

USING THE INR TO ADJUST THE
DOSE – SOME PRACTICAL
CONSIDERATIONS. (for “dosers”)

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How important is it ?

- Warfarin is one of the commonest drugs cited in medical negligence claims.
- About 0.5% of hospital admissions are due to adverse effects of warfarin
- Inappropriate warfarin dosing implicated in 40-60 deaths/year (UK)

How important is it ?

Philadelphia, August 2001

Lab error deaths may now total five

“Three more deaths may be linked to a laboratory error at St. Agnes Medical Center, bringing the total under investigation to five, the Philadelphia medical examiner's office said yesterday.

That number could climb as the South Philadelphia hospital continues reviewing records of 932 patients who may have taken overdoses of a blood-thinning medication based on the lab's miscalculation, said Jeff Moran, a city health department spokesman”.

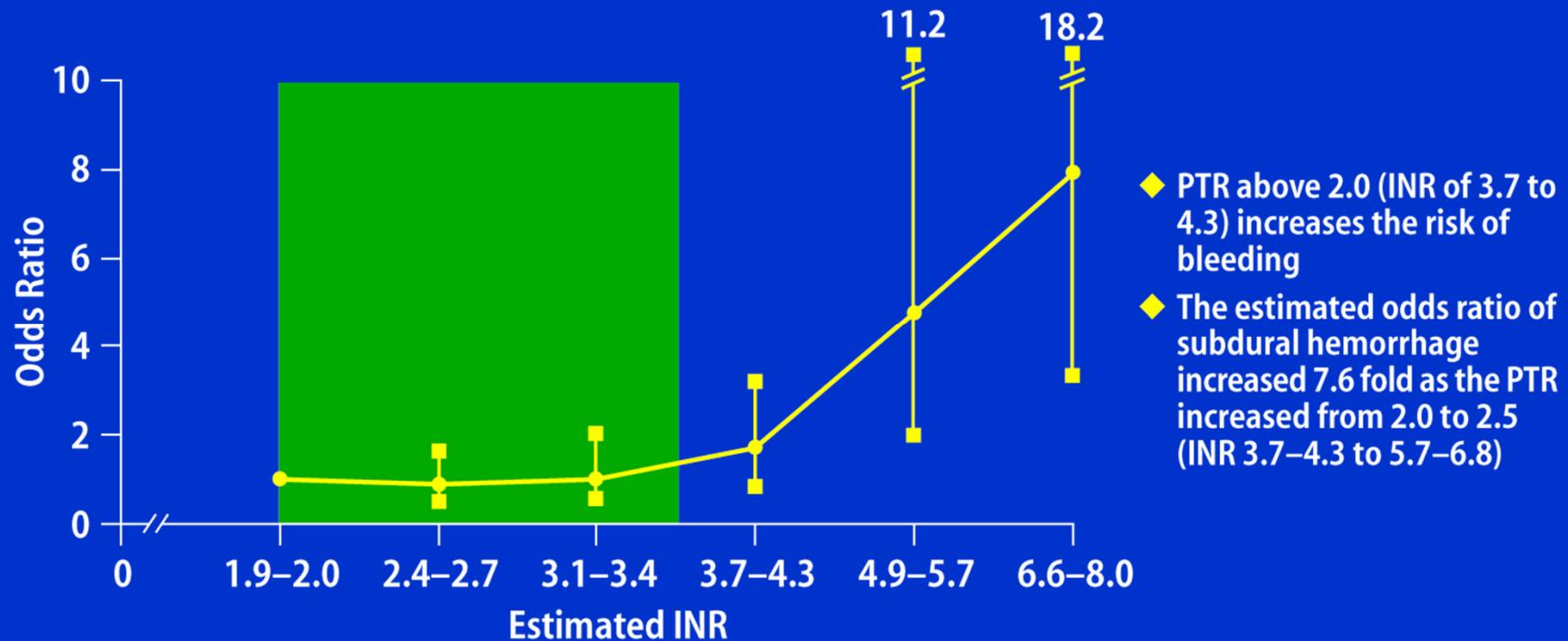
Published 8-3-2001, Philadelphia Inquirer. Marie McCullough, Philadelphia Inquirer staff writer

How important is it ?

- INR <1.5 negligible anticoagulant effect.
- Risk of major bleeding 1-2% / year (INR 2.0 – 3.0)
- Risk of fatal / intracranial bleed 0.5% / year (INR 2.0 – 3.0)
- INR >5.0 significant increase in bleeding risk

How important is it ? - Risk of Intracranial Hemorrhage in Outpatients

Adapted from: Hylek EM, Singer DE, Ann Int Med 1994;120:897-902



How important is it ?

- Its a risky business for patients and practitioners !
- Practitioners may be the subject of medical negligence claims.

Practical consideration 1

Keep good and secure records -

- Training and competency documentation in place and up to date
- Maintain and adhere to local written procedures.
- Clear, concise and timed records of communication with patients, GPs, consultants etc.
 - CDSS notes, telephone call log
 - Letters (eg DNA, non-compliance)

Oral Anticoagulation Management

Historical perspective – pre 1990

- Small numbers of patients seen in hospital based clinics
- Managed by clinicians
- Centralised laboratory testing – few reagents
- Manual INR - minimal automation
- Manual recording of INR (BCR) results and doses.
- No Computer Dosing Software Support (CDSS)

Oral Anticoagulation Management - Now

- Large numbers of patients
- Managed by a variety of health care professionals – nurse, pharmacist, laboratory scientist, GP. (patient)
- Many INR reagents / testing options
- Decentralised INR testing - POCT
- Various management models with trend to community based management
- Less manual handling and transcription of data
- Use of CDSS systems

Who does what ?

Traditionally 5 stages to the process



- Each stage tended to be associated with different professional groups with corresponding expertise.
- Increasing trend for stages to overlap or merge.

Practical consideration 2

Need for an understanding by “dosers” of the whole process and potential pitfalls at every stage in the process

What can go wrong ?

- The prescriber / referring clinician
- The patient
- The sample
- The Prothrombin Time and INR
- The doser

The prescriber / referring clinician

Has the patient been adequately assessed – is warfarin the best option - does the benefit outweigh the risk ?

Prior to starting patients on warfarin, prescribers should make the following judgements:

- Indication
- Suitability
- Control
- Bleeding
- Duration
- Consent
- People (communication)

These can be remembered by the mnemonic **“I Should Check Before Doing Crass Prescribing”**.

The prescriber / referring clinician

- Has the patient been adequately counselled ?
- Is the given target INR & duration in keeping with the given reason for anticoagulation ?
- Has the patient got the correct tablets ?

In theory the above are the responsibility of the prescriber and should not require consideration by the doser – in practice however.....

Practical considerations 3

Communication with patient (and prescriber)

Particularly important with new patients – clear and concise information / counselling – keep it simple !

Target INR and duration of treatment may be inappropriate or incorrect – check and discuss with referrer or relevant specialist if in doubt.

Ensure the patient fully understands the local system by which they are being managed.

Patients

Numerous patient associated factors will affect / influence the INR:

- Capacity to comprehend warfarin therapy
- Misconceptions and pre-conceived ideas
- Social factors
- Concurrent medication / medication changes
- Diet
- Alcohol
- Changes to general health
- Compliance / adherence and “DNA”

Patients – capacity to comprehend warfarin therapy

- Majority of patients are elderly - mean age 71 years. (Dawn benchmarking data)
- May have pre-conceived ideas / misconceptions
- Need to be carefully assessed before starting and continuously thereafter – things change !
- Use of carers / family
- Use of pre-prepared daily dose packs
- Dose - tablets? mg? single or multiple strength tablets? halving tablets?

Patients – social factors

- Work commitments
- Family support
- Living alone
- Nursing / residential care homes
- Contactability

Patients – concurrent medication / diet / alcohol

- Patients often on multiple medications - 32 million Americans are taking three or more medications daily ! (AHA data)
- Almost any drug can interact with oral anticoagulants.
- Be aware of interactions but in everyday practice most significant drug induced INR changes involve only a few drugs.
- BNF – appendix 1
- Diet
- Alcohol

Patients – changes to general health

Acute transient or chronic / progressive changes ?

- Liver disease
- Gastrointestinal changes
- Cardiac failure
- Infections
- Malignancy / metastatic disease
- Hearing / sight / speech

Patients – compliance / adherence

Unfortunately they aren't !

▼	Fri 25/09/2009	2.5	14.14	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	2 wk	1	
					4	5	5	5	4	5	5			
					WARFARIN 3mg (BLUE TABLETS)									
▼	Fri 04/09/2009	0.9	14.14	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	2 wk	1	
					4	5	5	5	4	5	5			
					WARFARIN 3mg (BLUE TABLETS)									
▼	Mon 10/08/2009	1.5	14.14	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	2 wk		
					4	5	5	5	4	5	5			
					WARFARIN 3mg (BLUE TABLETS)									
	Mon 27/07/2009	2.0	14.14	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	2 wk	2	
					4	5	5	5	4	5	5			
					WARFARIN 3mg (BLUE TABLETS)									
	Fri 03/07/2009	2.2	14.14	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	2 wk	1	
					4	5	5	5	4	5	5			
					WARFARIN 3mg (BLUE TABLETS)									
▼	Fri 12/06/2009	1.4	14.14	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	12 d	1	
					4	5	5	5	4	5	5			
					WARFARIN 3mg (BLUE TABLETS)									
▼	Mon 11/05/2009	1.4	13.71	d	Mon	Tue	Wed	Thu	Fri	Sat	Sun	3 wk	1	
					4	5	4	5	4	5	5			

Patients – compliance / adherence

And many are similar to this

Mon 12/04/2010	3.4	2.79	d	1	1	1	1	1	1	1/2	1	2 wk	
				WARFARIN 3mg (BLUE TABLETS)									
▼ Mon 15/03/2010	2.8	3.00	d	1	1	1	1	1	1	1	1	4 wk	
				WARFARIN 3mg (BLUE TABLETS)									
▼ Mon 01/03/2010	1.5	3.00	d	1	1	1	1	1	1	1	1	2 wk	
				WARFARIN 3mg (BLUE TABLETS)									
Mon 15/02/2010	1.6	3.21	d	1	1	1	1	1	1	1/2	1	2 wk	
				WARFARIN 3mg (BLUE TABLETS)									
Mon 01/02/2010	1.6	3.00	d	1	1	1	1	1	1	1	1	2 wk	
				WARFARIN 3mg (BLUE TABLETS)									
Mon 04/01/2010	1.9	3.00	d	1	1	1	1	1	1	1	1	4 wk	
				WARFARIN 3mg (BLUE TABLETS)									
▼ Mon 07/12/2009	2.4	3.00	d	1	1	1	1	1	1	1	1	4 wk	
				WARFARIN 3mg (BLUE TABLETS)									
▼ Mon 23/11/2009	1.3	3.00	d	1	1	1	1	1	1	1	1	2 wk	
				WARFARIN 3mg (BLUE TABLETS)									
▼ Mon 26/10/2009	2.7	3.00	d	1	1	1	1	1	1	1	1	4 wk	
				WARFARIN 3mg (BLUE TABLETS)									
▼ Mon 12/10/2009	1.3	3.00	d	1	1	1	1	1	1	1	1	2 wk	
				WARFARIN 3mg (BLUE TABLETS)									

Patients – compliance / adherence

- 22 percent of Americans take less of the medication than is prescribed on the label.
- 12 percent of Americans don't collect their prescription at all.
- 12 percent of Americans don't take medication at all after they collect their prescription.
- The No.1 problem in treating illness today is patients' failure to take prescription medications correctly, regardless of patient age.
- 10 percent of all hospital admissions are the result of patients failing to take prescription medications correctly.
- 23 percent of all nursing home admissions are due to patients failing to take prescription medications accurately.
- At any given time, regardless of age group, up to 59 percent of those on five or more medications are taking them improperly.
- The average length of stay in hospitals due to medication non-compliance is 4.2 days.
- More than half of all Americans with chronic diseases don't follow their physician's medication and lifestyle guidance.
- Two-thirds of all Americans fail to take any or all of their prescription medicines.

Patients – compliance / adherence

Medication non-compliance

[E.C Wright, The Lancet, Volume 342, Issue 8876, Pages 909 - 913, 9 October 1993](#)

“The compliance of patients with medication prescribed for them is a challenge. It seems that one-third of patients comply adequately, one-third more-or-less, and one-third are non-compliant, so that **compliance rates hover around 50%.**”

Patients – compliance / adherence

The Real Drug Problem: Forgetting to Take Them - Good patient compliance and adherence means taking the right drugs, on time and in the proper doses

(WSJ - Amy Dockser Marcus article)

Poor compliance is a major factor in unstable outpatient control of anticoagulant therapy.

Author: Kumar, S : Haigh, J R : Rhodes, L E : Peaker, S : Davies, J A : Roberts, B E : Feely, M P
Citation:Thromb-Haemost. 1989 Sep 29; 62(2): 729-32

Patients – compliance / adherence

Risk factors for non-adherence to warfarin: results from the IN-RANGE study.

Platt AB et al. Department of Medicine, University of Pennsylvania School of Medicine, PA, USA.

CONCLUSIONS: “Poor adherence to warfarin is common”

“25% of patients say they regularly miss a dose of warfarin”

Anticoagulation Europe questionnaire data

Patients – compliance / adherence

Effect of warfarin non-adherence on control of the International Normalized Ratio.

AD Waterman, PE Milligan, L Bayer, GA Banet, SK Gatchel, and BF Gage. American Journal of Health-System Pharmacy, Vol 61, Issue 12, 1258-1264

CONCLUSION: “Warfarin non-adherence was the most common cause of explainable aberrant INRs in patients taking warfarin”

Patients – compliance / adherence

- Average % time in range = 69.4 days
(Dawn benchmarking data)
- Non-compliance estimates 30%ish
- Coincidence ?

Practical considerations 4

Does the patient have any misconceptions or “myths” surrounding warfarin ?

Patients circumstances change – social circumstances, mental / physical health - is warfarin still appropriate ? – communicate with the patient, prescriber and GP.

Do “dosers” attach enough importance to poor or variable compliance ?

Practical considerations 4

Does the compliance of some patients improve as a blood test approaches ?

Use notes/alerts in Dawn – eg “? Poor / variable compliance – be cautious of increasing dose”

The proven therapeutic benefits of warfarin only apply when the INR is stable and in range

Consider alternatives eg LMWH, aspirin – are non-complaint patients a group to consider for treatment with new generation direct thrombin / anti Xa inhibitors ?

Self testing (and possible self dosing) for selected patients

Samplers

Venous and capillary

- A good sample (venous or capillary) is crucial - pay attention to technique.
- Biochemical changes that affect the INR begin as soon as blood vessels are damaged – sample procurement induces clotting !
- Venous – volume, mixing, storage, transport, lipaemia, haemolysis, icterus.
- Difficult venepuncture - “I managed to get two small samples, which I mixed together in one tube so the volume was OK” !
- “Clerical” errors – correct patient identification

Practical considerations 5

A poor sample will give a poor INR !

Don't underestimate the importance of sample quality.

Consider sample quality if spurious inexplicable INR. Repeat - urgently if necessary.

Testers – getting the INR right

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

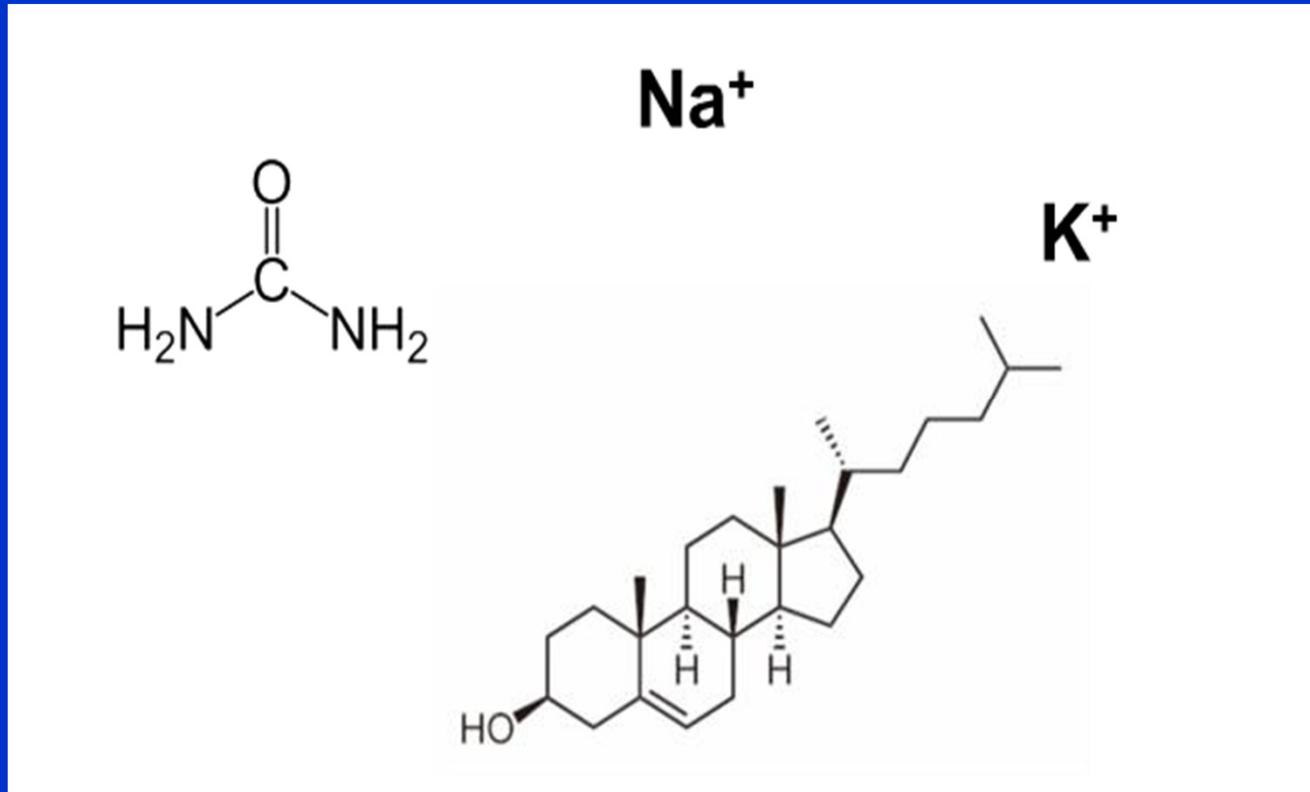
Where:

PT	= Patients Prothrombin Time in seconds
LMNPT	= Local geometric mean Prothrombin Time in seconds
ISI	= International Sensitivity Index of local reagent / system

- Introduced by WHO in 1983
- Simple concept - The same sample should give the same INR irrespective of method and reagent used to estimate the Prothrombin Time - but a lot can go wrong

Testers – getting the INR right

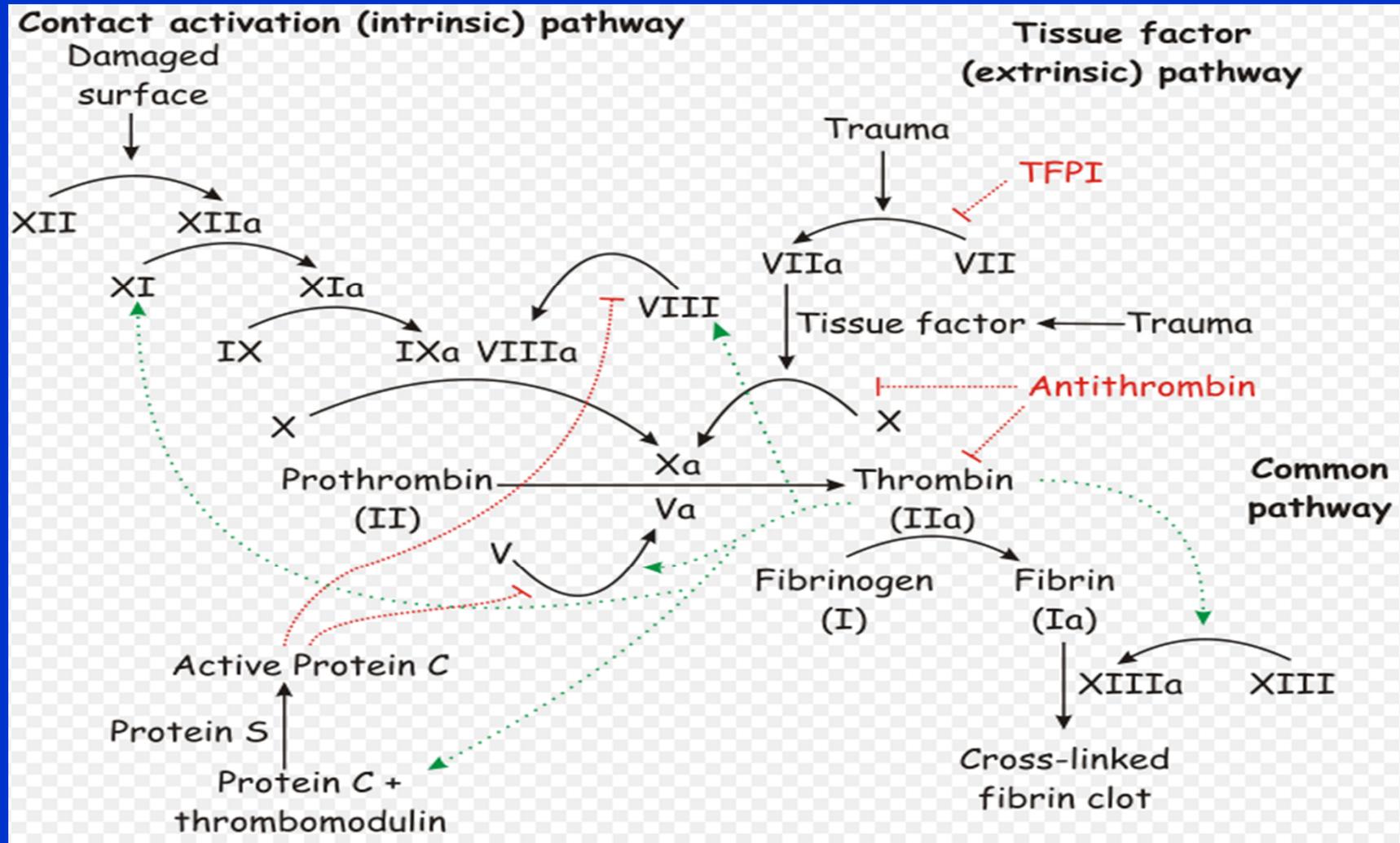
Clinical chemistry



Testers – getting the INR right

Haematology

Testers – getting the INR right



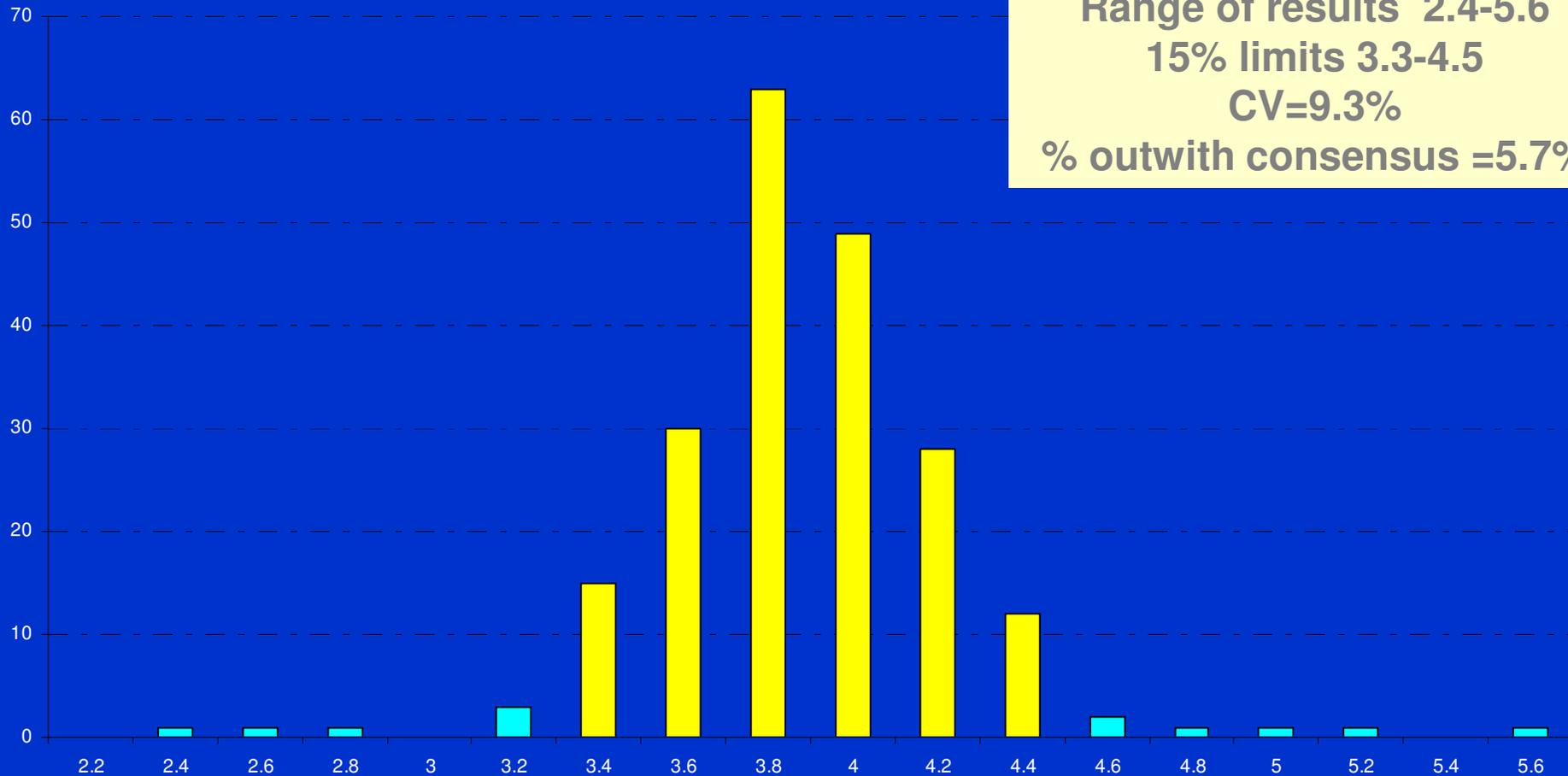
Testers – getting the INR right

What can (and does) go wrong ?

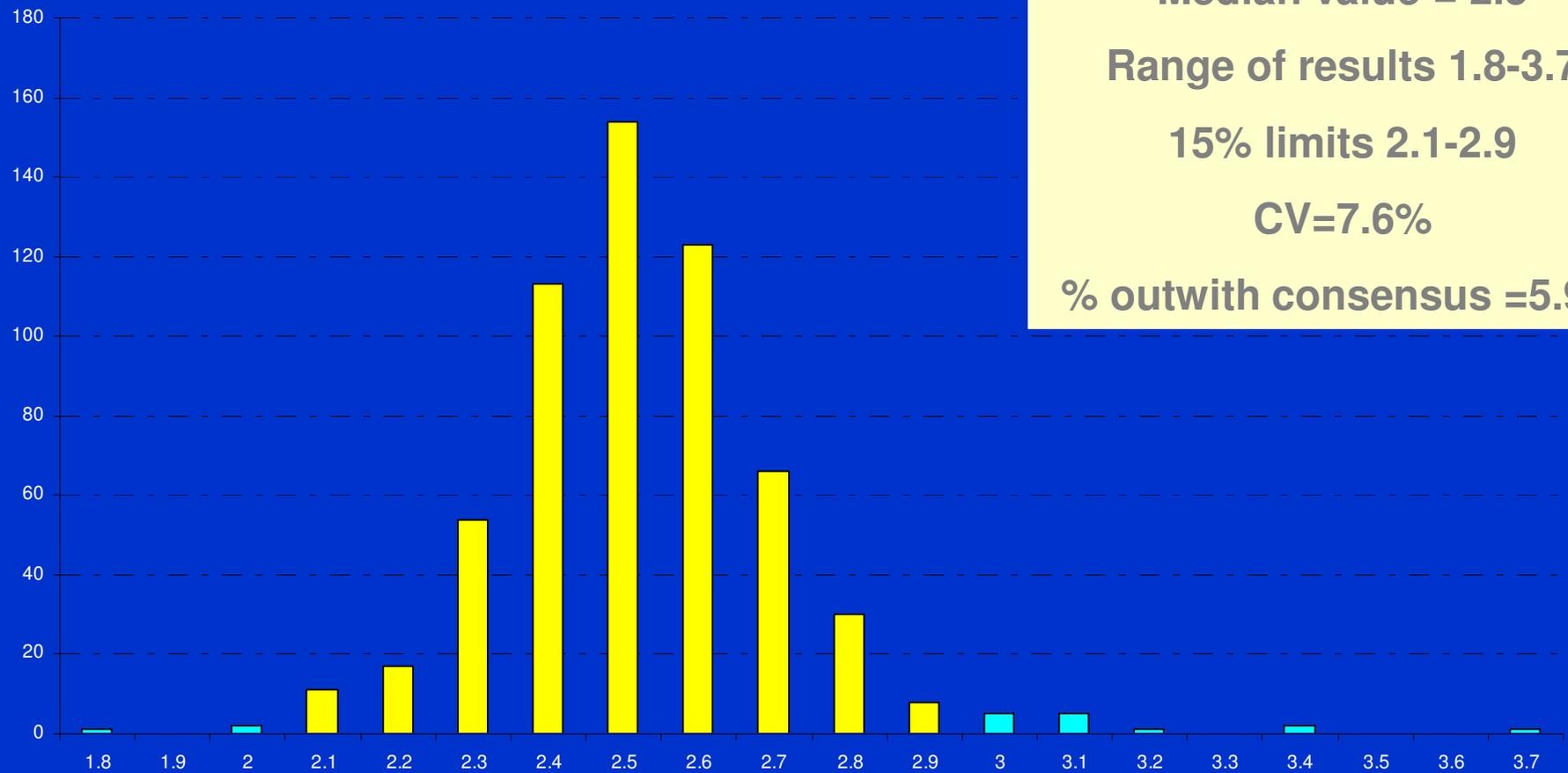
- Incorrect Prothrombin Time – machine or reagent problem.
- Operator issues
- Incorrect ISI (or POCT conversion algorithm)
- Incorrect MNPT
- Presence of antiphospholipid antibodies
- Poor sensitivity & increased imprecision at INR of >5.0

Testers – getting the INR right - Laboratory INR results for Innovin S150 (UK NEQAS data)

Median value=3.9
Range of results 2.4-5.6
15% limits 3.3-4.5
CV=9.3%
% outwith consensus =5.7%



Testers getting the INR right - POC EQA results for sample NP05:05 for CUC S devices. (UK NEQAS data)



Median value = 2.5

Range of results 1.8-3.7

15% limits 2.1-2.9

CV=7.6%

% outwith consensus =5.9%

Testers – getting the INR right (UK NEQAS data)

Reagent	Total Users	Total Median
Biomerieux Simplastin Excel S	1	3.99
Biomerieux Simplastin HTF (non-MDA)	5	4.30
Dade-Behring Innovin	239	4.60
Dade-Behring Thromboplastin IS	2	4.65
Dade-Behring Thromborel S	47	3.82
Diagen Ca Thromboplastin	4	4.13
Grifols DG-PT	12	3.26
Helena Manchester R	22	3.50
Helena Thromboplastin LI	3	3.52
IL HemosIL PT-FIB HS	2	4.14
IL HemosIL PT-FIB	1	3.98
IL HemosIL PT-FIB HS Plus	85	3.60
IL HemosIL PT-Fib recombinant	3	3.80
IL Hemosil PT-Rec (local cal)	1	3.74
IL HemosIL Recombiplastin	46	3.90
IL HemosIL Recombiplastin 2G	191	3.95
MDA Simplastin HTF	38	4.60
Nycomed Nycoplastin	1	4.07
Nycotest PT	1	3.92
Pacific Hemostasis Tpn- DS	2	3.85
STA Neoplastin CI	5	3.90
STA Neoplastin CI Plus	26	4.08
STA Neoplastine R	44	4.98
STA-SPA 50/+	1	4.29
Stago Neoplastine CI Plus	6	3.95
Sysmex PT [CA]	1	3.78
Technoplastin	1	3.00
Thrombosis Ref. Centre PT reagent	1	4.10
Triniclot PT Excel S	12	4.03
Overall	818	4.11

Testers – getting the INR right (UK NEQAS data)

Reagent	Total Users	Total Median
Biomerieux Simplastin Excel	1	3.10
Biomerieux Simplastin Excel S	2	3.03
Biomerieux Simplastin HTF (non-MDA)	5	3.30
Dade-Behring Innovin	246	3.00
Dade-Behring Thromboplastin IS	1	2.99
Dade-Behring Thromborel S	54	3.11
Diagen Ca Thromboplastin	4	2.99
Diagon, Hungary	1	2.70
Grifols DG-PT	10	2.59
Helena Manchester R	23	2.88
Helena Thromboplastin LI	3	2.89
IL HemosIL PT-FIB HS	13	2.73
IL HemosIL PT-FIB	2	2.67
IL HemosIL PT-FIB HS Plus	96	2.73
IL HemosIL PT-Fib recombinant	9	3.17
IL Hemosil PT-Rec (local cal)	1	2.99
IL HemosIL Recombiplastin	61	2.82
IL HemosIL Recombiplastin 2G	164	2.90
Locally produced	1	3.41
MDA Simplastin Excel S	1	2.20
MDA Simplastin HTF	45	3.30
Not Stated	2	2.77
Nycomed Nycoplastin	1	2.83
Nycotest PT	1	2.90
Pacific Hemostasis Tpn- DS	2	3.00
Renamplastin	1	2.66
STA Neoplastin CI	6	2.80
STA Neoplastin CI Plus	25	2.93
STA Neoplastine R	47	3.28
STA-SPA 50/+	1	2.98
Stago Neoplastine CI Plus	4	2.82
Sysmex PT [CA]	2	2.81
Thrombosis Ref. Centre PT reagent	1	3.05
Triniclot PT Excel S	4	3.01
Overall	853	2.97

Testers – getting the INR right

Minimising the errors

- Training and education
- External quality assessment schemes
- Internal quality control
- POCT - can local laboratory help / advise
- Follow manufacturers instructions
- Use recognised and established guidelines

Practical considerations 6

Consider the INR result in context of its analytical imprecision.

Does your method show a consistent bias on EQA ?

The INR is the best we have but it is far from perfect.

Dosers – who are we

- Nurses
- GP
- Consultant haematologists
- Pharmacists
- Laboratory scientists
- CDSS
 - Dawn
 - INR Star
 - RAT
 - Others

Dosers – concerns and pitfalls

- Eclectic mix with different educational and academic backgrounds.
- Processes and procedures tend to be poorly standardised
- Do different groups place different emphasis on different aspects of management ?
- Rapid staff turnover – lack of continuity
- Inadequate or inappropriate training – “Chinese Whispers”

Dosers – are we any good at it ?

- Systematic or specific personnel problems may only come to light when there is a significant incident
- Little in the form of internal QC and external QA
- Evidence from Neqas “dosing” exercises

Dosers – are we any good at it ?

Evidence from Neqas “dosing” exercises

A 36 year old woman who is on warfarin for a post-partum DVT. She is on no other medications. She was discharged from hospital 6 weeks ago on 6mg warfarin daily.

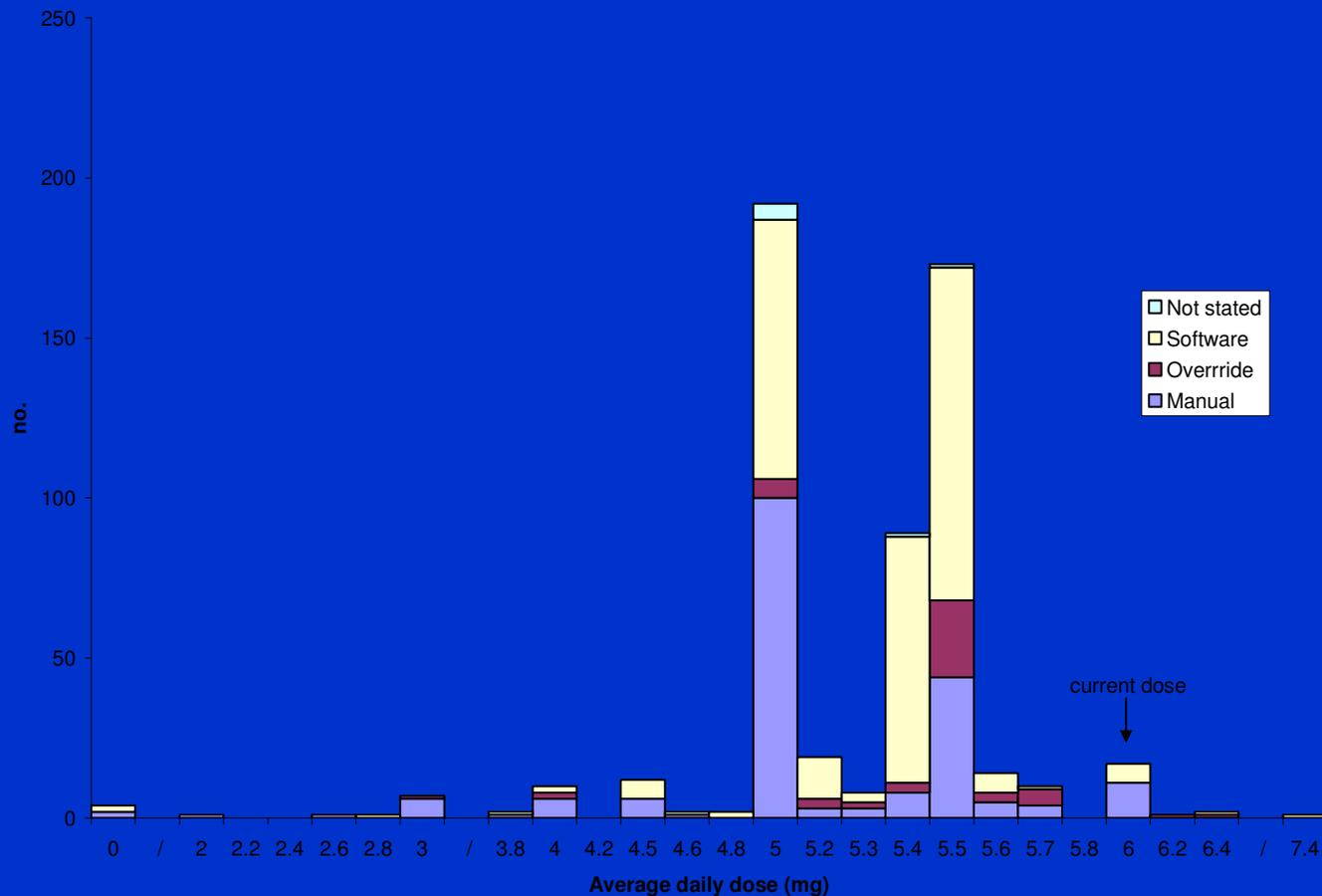
INR results:

35 days ago	2.5	Dose	6mg/d
28 days ago	2.7	Dose	6mg/d
14 days ago	2.4	Dose	6mg/d
Today	3.9		????

(UK NEQAS data)

Dosers – are we any good at it ?

Recommended Dose: 682 centres made a dose recommendation for this patient. Of these, 279 returned a manually determined dose, 324 reported a dose determined by a software system, and 68 reported that they overrode the recommendation made by their CDSS.



(UK NEQAS data)

Dosers – are we any good at it ?

Dose Recommendation	No. of centres
2mg for 1 day then 6mg	1
3mg today then 5.79mg	1
3mg day 1, 5mg for 2days, 6mg for 5days	1
4.5mg but 6mg sun and wed	1
4.5mg 2/7, 6mg 5/7	1
4.5mg then 6mg for 4 days, then 4.5mg for 2 days	1
6mg <u>mon</u> to <u>thurs</u> , 8mg <u>fri</u> to sun	1
miss 1 day then 4mg daily	1
miss 1 day then 5.25mg daily	1
miss 2 days	1
miss 2 days then 4mg daily	1
miss 2 days then 6mg daily	1
miss day 1 then 2, 6, 6, 6	1
miss one day then 5mg but 4mg sun and fri	1
Miss one day then 5mg for 3 days then 4mg for 1	1
miss one day then 5mg for 3 days then 6mg for 3	1
miss one day then 5mg, 6mg <u>fri</u> , <u>sat</u> , <u>sun</u>	1
miss one day then 6mg for 3 then 7 mg for 3	1
miss one dose then 5mg for 4days, 6mg for 3days	1
miss one dose then 6mg during week and 5mg during weekend	1
miss one then 6mg for 5 days then 5mg for 2	1
none for 3 days	1
omit 1 then 5mg <u>mon-fri</u> , 6mg after	1
omit 1 then 5mg daily	1
omit 1 then 6mg daily but 5mg wed	1
omit 1 day then 6.5mg daily	1
omit one dose, 5mg for 2days, 6mg for 4days	1
omit one dose, then 5mg <u>mon</u> to <u>fri</u> , 6mg sat and sun	1
stop 2/7 then 5,6,6	1
miss one day then 6mg for 3 then 5mg for 3	3
miss 2 days then 5mg daily	8
miss 1 day then 5.5mg daily	21
miss 1 day then 6mg daily	22
miss 1 day then 5mg daily	27

Dosers – how can we improve ?

- Appropriate training, competency assessment and supervision by individuals who are competent to deliver it
- External training courses / competency assessments – some “web” based (eg BMJ e-learning)
- National and international guidelines. (BCSH, ACCP, NPSA)
- Have a consistency of approach at local level - SOPs
- Use locally devised internal QC dosing exercises
- National External QA schemes – NEQAS
- International QA collaboration (NOKLUS, EQALM)
- Effective incident reporting system
- Use CDSS
- Audits

Dosers – Evidence for using CDSS

Effects of Computerized Clinical Decision Support Systems on Practitioner Performance and Patient Outcomes - A Systematic Review

[Amit X. Garg, MD; Neill K. J. Adhikari, MD; Heather McDonald, MSc; M. Patricia Rosas-Arellano, MD, PhD; P. J. Devereaux, MD; Joseph Bevene, PhD; Justina Sam, BHSc; R. Brian Haynes, MD, PhD](#) - JAMA. 2005;293:1223-1238

CONCLUSIONS - Many CDSS improve practitioner performance. To date, the effects on patient outcomes remain understudied and, when studied, inconsistent.

Evaluation of computerized decision support for oral anticoagulation management based in primary care.

[D A Fitzmaurice, F D Hobbs, E T Murray, C P Bradley, and R Holder, Department of General Practice, University of Birmingham](#)

CONCLUSION: Computerized DSS enables the safe and effective transfer of anticoagulation management from hospital to primary care and may result in improved patient outcome in terms of the level of control, frequency of review and general acceptability.

Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation.

[Poller L, Shiach CR, MacCallum PK, Johansen AM, Münster AM, Magalhães A, Jespersen J. Department of Pathological Sciences, University of Manchester, UK.](#)

INTERPRETATION: The computer program gave better INR control than the experienced medical staff and at least similar standards to the specialised centres should be generally available. Clinical outcome and cost effectiveness remain to be assessed.

Practical considerations 7

Does the dose really need to be changed ? – try to keep dose changes to a minimum.

By how much does the dose need to be changed ? - be guided by CDSS but there is not a defined absolute amount by which to increase or decrease a dose.

Leave as long as is reasonably possible between INR tests.

There is more being competent than satisfactorily completing a series of competency assessments.

Get advice or second opinion from more experienced colleague.

CONCLUSION

“Effective and safe management of patients on oral anticoagulants is a subjective art that is underpinned by good science and dependent on well trained, competent and experienced individuals following standardised procedures”