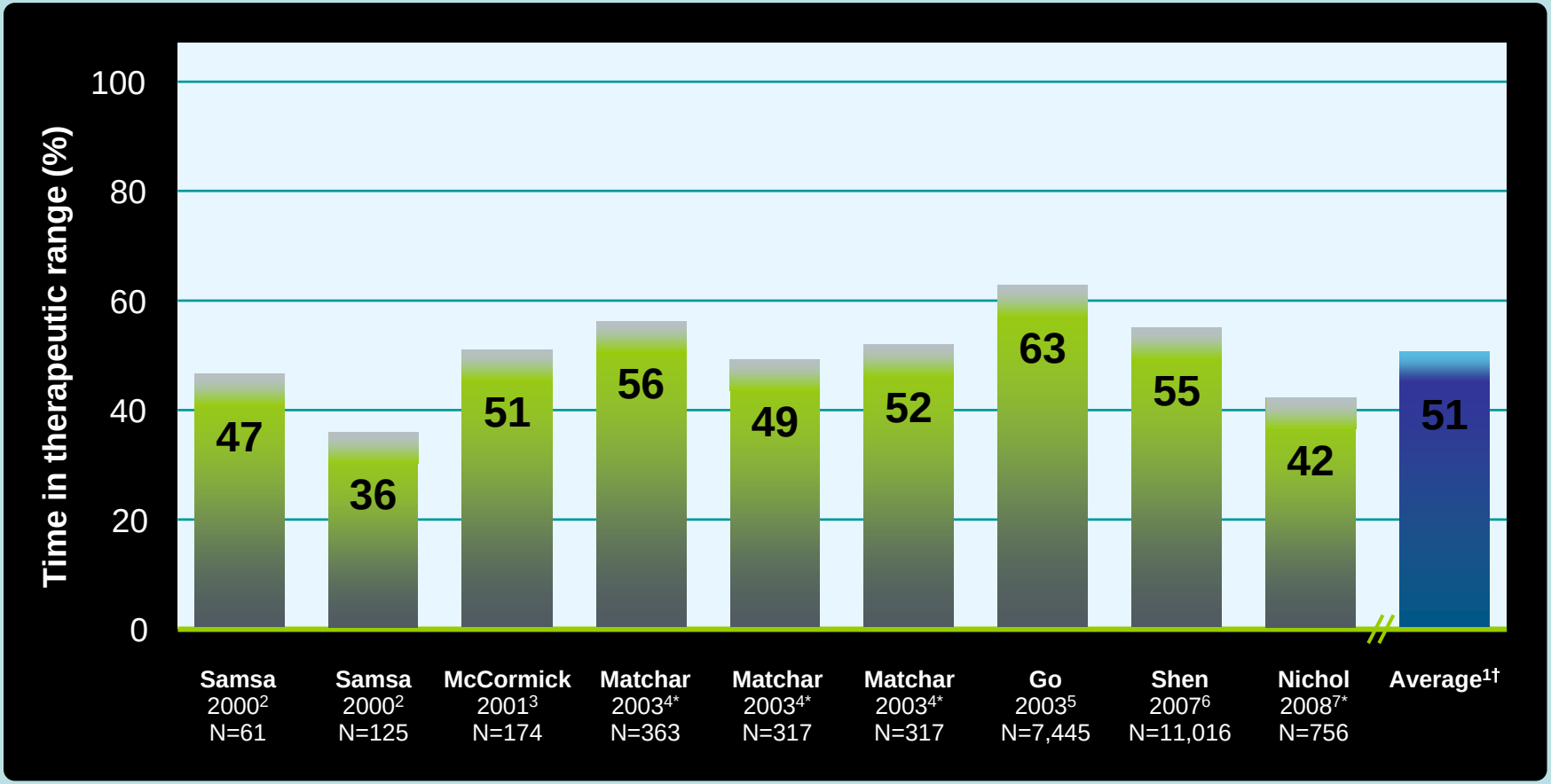
- Action:
  - **Increased**: erythromycin, clarithromycin, metronidazole, sulphonamides, cimetidine, thyroxine, amiodarone, citalopram, omeprazole, simvastatin
  - **Reduced**: carbamazepine, barbiturates, griseofulvin, rifampicin

Remember: clinical state, platelet function!

Warfarin – Other Interactions

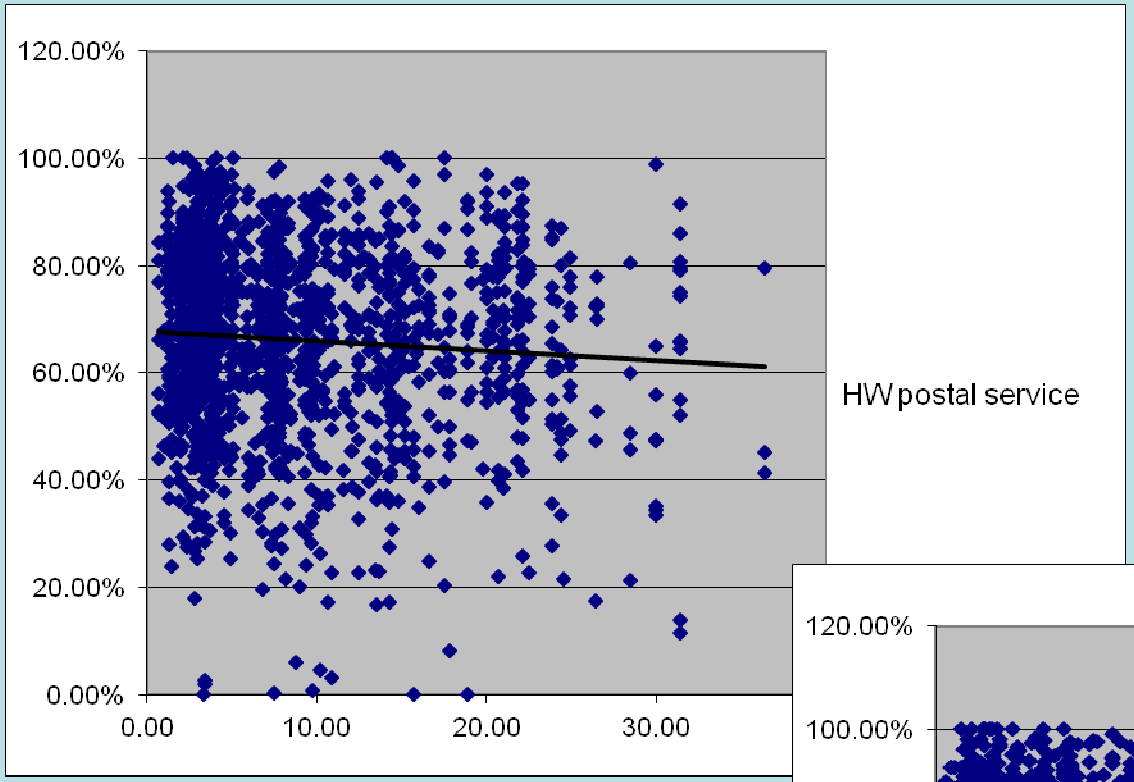
http://hypericum.myspecies.info/

RANGE WITH WARFARIN USE IN CLINICAL PRACTICE

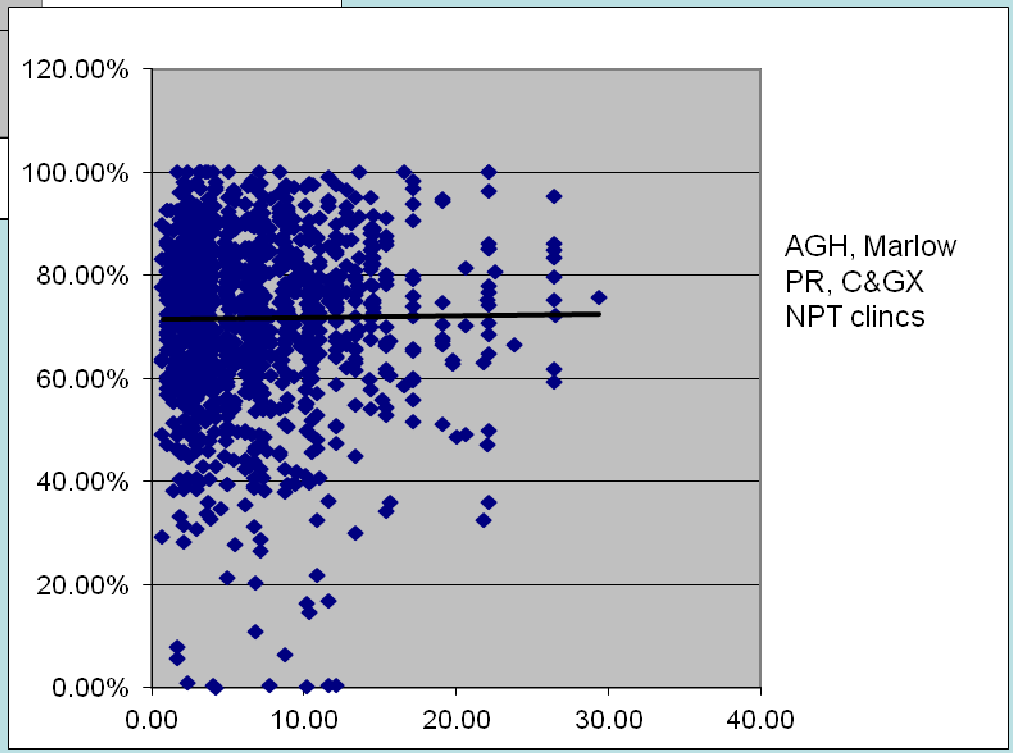


* Linear interpolation method not used. † Overall effect = 0.55.

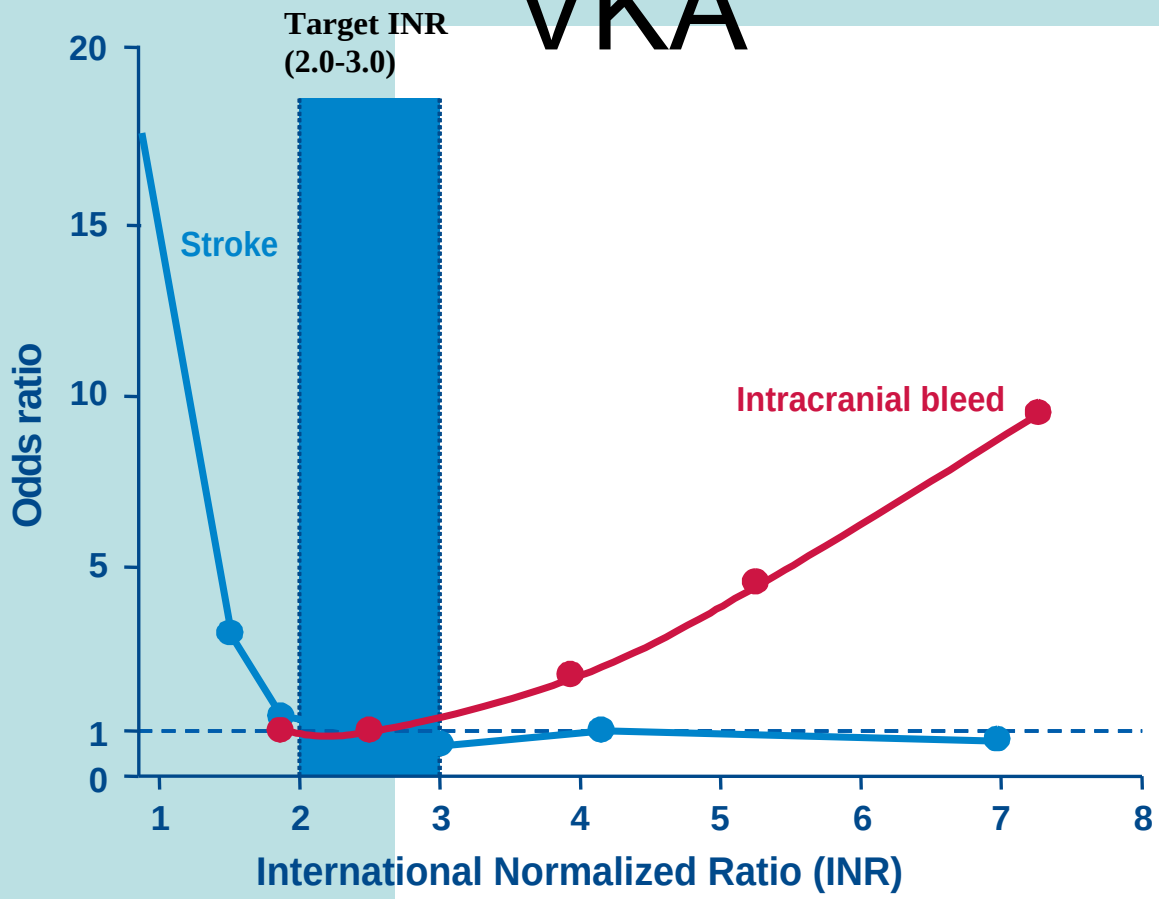
1. Baker WL, et al. *J Manag Care Pharm* 2009;15:244-252. 2. Samsa GP, et al. *Arch Intern Med* 2000;160:967-973.
3. McCormick D, et al. *Arch Intern Med* 2001;161:2458-2463. 4. Matchar DB. *Card Electrophysiol Rev* 2003;7:379-381.
5. Go AS, et al. *JAMA* 2003;290:2685-2692. 6. Shen AY, et al. *J Am Coll Cardiol* 2007;50:309-315.
7. Nichol MB, et al. *Ann Pharmacother* 2008;42:62-70.



INR control vs social deprivation score all AFpatients between 2008 and end 2009 (overall TTR in postal group is 68% and NPT group is 72%)



Narrow therapeutic range with VKA



Fuster V et al. Circulation 2006;114:e257–e354

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range

Stuart J. Connolly, Janice Pogue, John Eikelboom, Gregory Flaker, Patrick Commerford, Maria Grazia Franzosi, Jeffrey S. Healey, Salim Yusuf and on behalf of the ACTIVE W Investigators

Circulation 2008;118;2029-2037; originally published online Oct 27, 2008;
DOI: 10.1161/CIRCULATIONAHA.107.750000
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

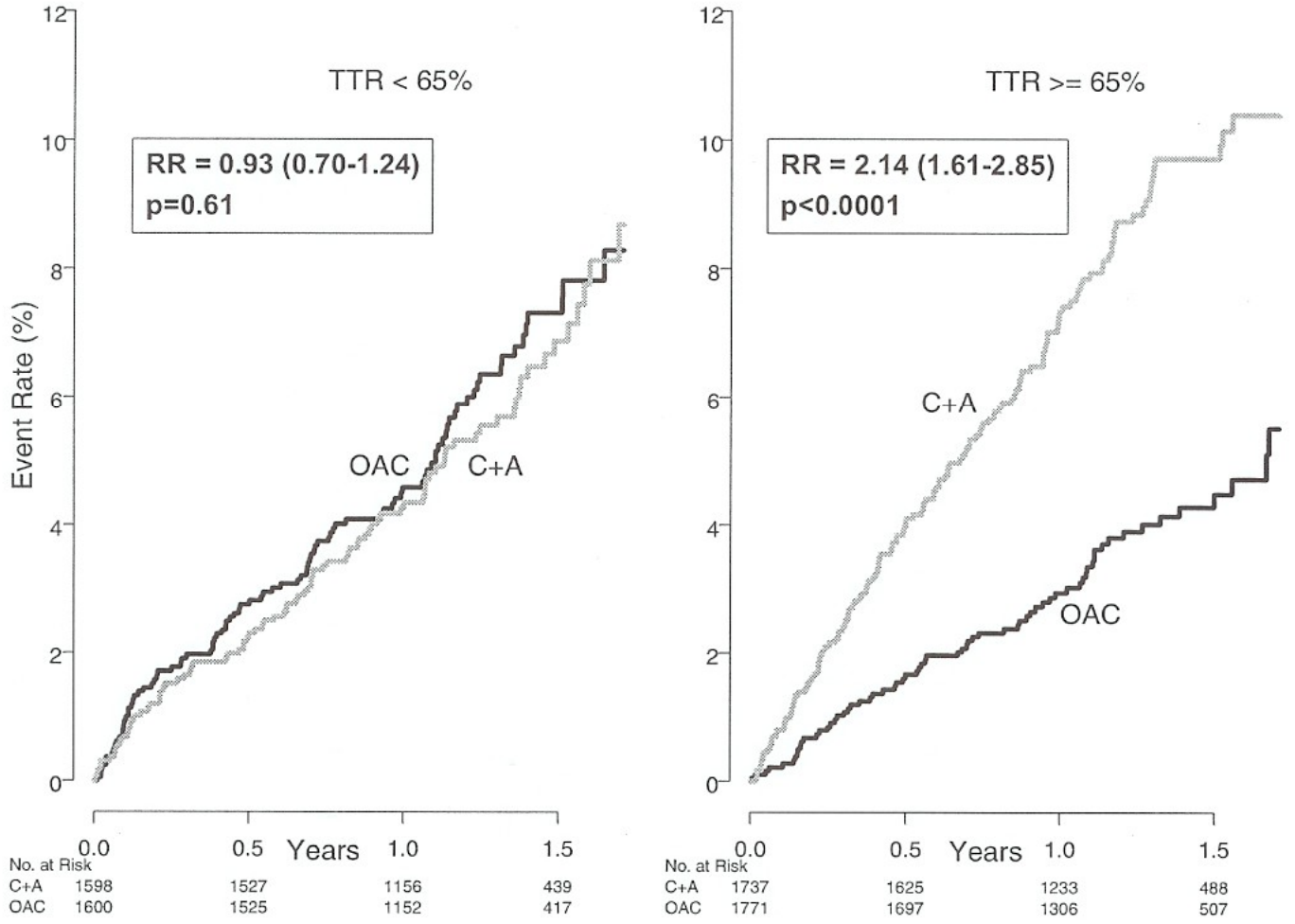


Figure 1. Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%). RR indicates relative risk: C+A, clopidogrel plus aspirin.

LIMITATIONS OF VKA THERAPY

Unpredictable response

Narrow therapeutic window (INR range 2.0–3.0)

Slow onset/ offset of action

VKA therapy has several limitations that make it difficult to use in practice

Numerous food–drug interactions

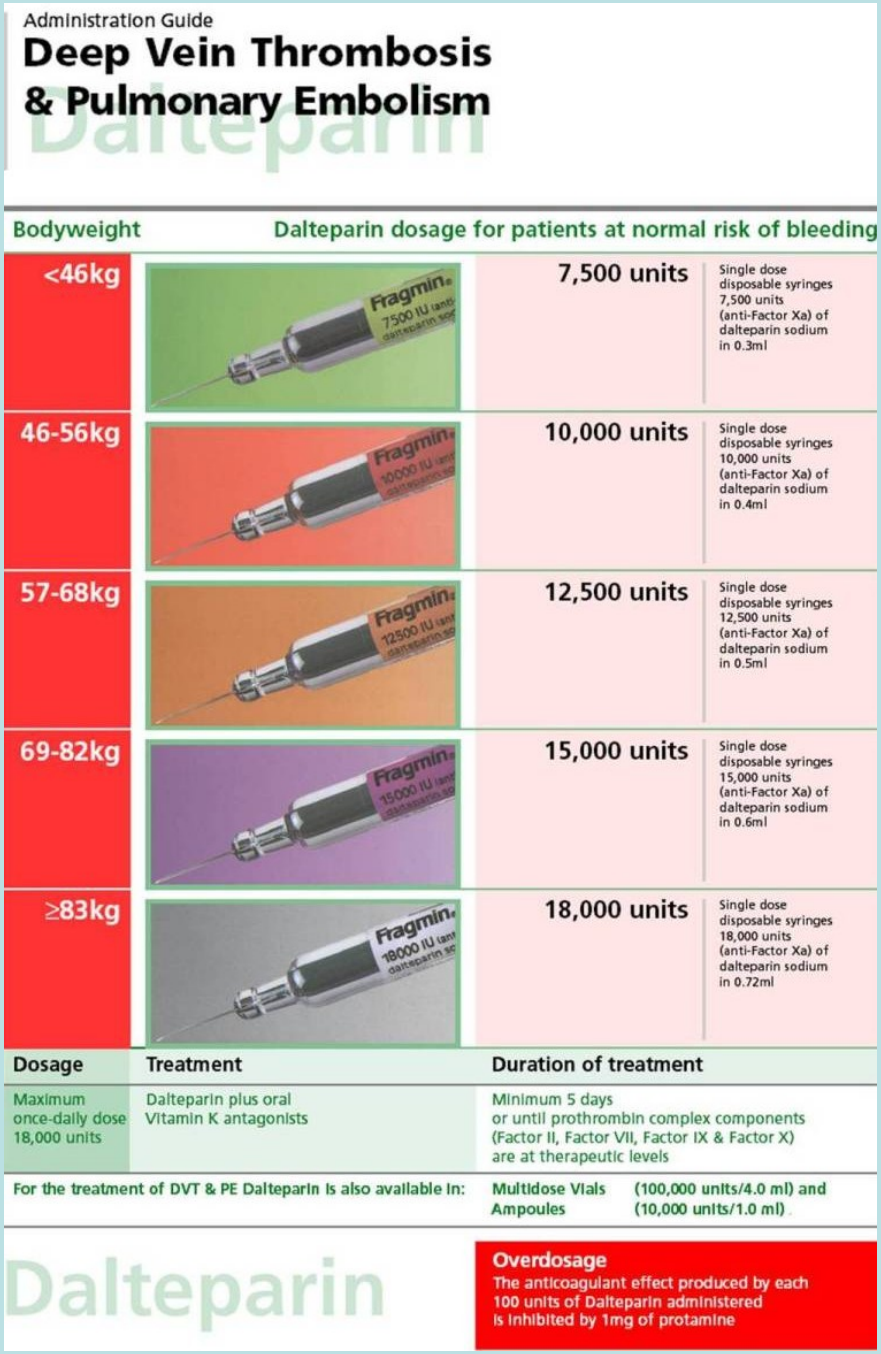
Numerous drug–drug interactions

Warfarin resistance

Routine coagulation monitoring → Frequent dose adjustments

INR = International normalized ratio; VKA = vitamin K antagonist.

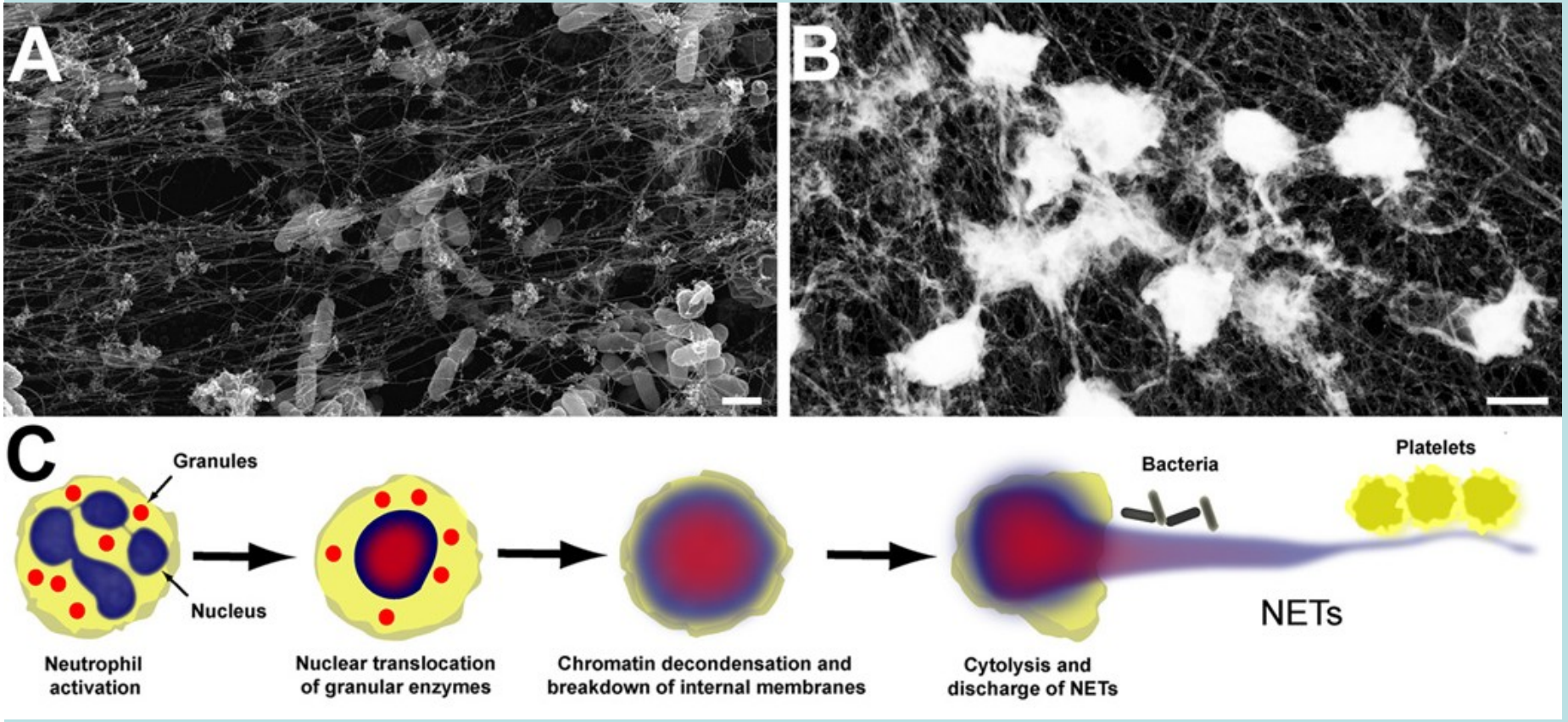
Ansell J, et al. *Chest* 2008;133;160S-198S. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008;22:129-137. Nutescu EA, et al. *Cardiol Clin* 2008;26:169-187.



Low Molecular Weight Heparin

- Mechanism: similar to UFH but more inhibition of Xa
- Advantages over UFH
  - Dose is dependent on the patient's ***weight*** so no need to monitor
    - (except with ***renal failure*** or pregnancy)
    - APTT is not helpful – ask your haematologist!
  - Daily S/C dosage
  - Much less HITT and osteoporosis

Should we be anticoagulating at all?

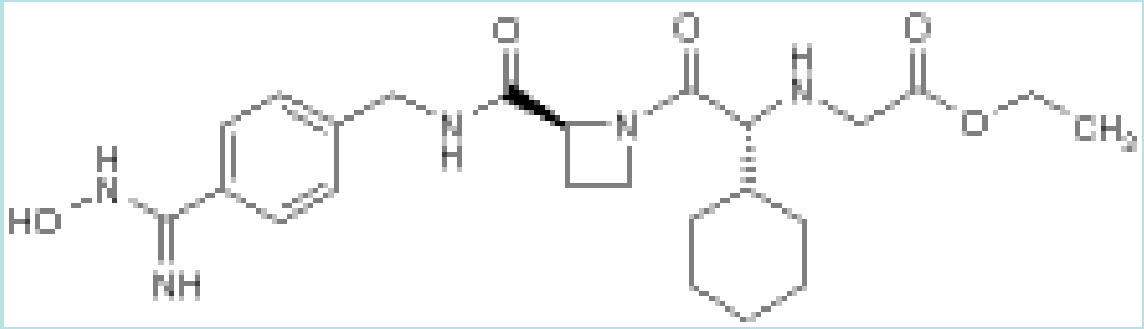


NET inhibition in VTE

Should we be anticoagulating at all?

- Watchman device in AF
- Cost of device + insertion £7-10k
- Ablations etc

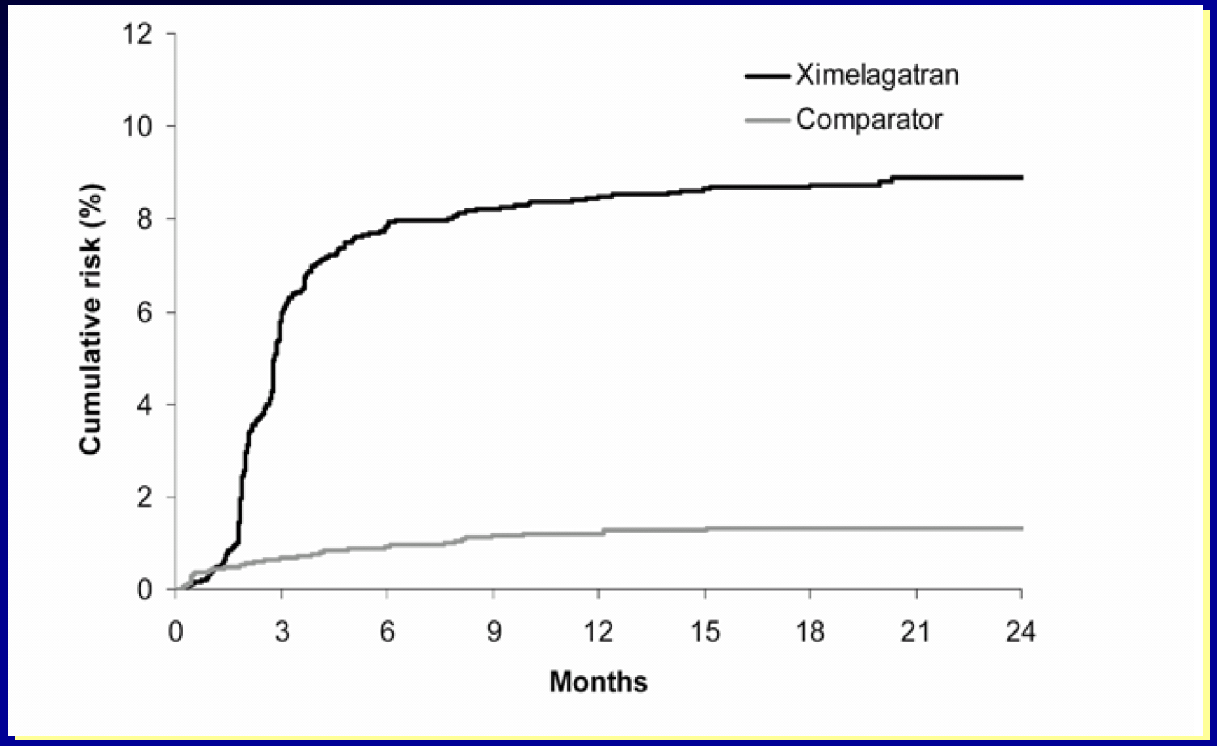
What?



Mechanism of action of the oral direct thrombin inhibitor ximelagatran.
Mattsson C, Sarich TC, Carlsson SC.AstraZeneca, Mölndal, Sweden.

Ximelagatran is the first oral agent in the new class of direct thrombin inhibitors and is rapidly absorbed and bioconverted to the active moiety, melagatran, which inhibits fluid-phase and clot-bound thrombin with similar high potency. Binding to the active site of thrombin is direct and competitive and does not require the presence of co-factors. *Inhibition of thrombin generation and platelet activation* has been demonstrated in vitro with melagatran as well as ex vivo after oral administration of ximelagatran to healthy human volunteers. Oral ximelagatran dose dependently reduced the total thrombus area in an ex vivo flow chamber model of arterial thrombosis, reflecting the cumulative effect of inhibition of thrombin activity, thrombin generation, and platelet activation. Melagatran has also been shown to reduce *thrombin-mediated inflammation in vitro.*

ALT > 3X in Long Term Trials
Cumulative Risk Over Time



The Pharmaceutical Journal
Vol 276 No 7389 p222
25 February 2006

Ximelagatran withdrawn due to liver safety concerns

The oral anticoagulant ximelagatran (Exanta), a direct thrombin inhibitor, has been withdrawn from the market and its development has been terminated, AstraZeneca announced last week.

Ximelagatran is not marketed in the UK but its launch had been expected for some time (*PJ*, 7 January, p23 PDF (110K)). In several European and South American countries it is licensed and marketed for 11 days' use for the prevention of venous thromboembolism for patients undergoing elective hip or knee replacement surgery.

Its withdrawal is the result of patient safety data from the EXTEND trial, which examines the prophylactic use of ximelagatran for up to 35 days after orthopaedic surgery.

In a statement, AstraZeneca said: "The new patient report indicates a potential risk of severe liver injury, with an observation of rapid onset of signs and symptoms in the weeks following the end of the 35 days' treatment." Supplies will continue for a short time to allow patients to be changed to alternatives.

The NEW ENGLAND JOURNAL of MEDICINE

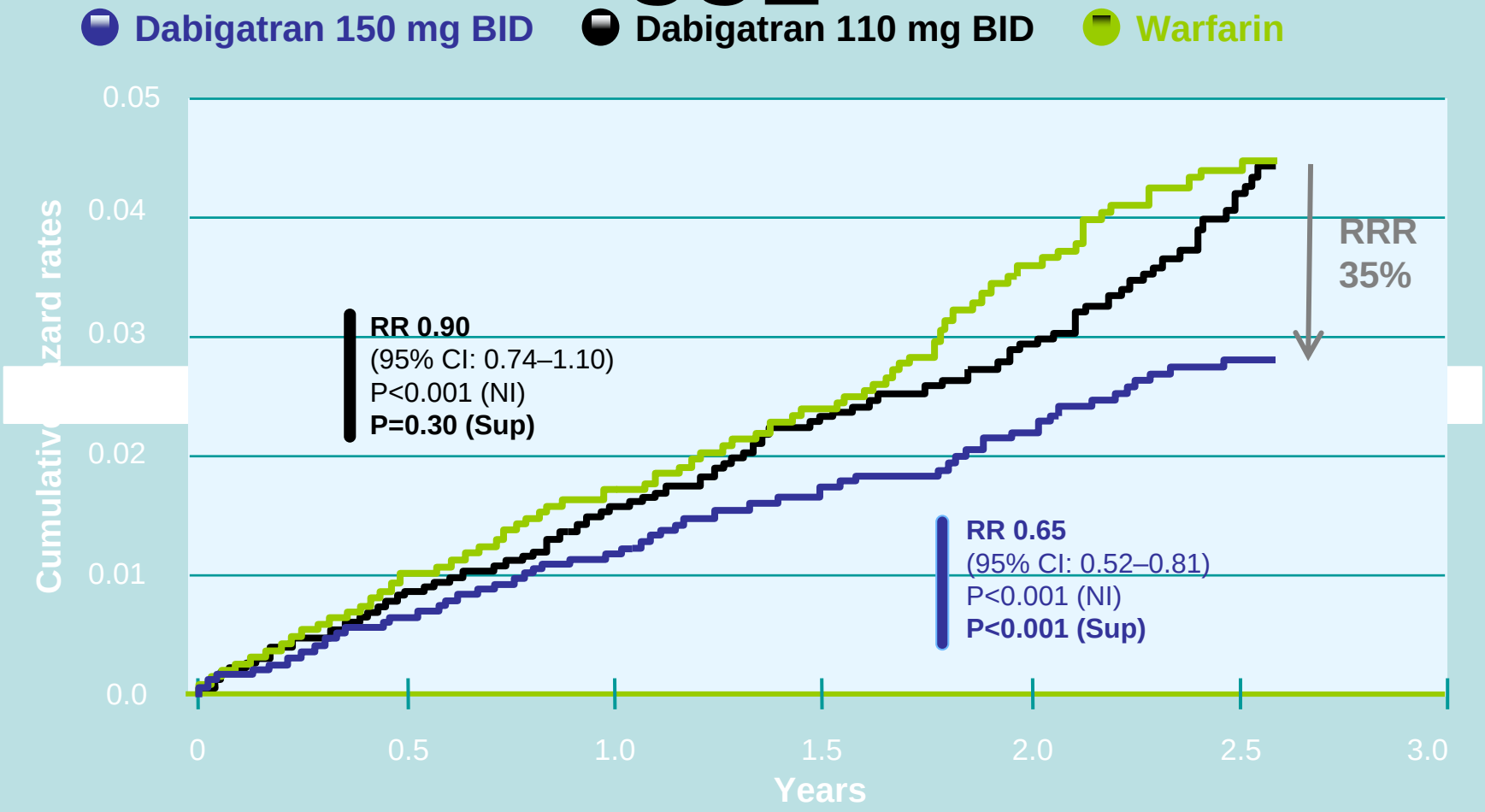
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*


50
YEARS
The first new oral anticoagulant licensed for stroke prevention in atrial fibrillation in 50 years!

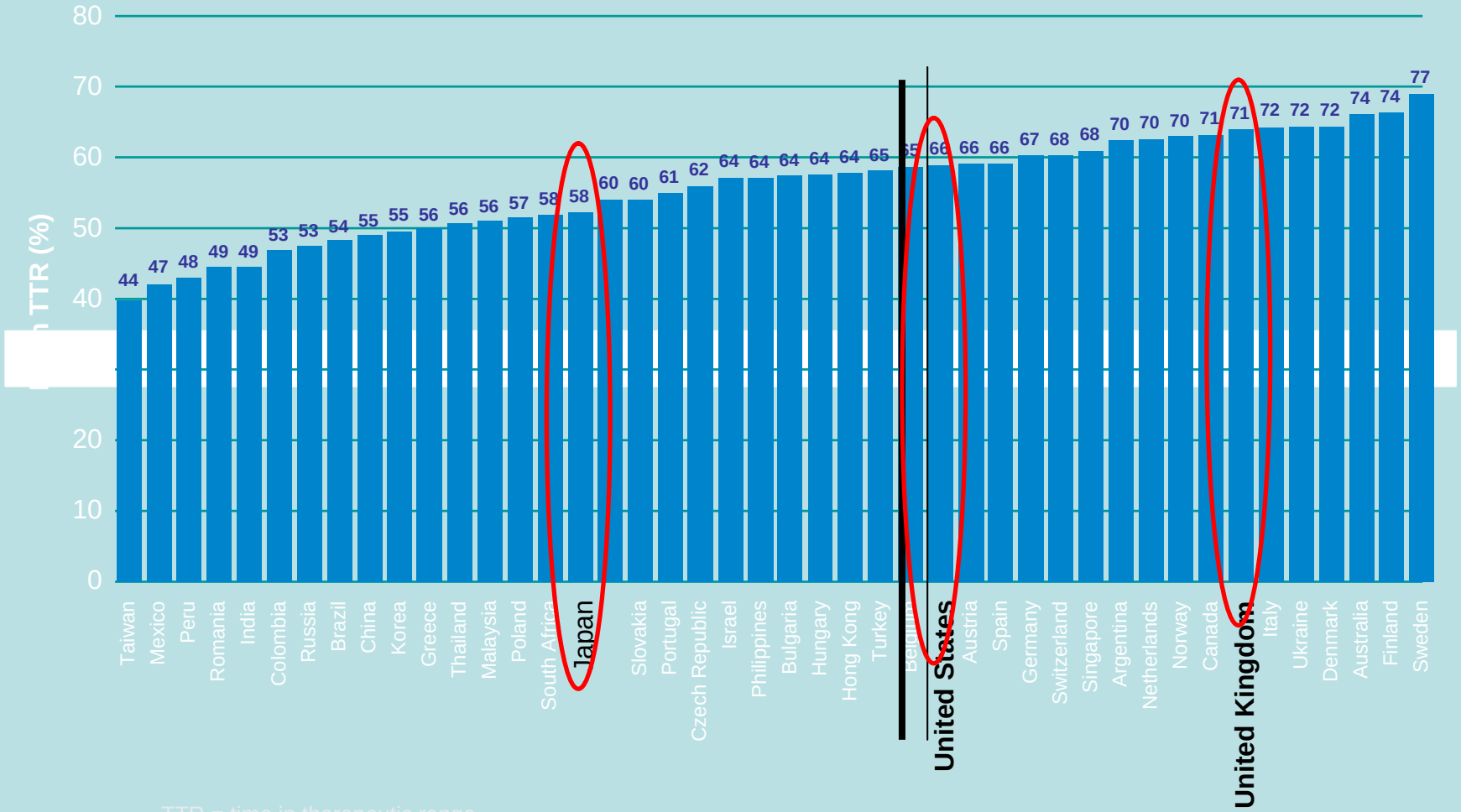
- **Dear Jonathan,**
- **Pradaxa® (dabigatran etexilate): New stroke prevention treatment for eligible patients with atrial fibrillation1,2**
- In the UK, the Atrial Fibrillation Association estimates that approximately 1.2 million people have atrial fibrillation, making it the most common of all the cardiac arrhythmias. Patients with atrial fibrillation (AF) have been shown to be at an increased risk of stroke compared with those without.
- NICE guidelines recommend patients diagnosed with AF are risk assessed and prescribed treatment with
  - Warfarin – for patients at moderate or high risk
  - Aspirin – for patients at low or moderate risk or for whom warfarin is contraindicated or not suitable
- **However, NICE estimates that 46% of patients that should be on warfarin are not receiving it.6**

TIME TO FIRST STROKE OR SSE



RR = relative risk; RRR = relative risk reduction; SSE = systemic embolism.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Connolly SJ, et al. *N Engl J Med* 2010;363:1875-1876.

TTR SUBGROUP ANALYSIS:
MEAN TTR BY COUNTRY



TTR = time in therapeutic range.

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.

Wallentin L, et al. *Lancet* 2010;376:975-983.

TTR SUBGROUP ANALYSIS: TOTAL DEATH

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs. warfarin		Dabigatran 150 mg vs. warfarin	
cTTR	Rate per 100-person yrs	Rate per 100-person yrs	Rate per 100-person yrs	HR (95% CI)	P value (interaction)	HR (95% CI)	P value (interaction)
<57.1%	4.17	3.85	5.72	0.73 (0.58–0.92)	-	0.67 (0.53–0.85)	-
57.1–65.5%	3.97	3.75	4.09	0.97 (0.75–1.24)	-	0.92 (0.71–1.18)	-
65.5–72.6%	3.19	3.64	3.70	0.86 (0.65–1.13)	-	0.98 (0.75–1.28)	-
>72.6%	3.60	3.30	3.04	1.18 (0.89–1.57)	0.066	1.08 (0.81–1.44)	0.052

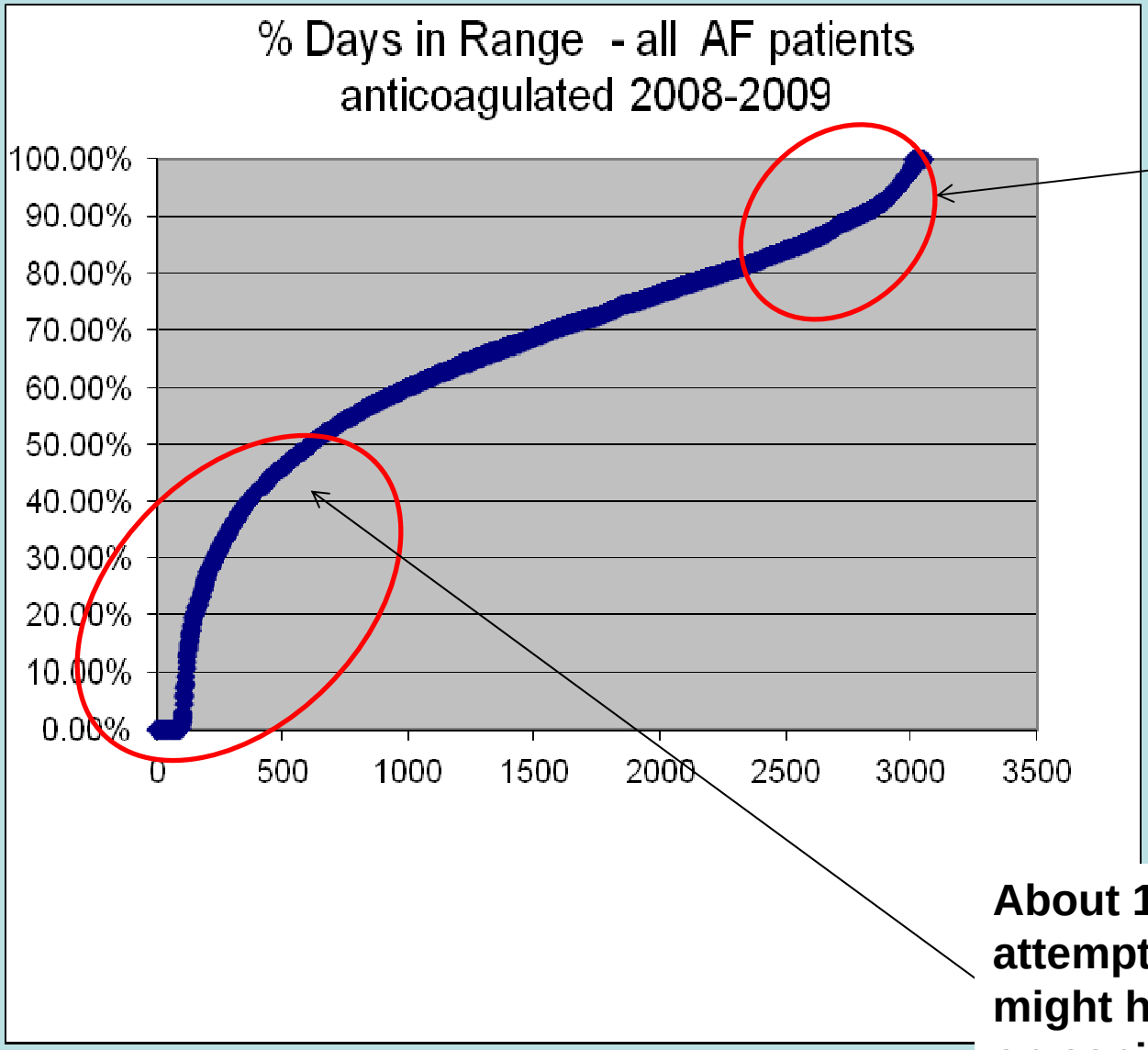
TTR = time in therapeutic range; cTTR = centre mean TTR; HR = hazard ratio; CI = confidence interval.
Interaction P value evaluated by a multivariate approach with centre-based TTR as a continuous variable.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Wallentin L, et al. *Lancet* 2010;376:975-983.

TTR SUBGROUP ANALYSIS: **INTRACRANIAL BLEEDING**

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs. warfarin		Dabigatran 150 mg vs. warfarin	
cTTR	**Rate per 100-person yrs**	**Rate per 100-person yrs**	**Rate per 100-person yrs**	**HR (95% CI)**	**P value (interaction)**	**HR (95% CI)**	**P value (interaction)**
<57.1%	0.28	0.34	0.64	0.43 (0.19–1.00)	-	0.53 (0.25–1.15)	-
57.1–65.5%	0.30	0.42	0.93	0.31 (0.15–0.66)	-	0.45 (0.24–0.88)	-
65.5–72.6%	0.13	0.24	0.67	0.20 (0.07–0.58)	-	0.35 (0.15–0.82)	-
>72.6%	0.21	0.30	0.77	0.27 (0.11–0.66)	0.71	0.39 (0.18–0.84)	0.89

So – in a logical world who gets what - patients already on warfarin?

- >70% TTR on warfarin
  - Warfarin no worse , or may be better
- 60-70% TTR
  - Dabigatran may be better
- <60% TTR
  - Dunno
    - Dabigatran if medically complex and compliant ? 110mg dose
    - ? What for non-compliant patients



About 1/4 of patients we attempted to anticoagulate were in range >80% and 1/2 >70%

About 1/3 of patients we attempted to anticoagulate might have been better off on aspirin! (in range <60%)

SPAF trials versus warfarin

	Dabigatran[1-3]	Rivaroxaban[4,5]	Apixaban[6,7]
Study	RE-LY	ROCKET-AF	ARISTOTLE
Design	PROBE	Double Blind	Double Blind
Follow up	2 yrs	1.5 yrs	1.5 yrs
Population size	>18,000	>14,000	>18,000
Inclusion	Nonvalvular AF + 1 risk factor	Nonvalvular AF + 2 risk factors (i.e. moderate to high risk)	Nonvalvular AF + 1 risk factor
Inclusion (CHADS)	2.1	3.5	2.1
Primary Endpoint	Stroke and systemic embolism	Stroke and systemic embolism	Stroke and systemic embolism
Warfarin comparator INR control (mean TTR)	64%	55%	62%

1. Ezekowitz MD et al. Am Heart J 2009;157:805–10; 2. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 3. Connolly SJ et al. N Engl J Med 2010;363:1875–1876; 4. Rocket Investigators. Am Heart J 2010;159:340-347; 5. Patel MR et al. NEJM 2011;365:883–91; 6. Lopes et al. Am Heart J 2010;159:331-9; 7. Granger et al. N Eng J Med 2011;365:981-92. PROBE = prospective randomised open blinded end-point;

Pharmacology

	Dabigatran[1-3]	Rivaroxaban[4,5]	Apixaban[6,7]
Half life	12-14 hrs	7-11 hrs	12 hrs
(atrial fibrillation)	B.D.	O.D.	B.D.
Metabolism	Esterase catalysed hydrolysis	CYP P450 dependant and independent mechanisms	CYP P450
Excretion	80% Renal	1/3 Renal 2/3 Hepatic	1/4 Renal 3/4 Non Renal
Form	Capsule	Tablet	Tablet
Dose	150 mg 110 mg (>80 yrs, verapamil or increased bleeding risk)	20 mg 15 mg (CrCL 30-49 ml/min)	5 mg 2.5 mg (2 or more: >80yr; weight <60 kg; Cr >1.5 mg/dL)

1. Ezekowitz MD et al. Am Heart J 2009;157:805–10; **2.** Connolly SJ et al. N Engl J Med 2009;361:1139–51; **3.** Connolly SJ et al. N Engl J Med 2010;363:1875–1876; **4.** Rocket Investigators. Am Heart J 2010;159:340-347; **5.** Patel MR et al. NEJM 2011;365:883–91; **6.** Lopes et al. Am Heart J 2010;159:331-9; **7.** Granger et al. N Eng J Med 2011;365:981-92.

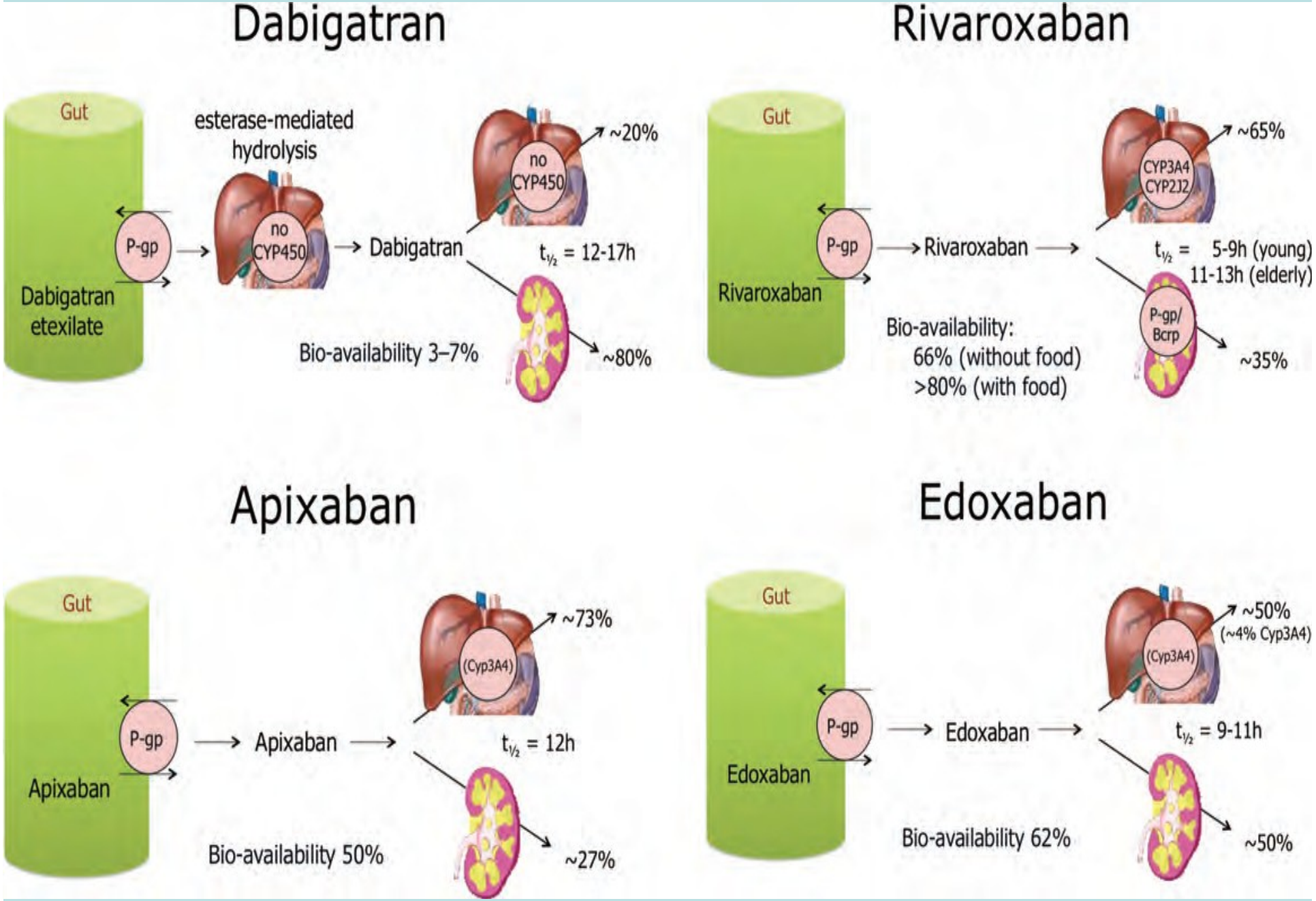
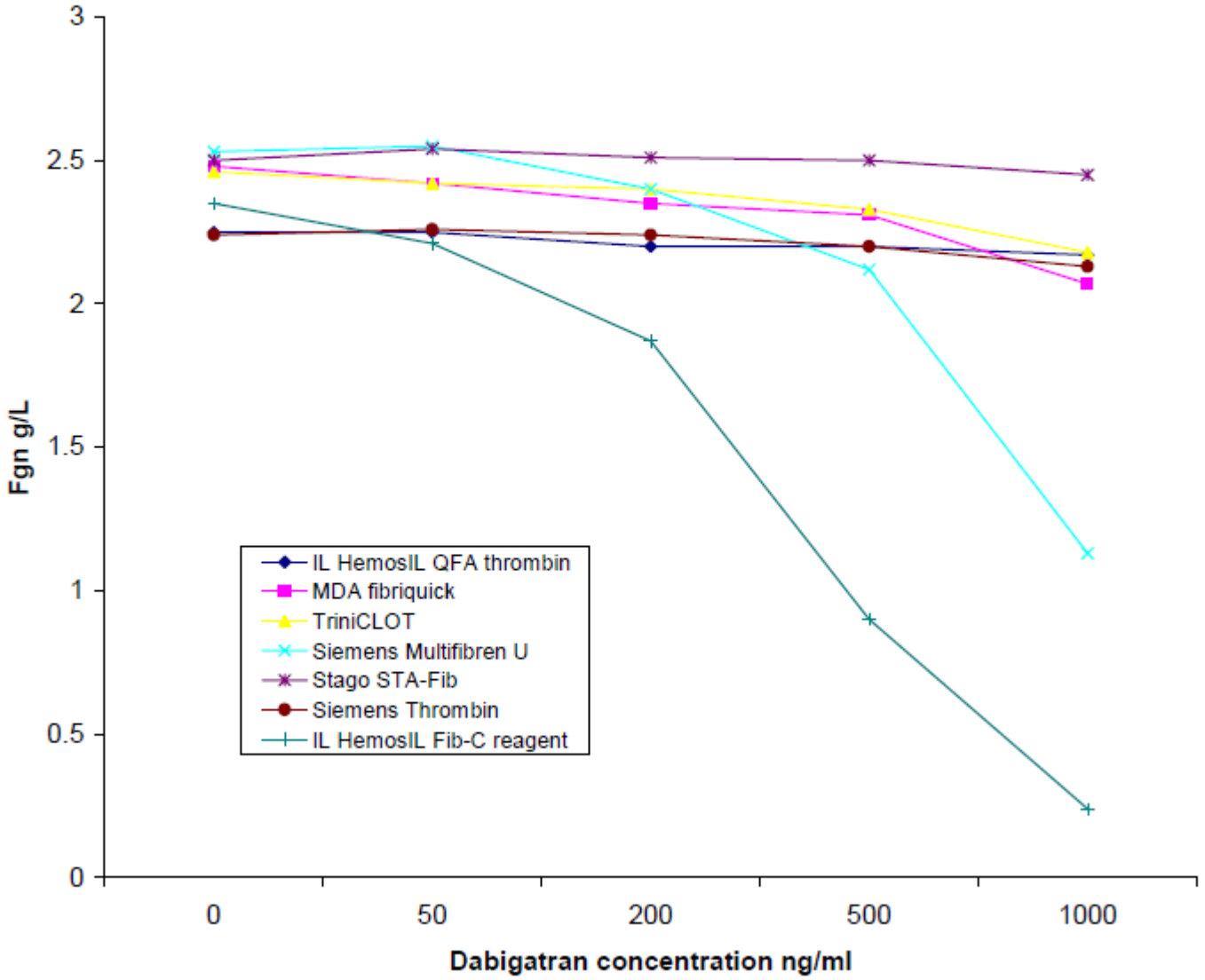

Dabigatran
Gut
esterase-mediated hydrolysis
P-gp
Dabigatran etexilate
no CYP450
Dabigatran
no CYP450
~20%
$t_{1/2}$ = 12-17h
~80%
Bio-availability 3–7%
Rivaroxaban
Gut
P-gp
Rivaroxaban
Rivaroxaban
CYP3A4 CYP2J2
~65%
$t_{1/2}$ = 5-9h (young) 11-13h (elderly)
P-gp/ Bcrp
~35%
Bio-availability:
66% (without food)
>80% (with food)
Apixaban
Gut
P-gp
Apixaban
Apixaban
(Cyp3A4)
~73%
$t_{1/2}$ = 12h
~27%
Bio-availability 50%
Edoxaban
Gut
P-gp
Edoxaban
Edoxaban
(Cyp3A4)
~50%
(~4% Cyp3A4)
$t_{1/2}$ = 9-11h
~50%
Bio-availability 62%

Fig 3. Plot of median Fibrinogen concentration against Dabigatran concentration for reagents used by >10 centres



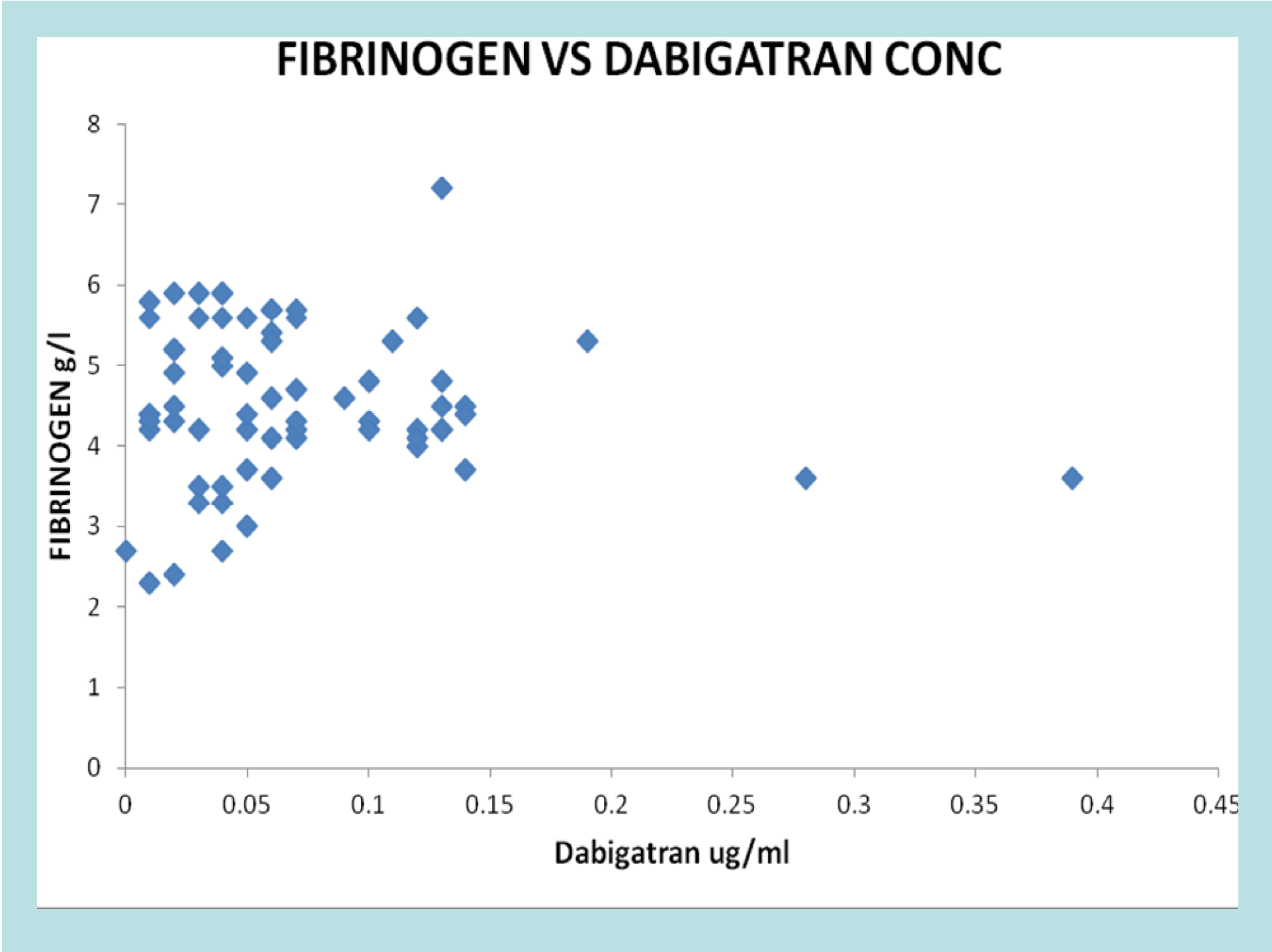
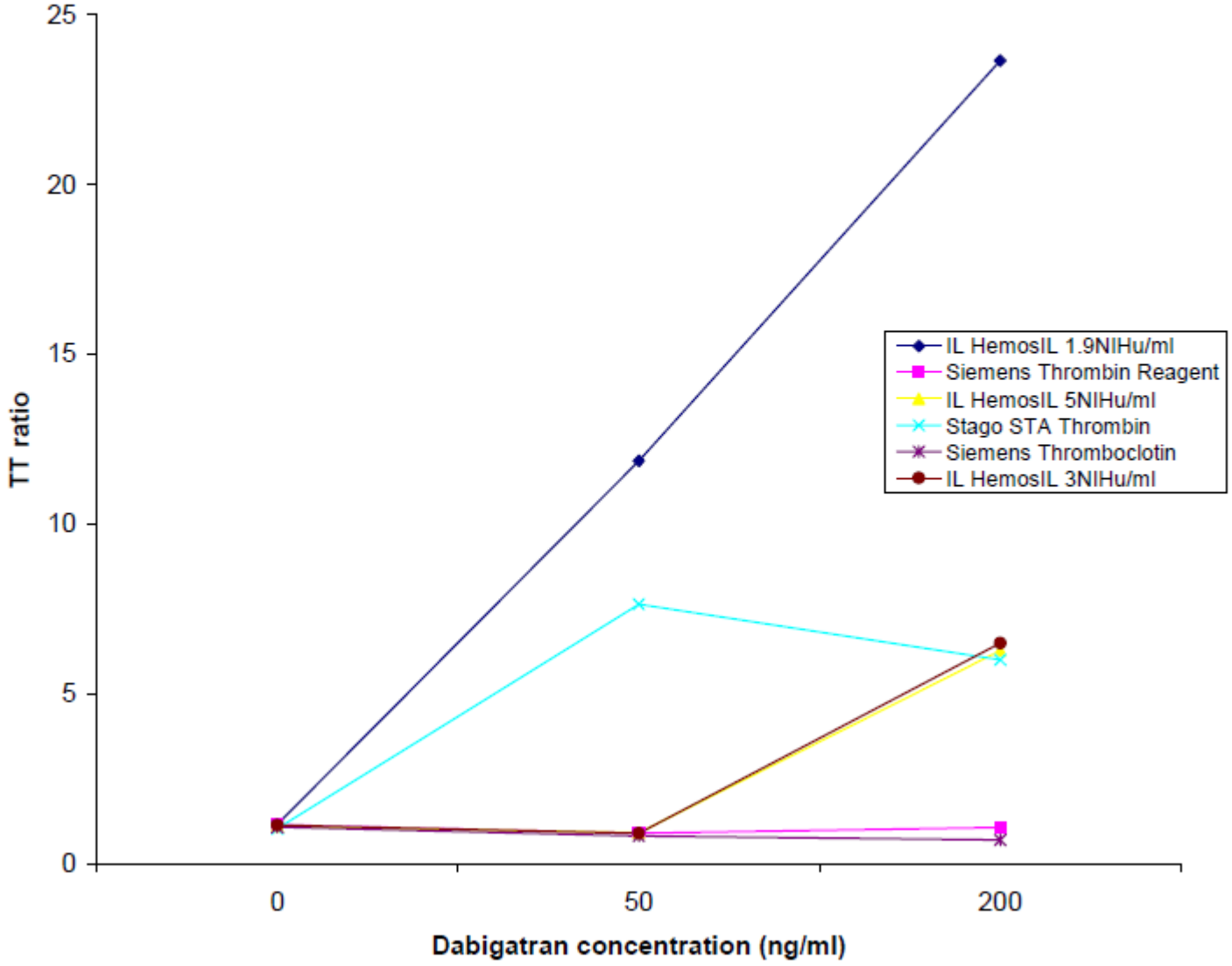

FIBRINOGEN VS DABIGATRAN CONC
FIBRINOGEN g/l
8
7
6
5
4
3
2
1
0
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
Dabigatran ug/ml

Fig 4. Plot of median TT ratio against Dabigatran concentration for reagents used by >10 centres



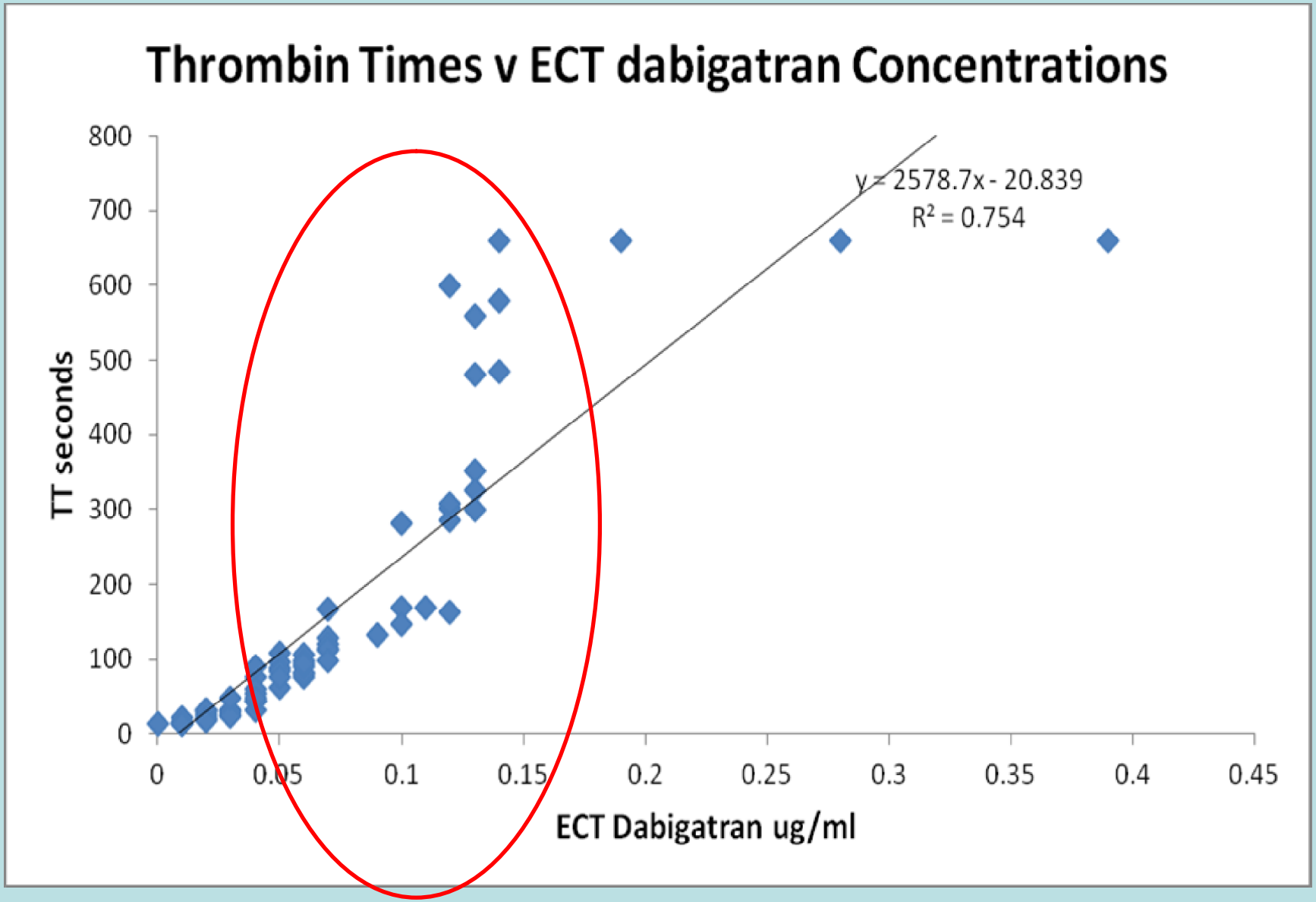
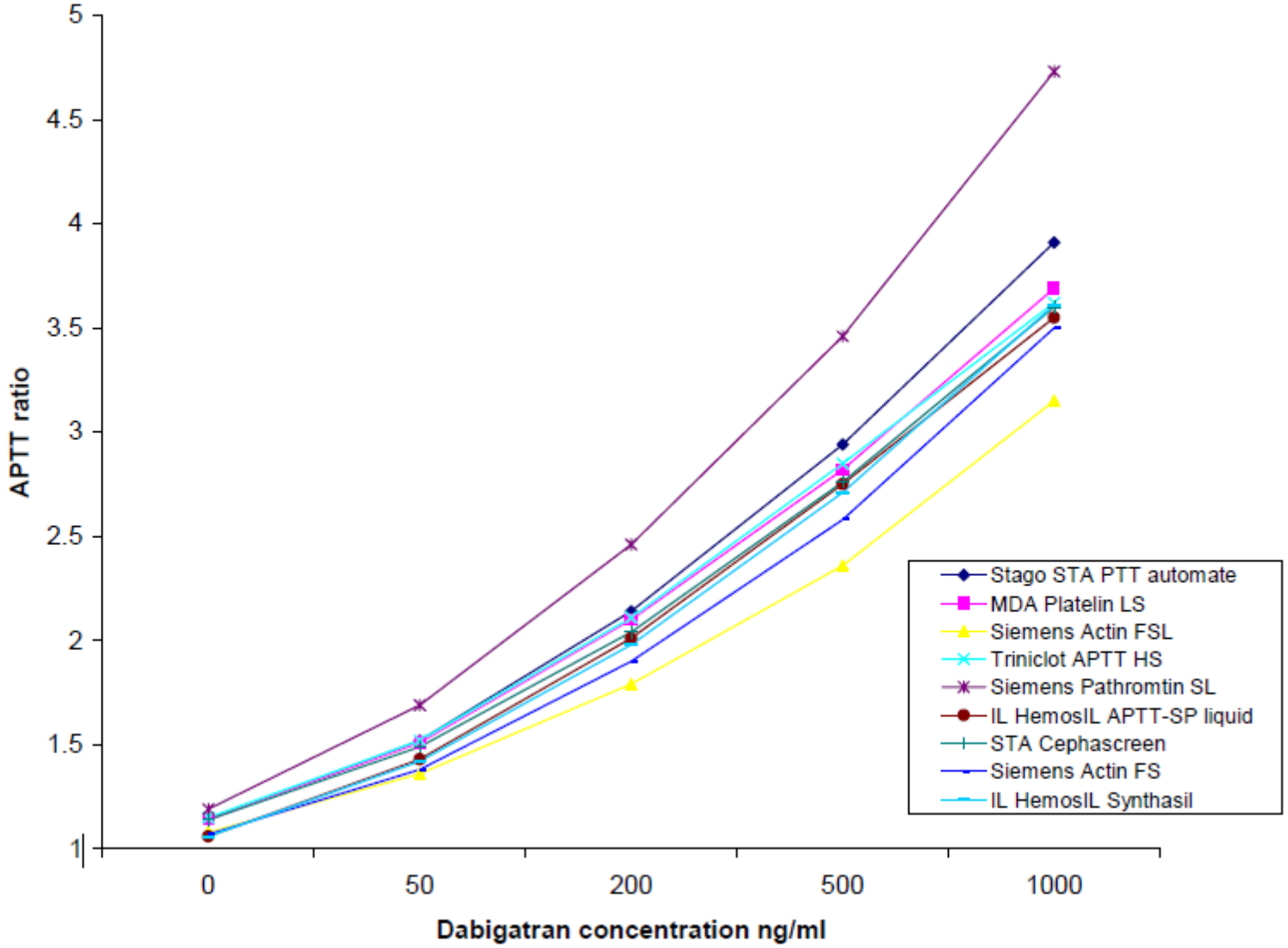
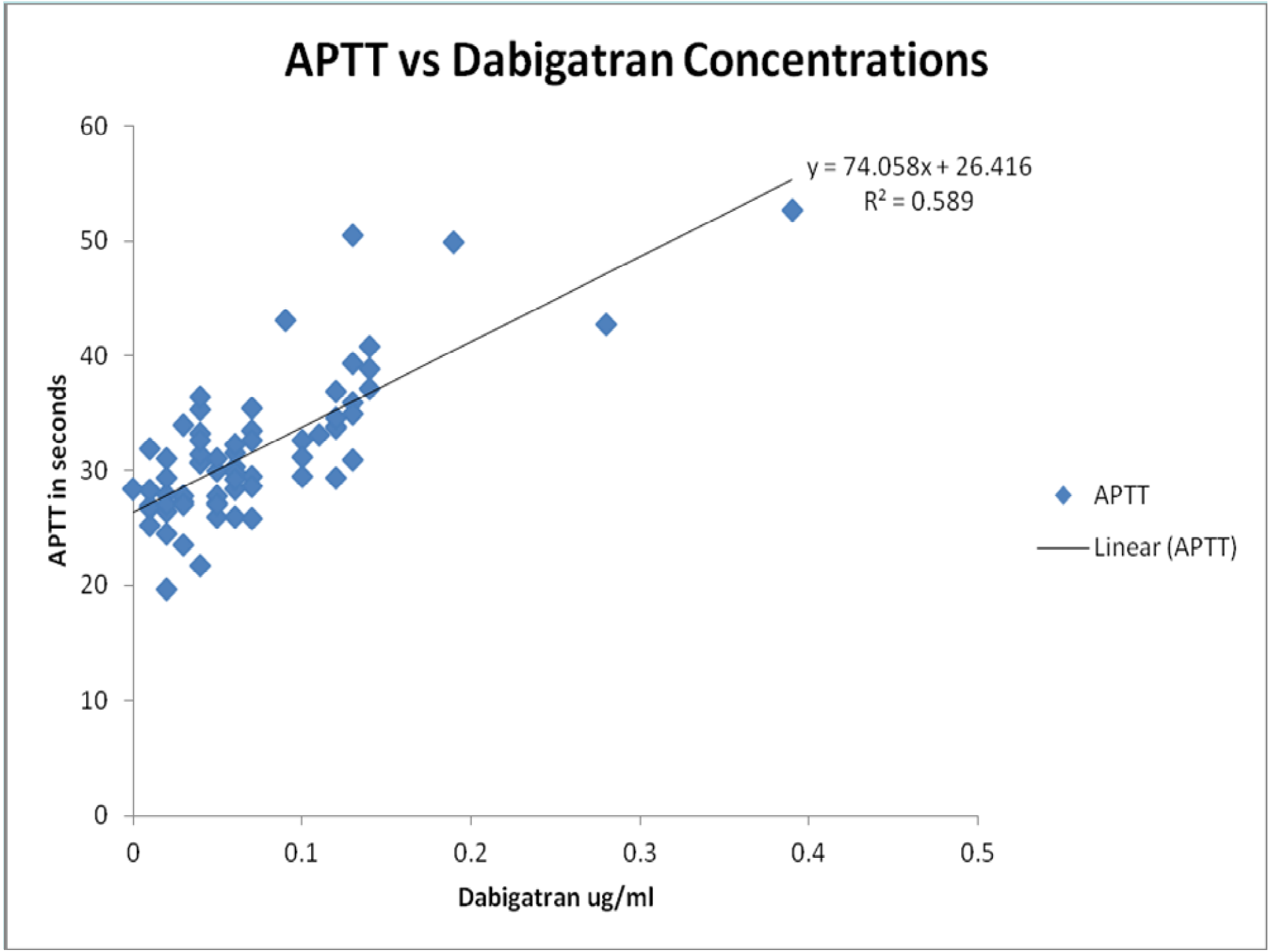
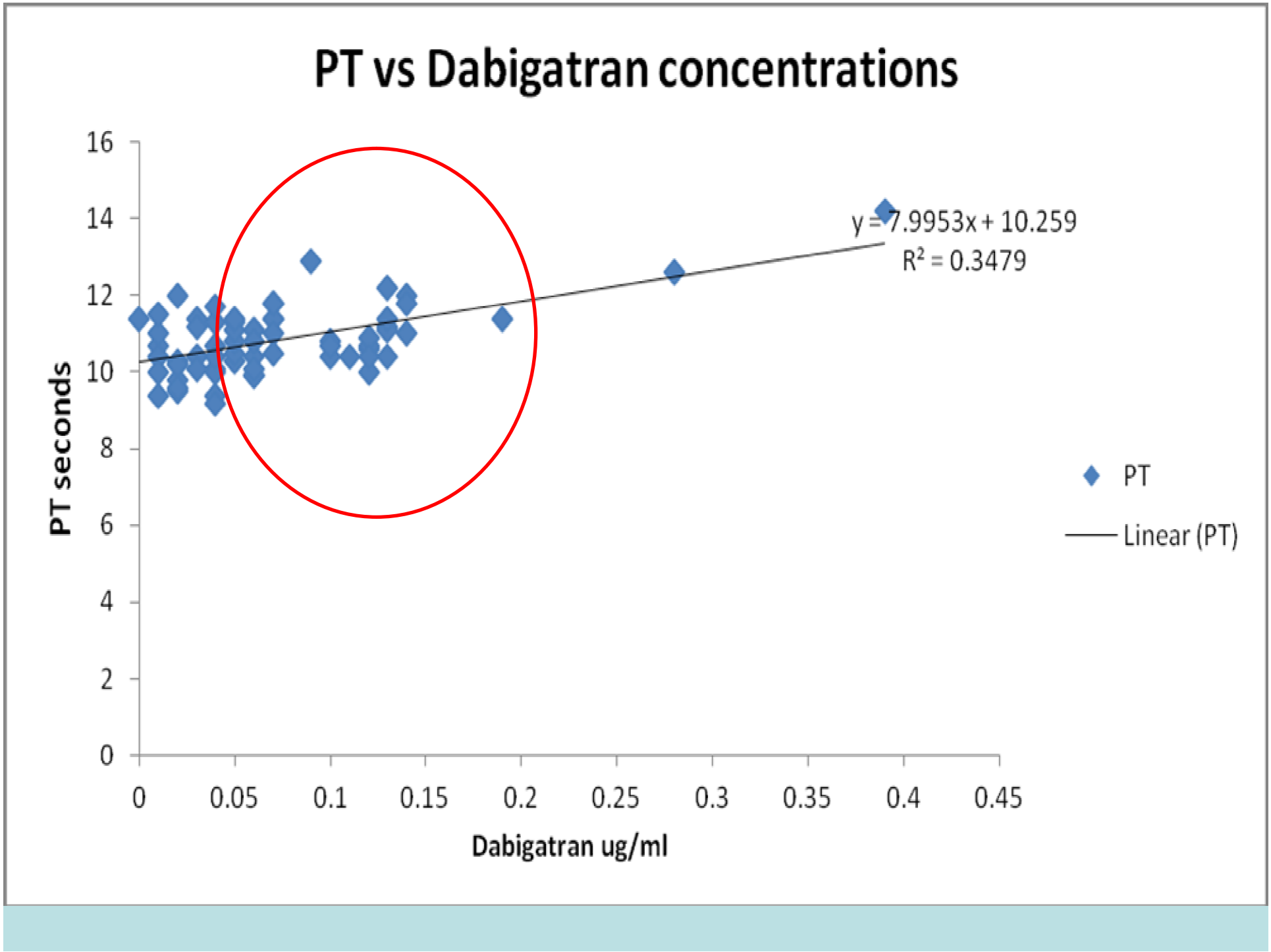

Thrombin Times v ECT dabigatran Concentrations
y = 2578.7x - 20.839
R² = 0.754
TT seconds
800
700
600
500
400
300
200
100
0
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
ECT Dabigatran ug/ml

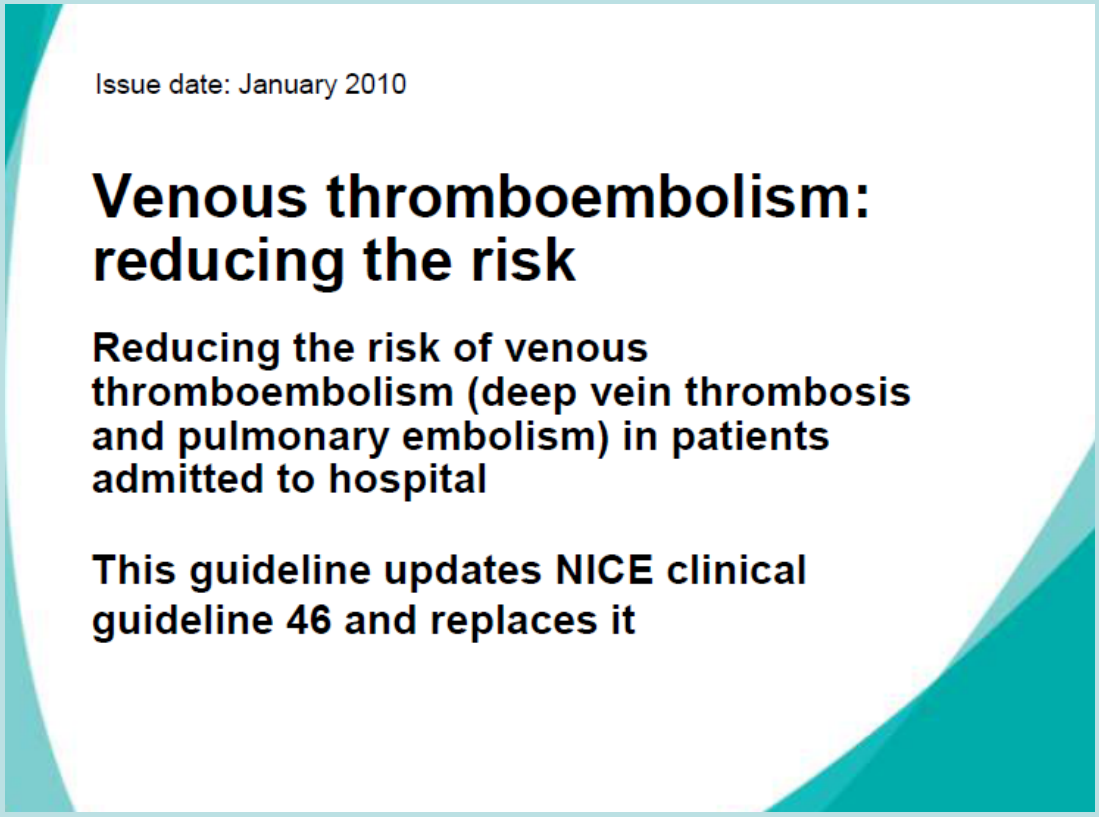
Fig 2. Plot of median APTT ratio against Dabigatran concentration for reagents used by >10 centres




APTT vs Dabigatran Concentrations
y = 74.058x + 26.416
R² = 0.589
APTT in seconds
Dabigatran ug/ml
APTT
Linear (APTT)
60
50
40
30
20
10
0
0
0.1
0.2
0.3
0.4
0.5

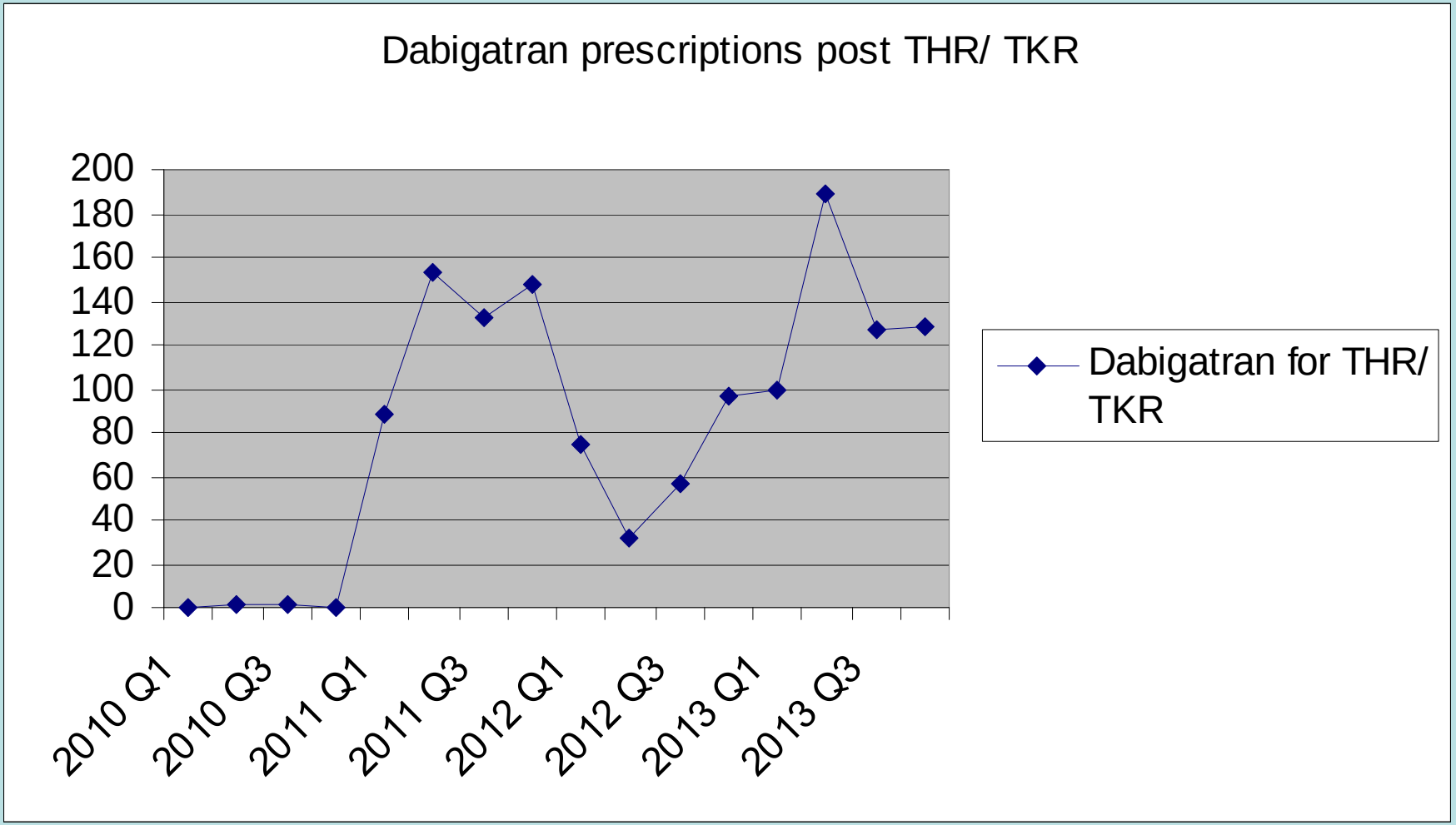

PT vs Dabigatran concentrations
y = 7.9953x + 10.259
R² = 0.3479
PT seconds
Dabigatran ug/ml
PT
Linear (PT)
0
2
4
6
8
10
12
14
16
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45

How?



Phase 1: orthopaedics
THR and TKR, 2010-11

Continue pharmacological VTE prophylaxis for 28–35 days, according to the summary of product characteristics for the individual agent being used.


Dabigatran prescriptions post THR/ TKR
200
180
160
140
120
100
80
60
40
20
0
2010 Q1
2010 Q3
2011 Q1
2011 Q3
2012 Q1
2012 Q3
2013 Q1
2013 Q3
Dabigatran for THR/ TKR

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

Issued: March 2012

NICE technology appraisal guidance 249

www.nice.org.uk/ta249

Phase 2: AF

1.2 The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control.

Buckinghamshire Traffic Light System Definitions

Black	**Not recommended for use because of lack of evidence of clinical effectiveness, cost effectiveness or safety.** Drugs which have been evaluated and rejected by the Formulary Management Group (FMG) Drugs defined as 'Low Priority' by the South Central Priorities Committee New drugs which have not as yet been evaluated by the FMG Any drug not listed in the Bucks Joint Formulary at http://www.nelm.nhs.uk/en/Formularies/Trusts/Buckinghamshire-Formulary/
Red	**Drugs which should only be prescribed in secondary care by a specialist.** Require specialist knowledge and/or equipment for patient selection and initiation, Require long term on-going monitoring and dose adjustment to ensure efficacy and minimise toxicity by a specialist Designated as "hospital only" by product licence, NICE, DoH or BNF May need further evaluation by a specialist Are hospital initiated clinical trial materials
Amber Protocol	**Drugs which should be initiated in secondary care by the specialist with follow-on prescription and monitoring according to a drug specific Shared Care Protocol (SCP). Prescribing may be continued in primary care following the SCP** Require specialist knowledge and/or equipment for patient selection and initiation Require short or medium term (eg. 3 to 6 months) specialist monitoring of efficacy or toxicity. The need for stabilisation will vary with different drugs and patients, but is usually a minimum of 2 months (see principles for shared care) Require significant long term monitoring Require ongoing communication between the GP and the specialist Have clearly defined consultant, GP and patient responsibilities documented in a shared care protocol (see responsibilities for amber protocol drugs)
Amber initiation	**Drugs suitable for primary care prescribing following specialist initiation** Require specialist knowledge and/or equipment for patient selection Monitoring does not require specialist knowledge or equipment If the drug is one with which the primary care prescriber is unfamiliar the specialist is expected to provide sufficient information on the drug indication, dose, duration , monitoring and any further necessary dose adjustments Require the first prescription to be written by the specialist
Amber recommendation	**Drugs suitable for primary care prescribing following specialist recommendation** As for amber initiation except that:- The first prescription may be written by the GP after specialist recommendation.
Green	**Drugs for which primary care prescribers would normally take full responsibility for prescribing and monitoring** Drugs not included in the Traffic Light list but included on joint formulary. New drugs classified as red or amber but as greater experience regarding their safety and efficacy is established may move to Green after re-consideration by the FMG and APC.

The dreaded Bucks Formulary Management Group!

So we got one of these..

Satinder

-set up a NOAC clinic
-wrote guidelines/forms
-all new AFs counselled
-1st month prescribed
-phone call at 2/52
-GP continued prescription
-PCT/CCGs prepared to pay

NHS Aylesbury Vale Clinical Commissioning Group

NHS Chiltern Clinical Commissioning Group

Buckinghamshire Healthcare NHS Trust

313.3 DABIGATRAN FOR ATRIAL FIBRILLATION
Amber Initiation Guideline

1. BACKGROUND FOR USE 2
   1.1. Risks/disadvantages of dabigatran compared to warfarin 2
   1.2. Benefits/advantages of dabigatran compared to warfarin 2

2. CRITERIA FOR USE 2
   2.1. NEW patients generally NOT suitable to start dabigatran 2
   2.2. NEW patients generally suitable to start dabigatran. 2
   2.3. EXISTING PATIENTS generally NOT suitable to start dabigatran (to remain on warfarin) 2
   2.4. EXISTING patients who may be suitable to consider dabigatran or warfarin 2
   2.5. EXISTING patients generally suitable to start dabigatran 2

3. CONTRAINDICATIONS AND PRECAUTIONS 2
   3.1. Absolute contraindications to both warfarin and dabigatran 2
   3.2. Relative contraindications to both warfarin and dabigatran 2

4. RESPONSIBILITIES 2
   4.1. Secondary/specialist responsibilities 2
   4.2. GP responsibilities 2

Appendix C: Referral Form 1 – GP to NOAC Clinic

NHS Aylesbury Vale Clinical Commissioning Group | NHS Chiltern Clinical Commissioning Group | Buckinghamshire Healthcare NHS Trust

GP Referral to New Oral Anticoagulant Service at BHNHST

Patient name: DoB: Sex:	GP Name: Address:
NHS No:	
Address:	
Postcode:	
Tel (day): Tel (mobile): Patient email:	Postcode:
Patient requires transport: ☐	Practice code:
Patient needs interpreter: ☐ Language: Ethnicity:	Tel: Fax:

Date of referral:

Reason for referral:

On warfarin ☐ **Time in range** **OR warfarin naive** ☐

Renal function info must be supplied:
Date **creatinine** **and weight** **kg**

Known history of poor compliance? **Give details**

In addition please provide a **Patient Summary** which details:

- Allergies, PMH, current medication and recent past medication, alcohol use if known, recent BP, FBC
- LFTs and INR (if any reason to suspect may be abnormal from history)

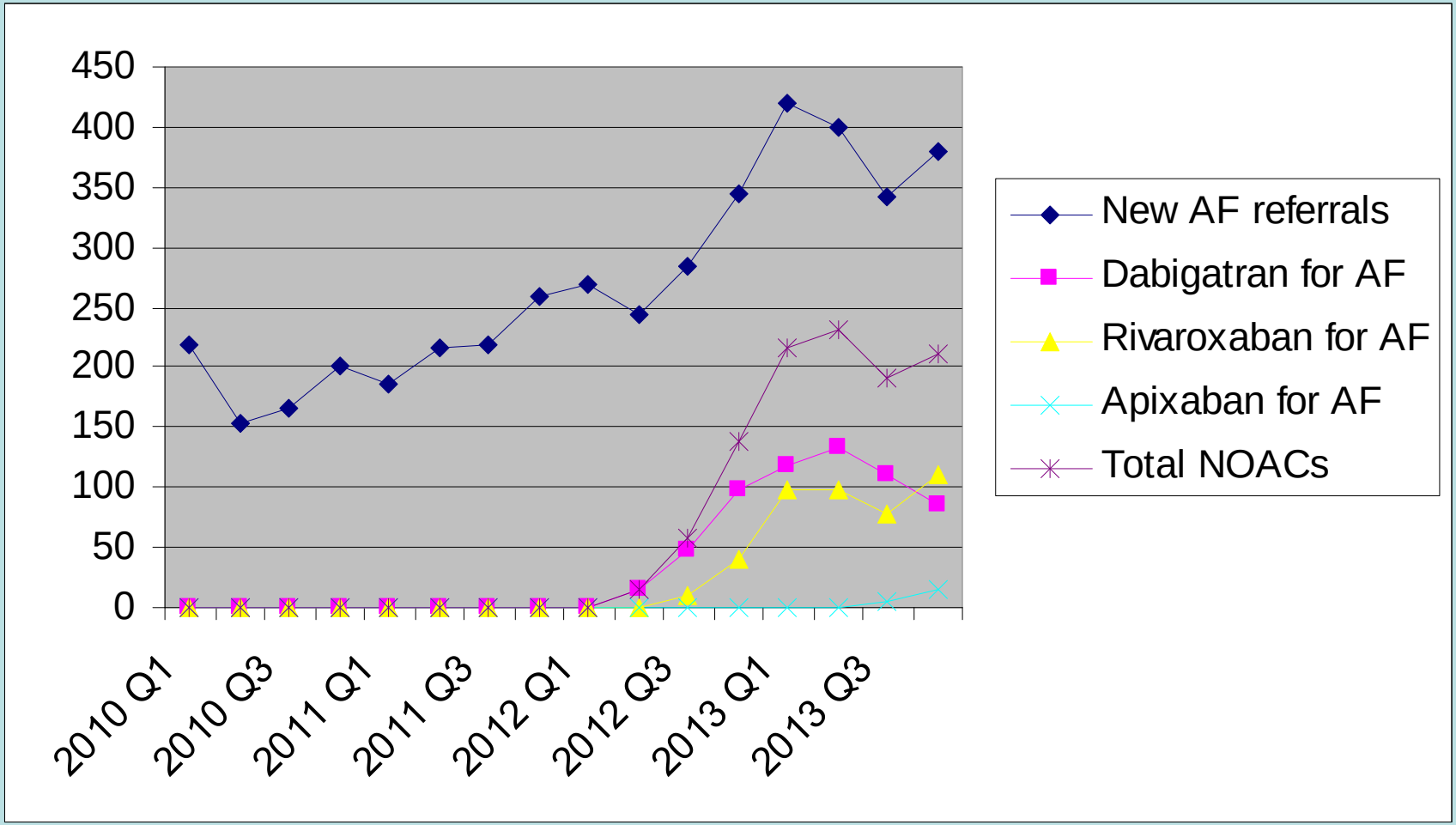
Please ring the scores for your patient:

		Points			Clinical Characteristic	Points
C	LVF/LVD dysfunction	1		H	Hypertension	1
H	Hypertension	1		A	Renal or LFTs abnormal	1 or 2
A_2	>75 years	2		S	Stroke	1
D	Diabetes mellitus	1		B	Bleeding	1
S_2	Prior stroke or TIA	2		L	Labile INRs	1
V	Vascular disease	1		E	>65 years	1
A	Age 64 – 74	1		D	Drugs or alcohol >8 U/week	1 or 2
Sc	Female	1				
	Total				Total	

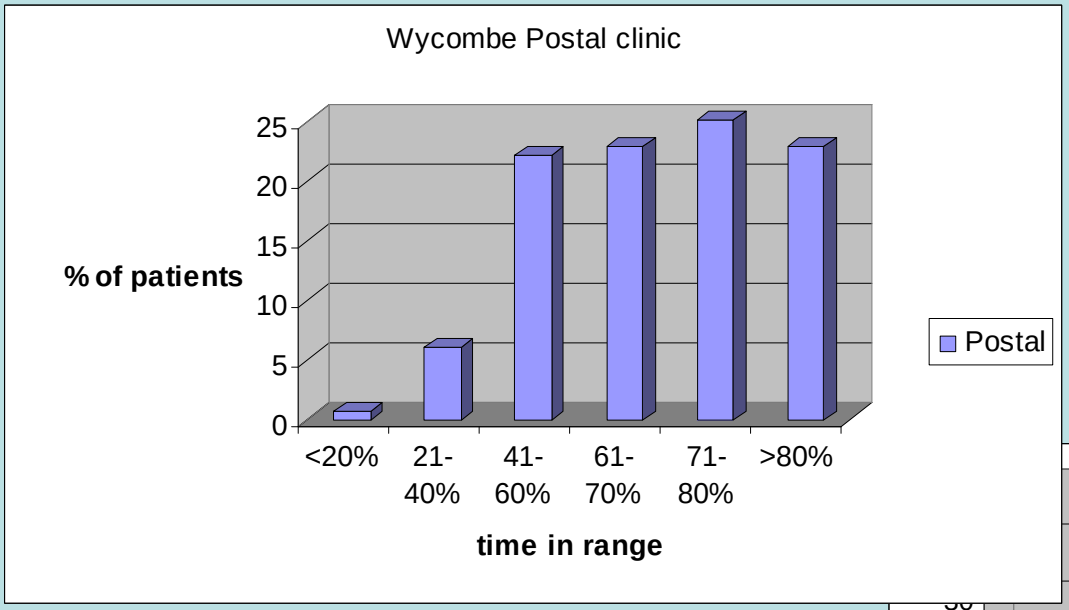
Signed..... (GP)

Phase 2a 2013: All new AFs counselled in NOAC clinic

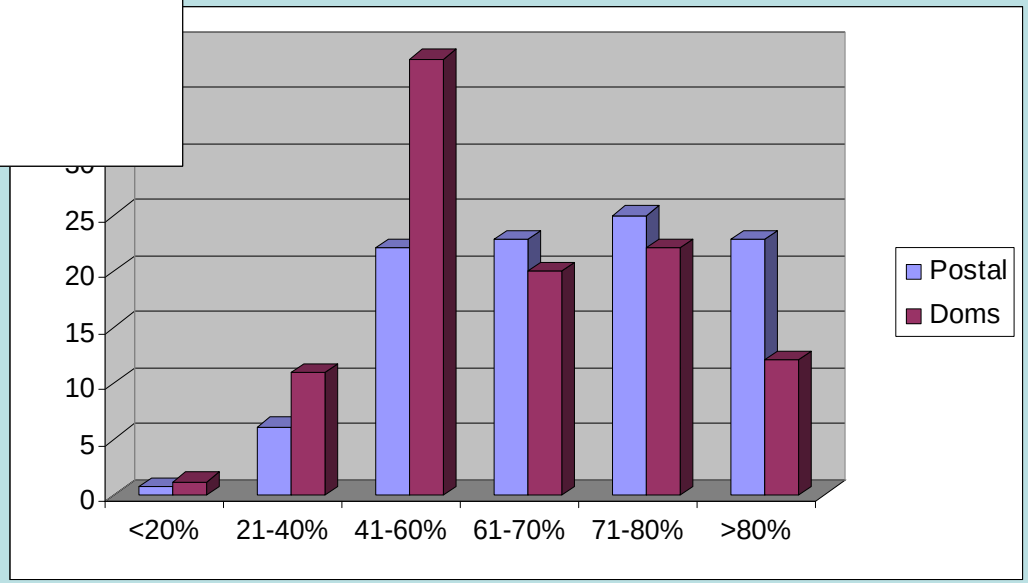
-About 60% of new AFs choose a NOAC
-About 10% of these subsequently switch to another NOAC or warfarin



Phase 2b 2014: switch over poorly controlled AF patients, starting with the worst clinic and patients in range <60%



Satinder currently being cloned…



The right anticoagulant?

- Poor TTR good, reasonable compliance, good GFR – dabigatran
- Poor TTR good, reasonable compliance, poorer GFR – rivaroxaban
- Poor TTR good, reasonable compliance, very poor GFR – warfarin or stop
- Poor compliance – address this!
- GIT problems ? apixaban