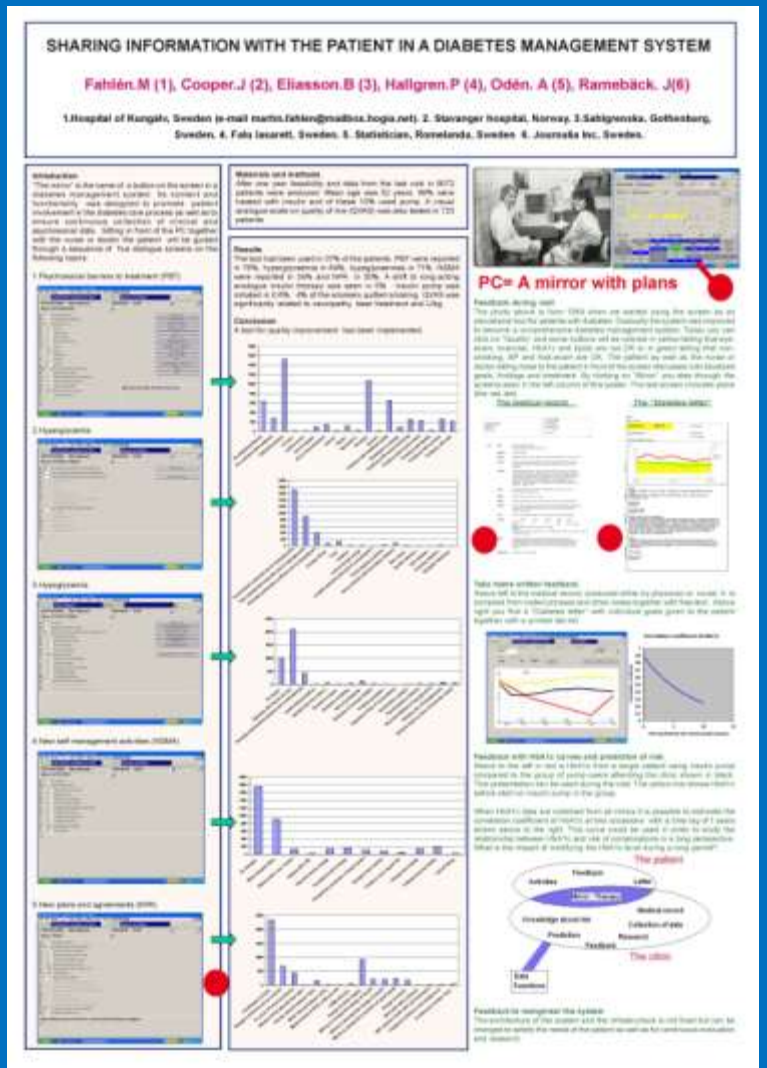
'AVK-brevet': A warfarin dose prediction algorithm in clinical use.

Martin Fahlén 2012-11-14

1984 - Diabetes care

Is it possible to use this <u>model</u> of chronic disease for other problems ?

Feedback loop and timing

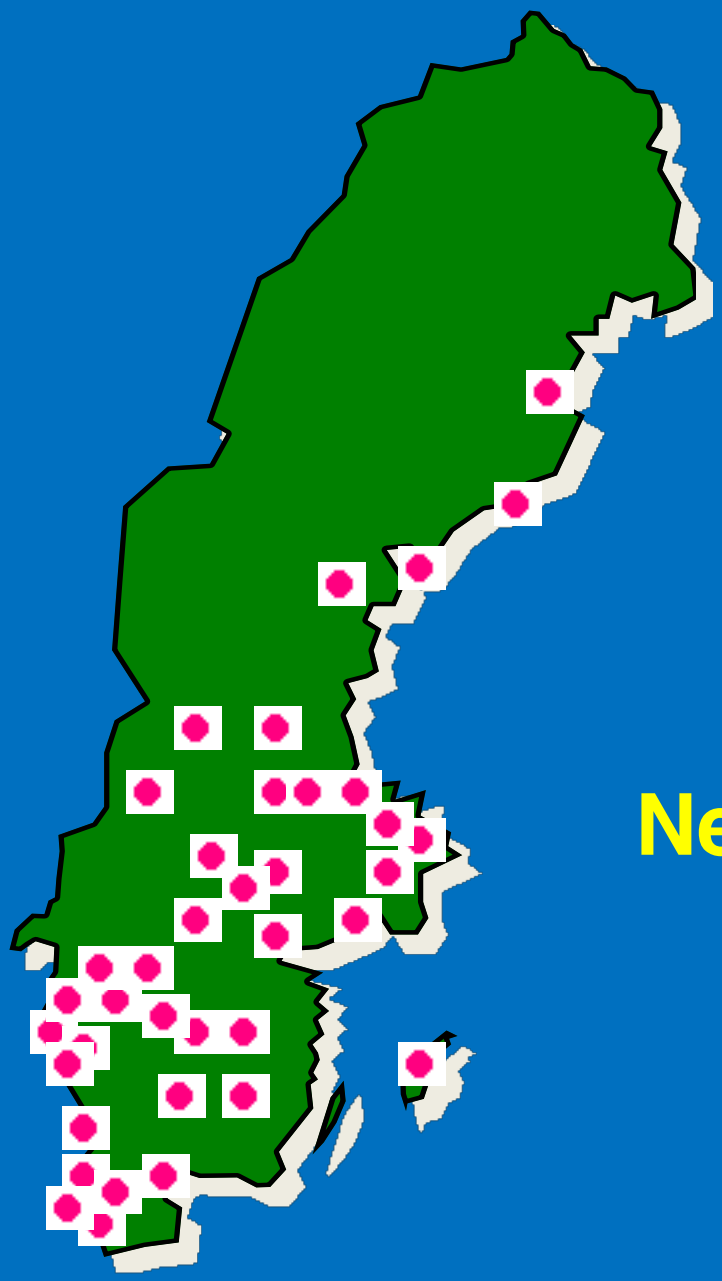


SHARING INFORMATION WITH THE PATIENT IN A DIABETES MANAGEMENT SYSTEM

Fahlén.M (1), Cooper.J (2), Eliasson.B (3), Hallgren.P (4), Odén. A (5), Ramebäck. J(6)

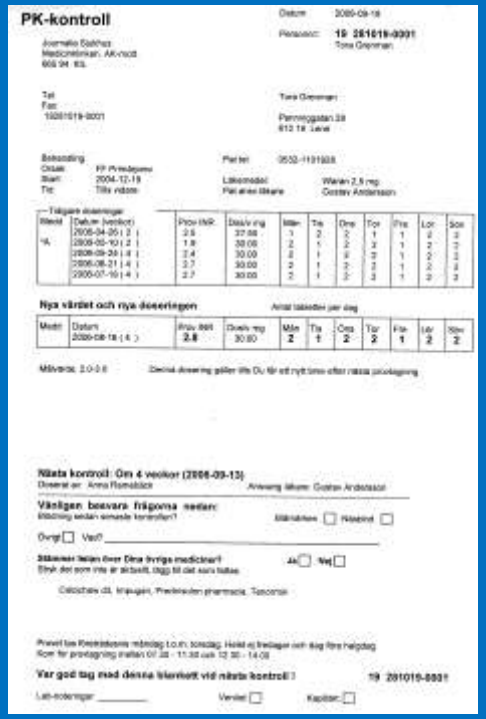
1.Hospital of Kungälv, Sweden (e-mail martin.fahlen@mailbox.hogia.net). 2. Stavanger hospital, Norway. 3.Sahlgrenska, Gothenburg, Sweden. 4. Folu lasarett, Sweden. 5. Statistician, Romelanda, Sweden. 6. Journalia Inc. Sweden.

PC= A mirror with plans



AVK and LMH

Network for Quality of Anticoagulation in Sweden 1984-


PK-kontroll

Nya värdet och nya doseringen

Nästa kontroll: Om 4 veckor (2008-09-13)

Var god ta med denna blankett vid nästa kontroll!

Development

Jan Ramebäck
Anna Ramebäck
Programmers

Education of nurses

Research

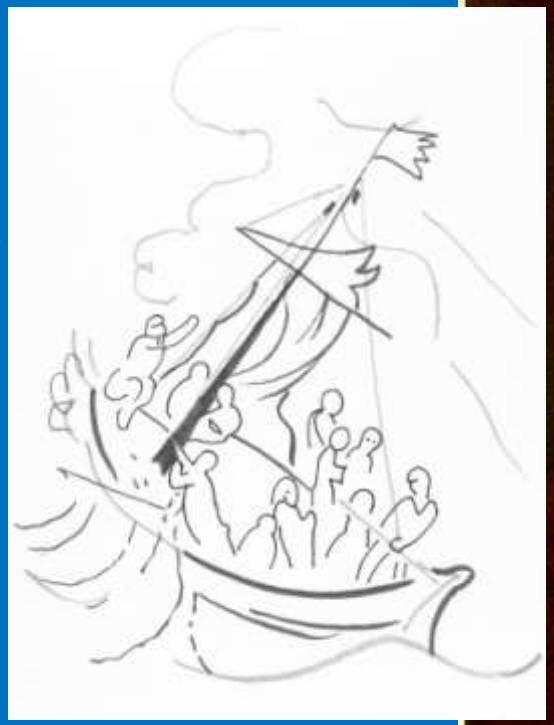
Anders Odén
Professor of biostatistics

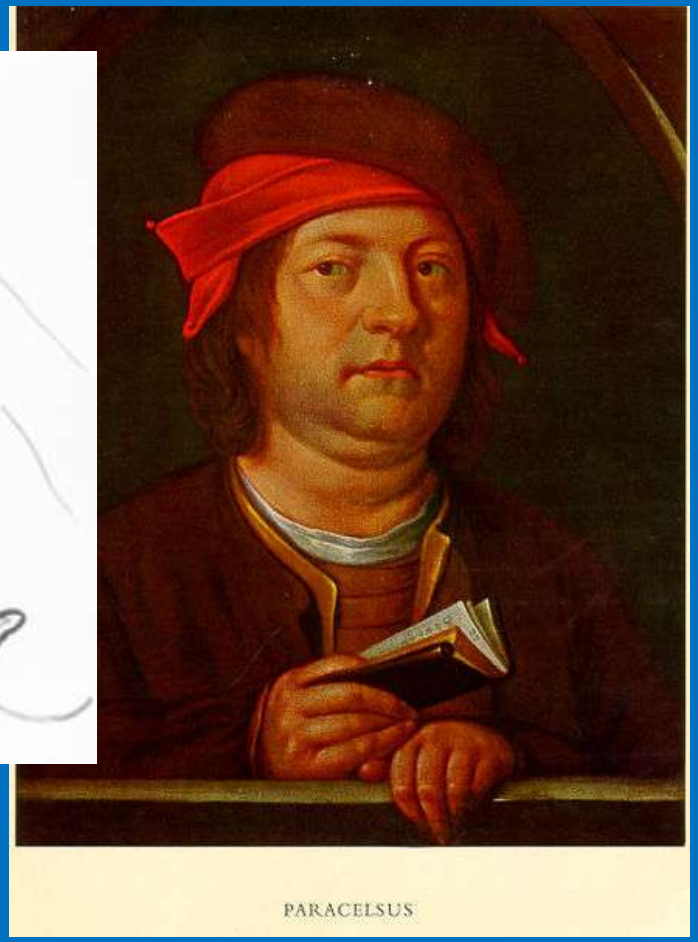
Warfarin toxcicity

Paracelsus
1493-1541

Physician

Rodenticide
Teratogen
Fetal mortality
Calcification
Osteoporosis
Skin necrosis
Bleeding
Infarction
…





The dose is the poison

Early aims and findings

Thrombosis Research 2012

1. Find best practices.
2. Standardize and computerize.
3. Individualize dosage but how?.
4. We need a predictor, but what and of what?.
5. What do we know about death?

BMJ 2002

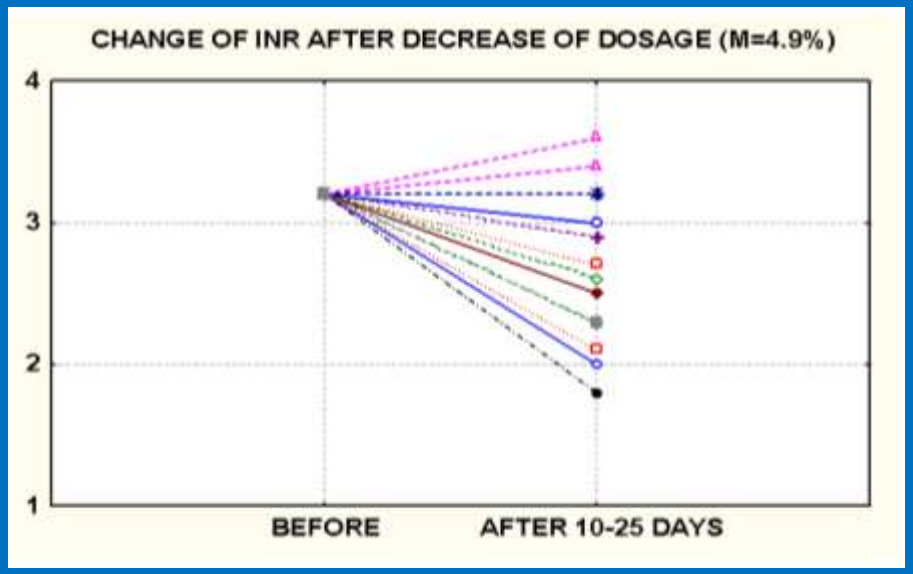
A primitive algorithm

Short perspective
Long perspective

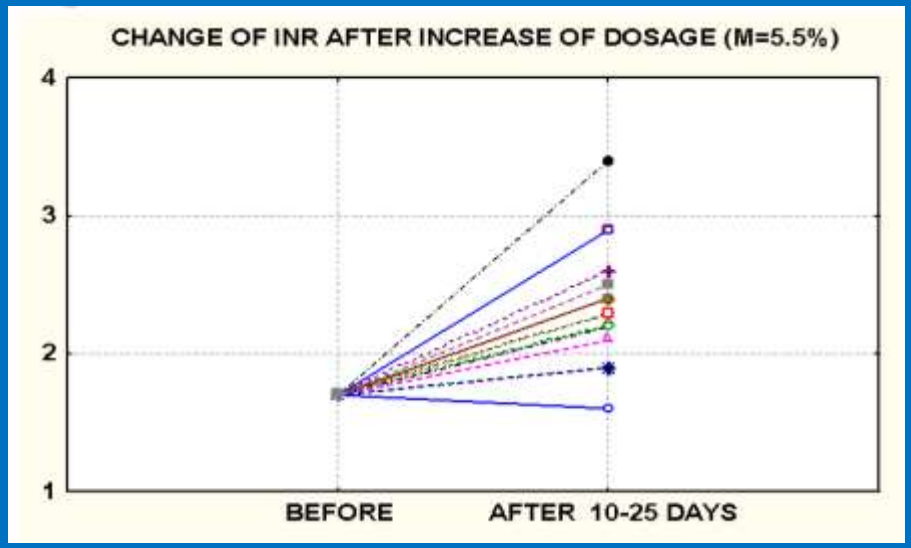
INR-Level
Dose

Change of dose
”Push-dose”
”Skip-day”

Decrease



Increase



Hamilton General Warfarin Dosing Nomogram
Target INR 2 - 3 (2.5 Mg tablets)

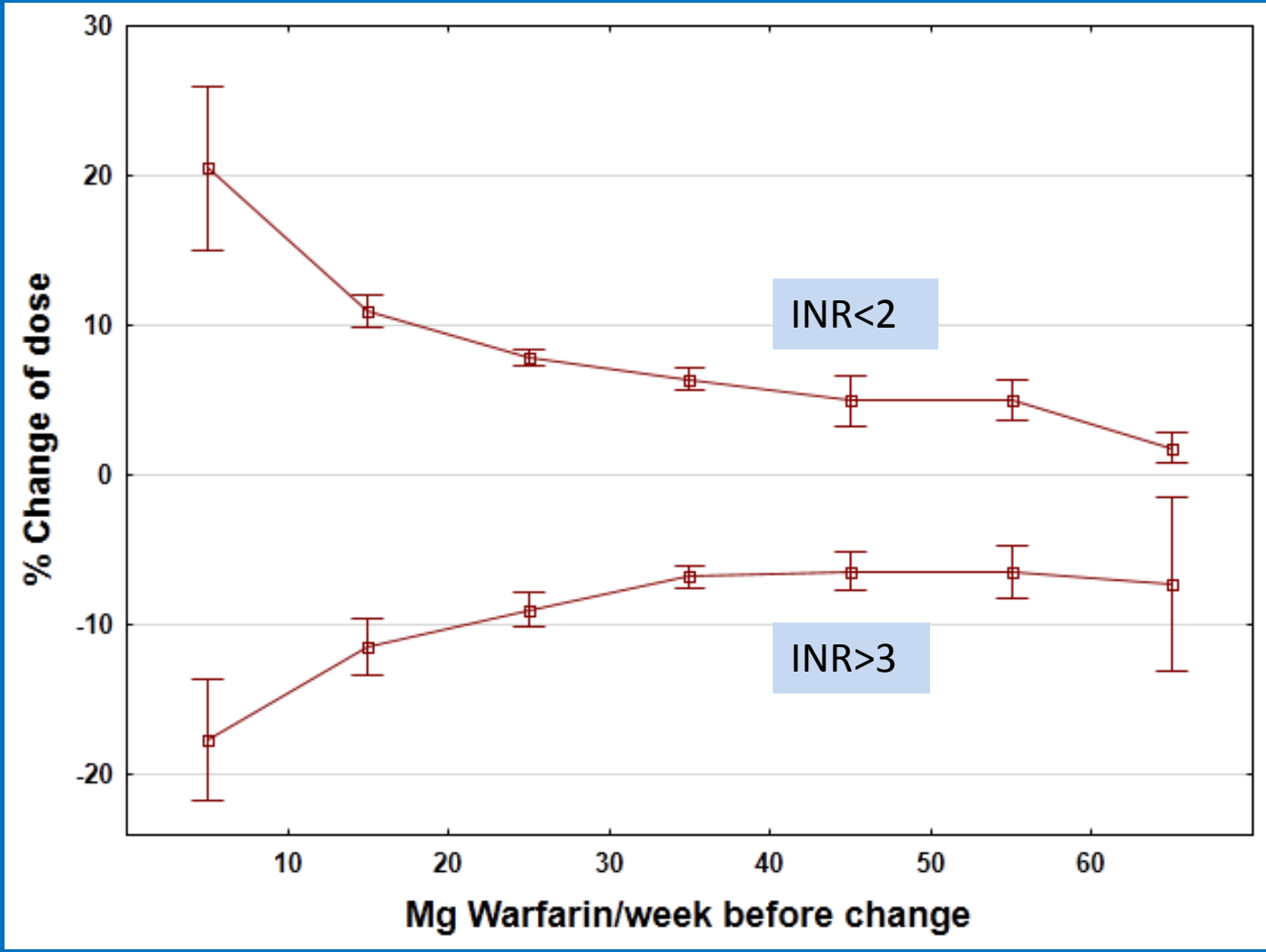
CURRENT WEEKLY DOSE			NEW WEEKLY DOSE (Pills)					NEW WEEKLY PILL SCHEDULE						
Mg	PILLS	INR	<=1.5	1.51-1.99	2.00-3.00	1st Visit 3.01-3.99	2nd Visit 3.01-3.99	MON	TUE	WED	THU	FRI	SAT	SUN
5.0	2		2.5	2	No Change		2	1/2		1/2		1/2		1/2
6.25	2.5		3	3	No Change		2.5	1/					1/2	1/2
7.5	3		3.5	3.5	No Change		2.5	1/				1/2	1/2	1/2
8.75	3.5		4	4	No Change		3	1/2	1/2	1/2	1/2	1/2	1/2	1/2
10.0	4		4.5	4.5	No Change		3.	1/2	1/2	1/2	1	1/2	1/2	1/2
11.25	4.5		5	5	No Change		4	1/2	1	1/2	1/2	1	1/2	1/2
12.5	5		6	5.5	No Change		4.5	1/2	1	1/2	1	1/2	1	1/2
13.75	5.5		6.5	6	No Change		5	1	1/2	1	1/2	1	1/2	1
15.0	6		7	6.5	No Change		5.5	1	1/2	1	1	1/2	1	1
16.25	6.5		7.5	7	No Change		6	1	1	1	1/2	1	1	1
17.5	7		8	7.5	No Change		6.5	1	1	1	1	1	1	1
18.75	7.5		8.5	8	No Change		7	1	1	1	1 1/2	1	1	1

12,5%

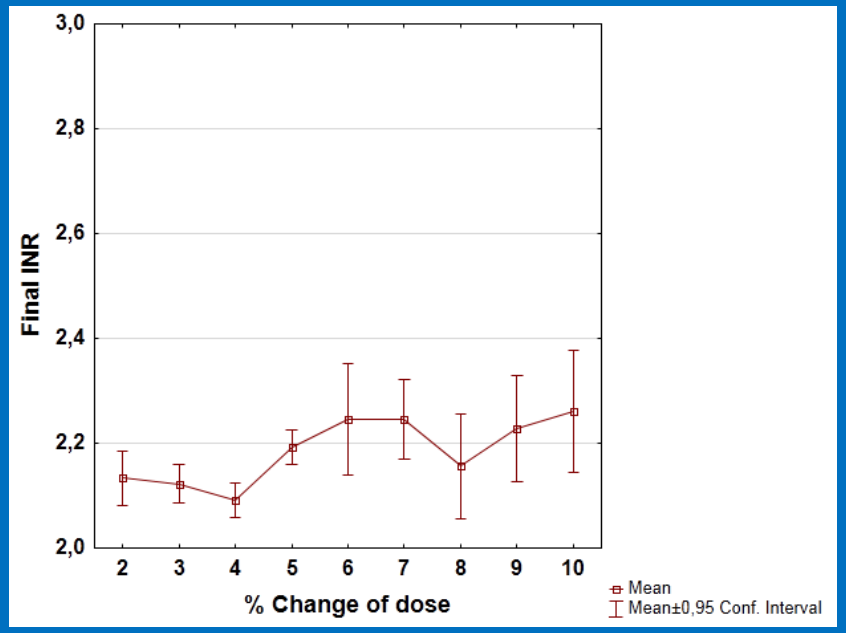
16.25	6.5		7.5	7	No Change	6		1	1	1	1/2	1	1	1
17.5	7		8	7.5	No Change	6.5		1	1	1	1	1	1	1
18.75	7.5		8.5	8	No Change	7		1	1	1	1 1/2	1	1	1
20.0	8		9	9	No Change	[illegible]		1	1	[illegible]	[illegible]	[illegible]	1	1
21.25	8.5		10	9.5	No Change	7.5		1	1 1/2	[illegible]	[illegible]	[illegible]	1/2	1
22.5	9		10.5	10	No Change	8		1	2	1	1	2	1	1
23.75	9.5		11	10.5	No Change	8.5		1 1/2	1	1 1/2	1 1/2	1	1 1/2	1 1/2
25.0	10		11.5	11	No Change	9		1	2	1	2	1	2	1
26.25	10.5		12	11.5	No Change	9.5		1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2
27.5	11		12.5	12	No Change	10		2	1	2	1	2	1	2
28.75	11.5		13	12.5	No Change	10.5		1 1/2	2	1 1/2	1 1/2	2	1 1/2	1 1/2
30.0	12		14	13	No Change	11		2	1	2	2	2	1	2
31.25	12.5		14.5	14	No Change	11.5		2	1 1/2	2	1 1/2	2	1 1/2	2
32.5	13.0		15	14.5	No Change	11.5		2	2	2	1	2	2	2
33.75	13.5		15.5	15	No Change	12		2	2	2	1 1/2	2	2	2
35.0	14.0		16	15.5	No Change	12.5		2	2	2	2	2	2	2

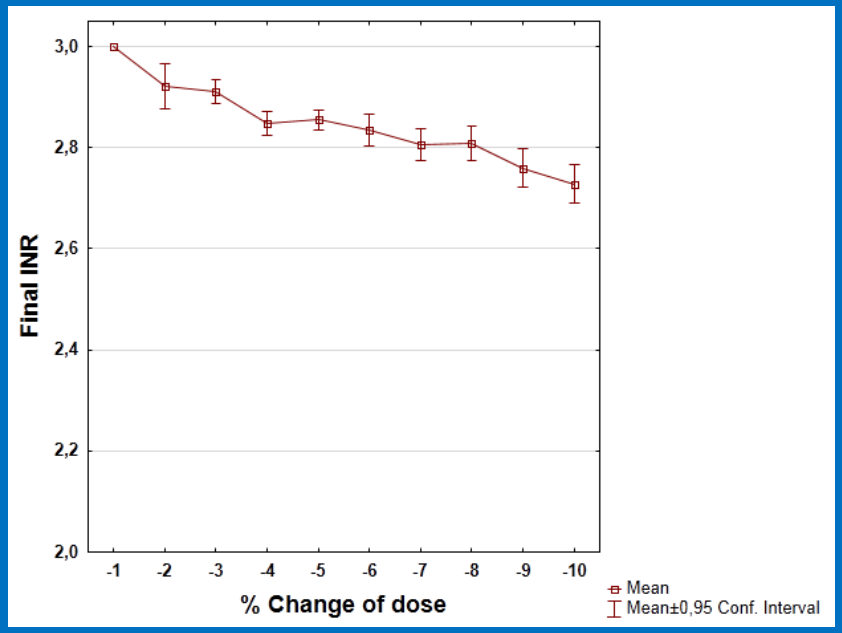
12,5%

Change of dose with 2,5 mg tablets. Final INR 2,3.



Underestimation of dosereduction

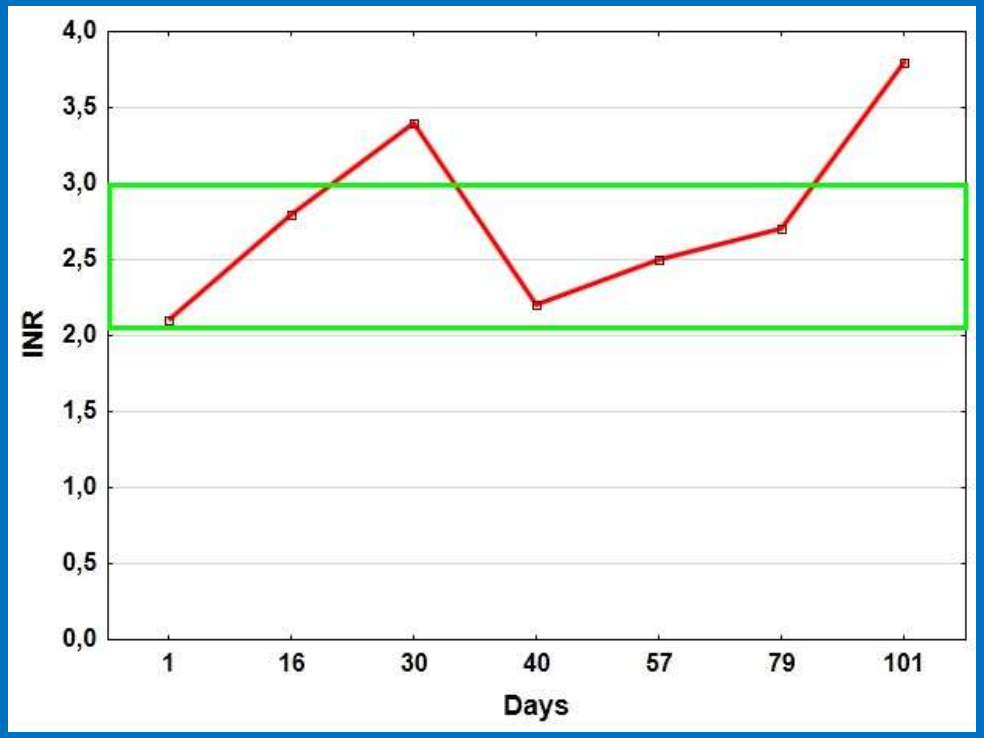




Increase

Decrease

Effort to decrease



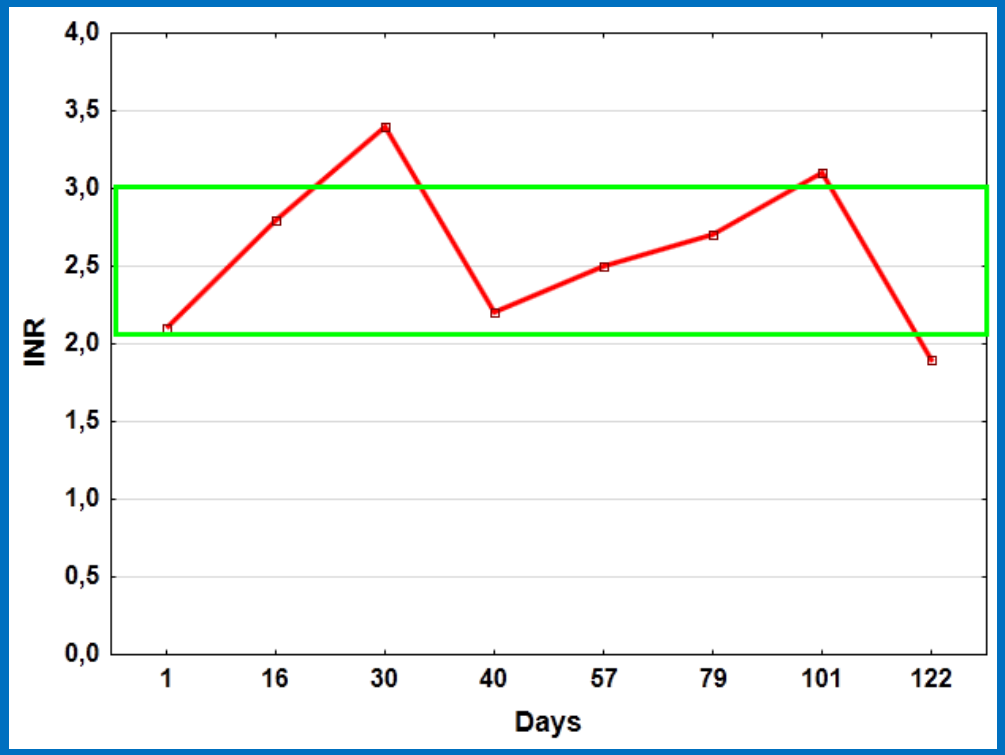
Decrease 10 % - Algorithm A
Death hazard: 0.0187

Decrease : 20% - Algorithm B
Death hazard 0.0161

Hazard ratio 1.16

A - Circulation October 2012 Van Spall et al
B - A preliminary algorithm from Journalia

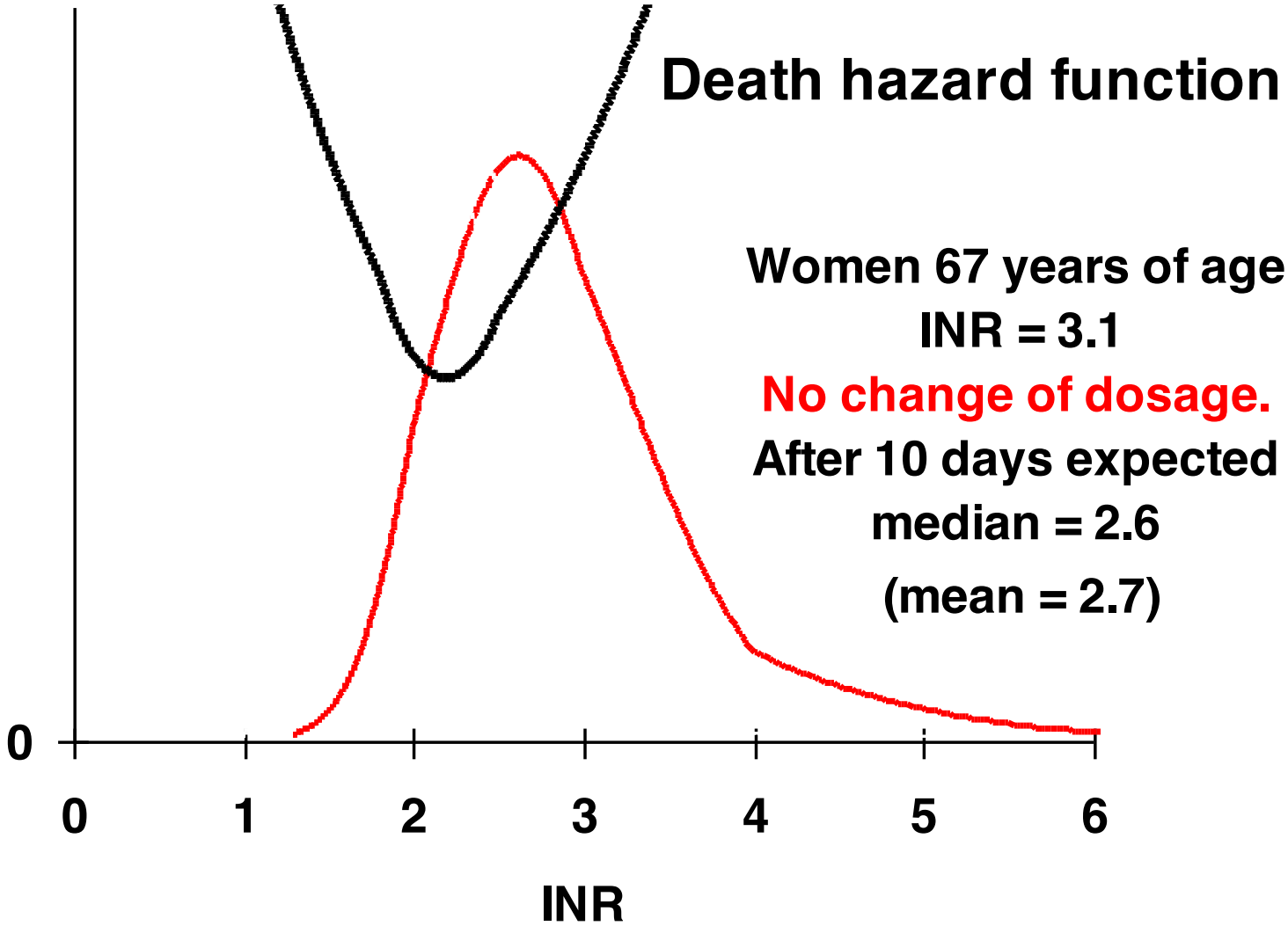
Effort to increase

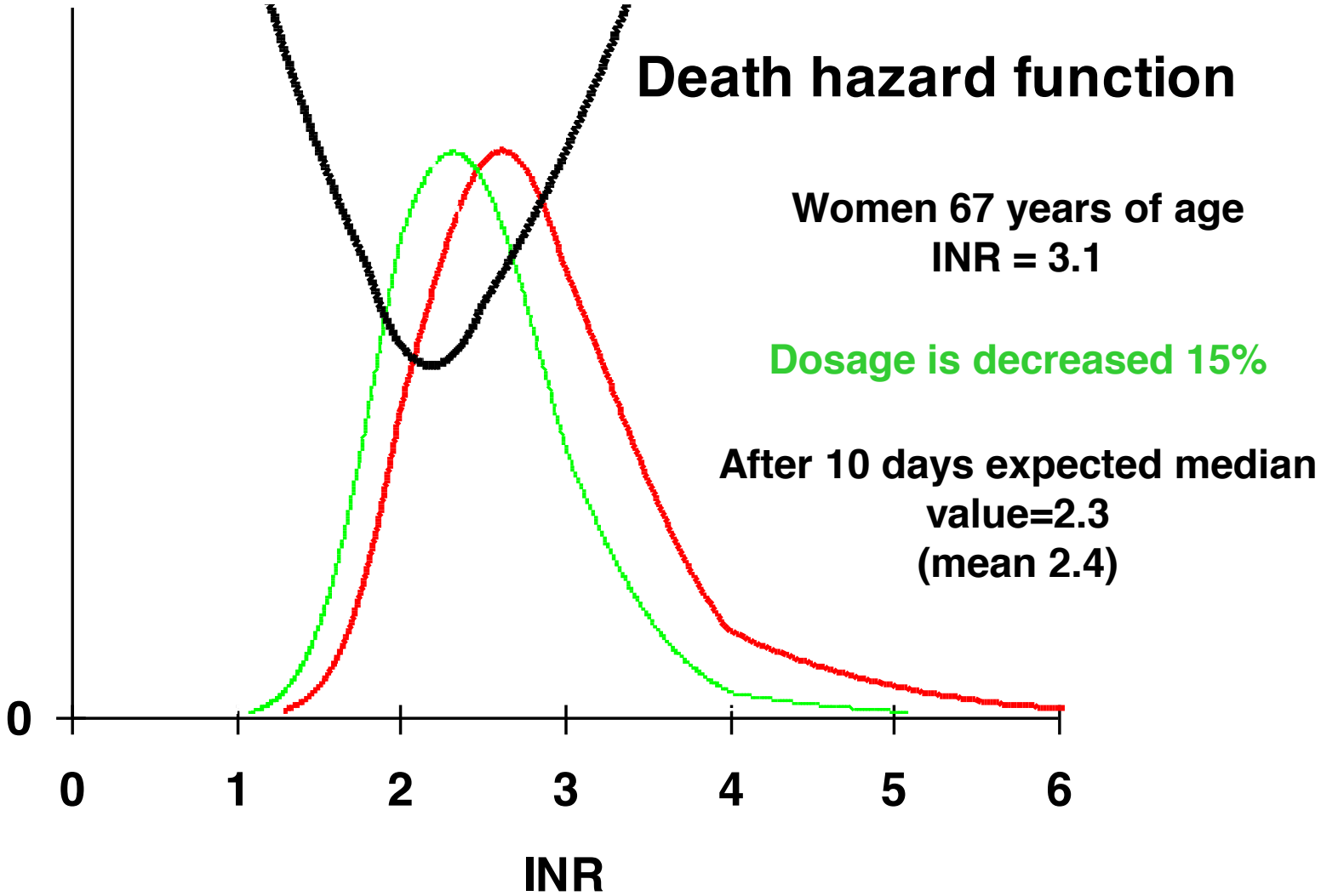


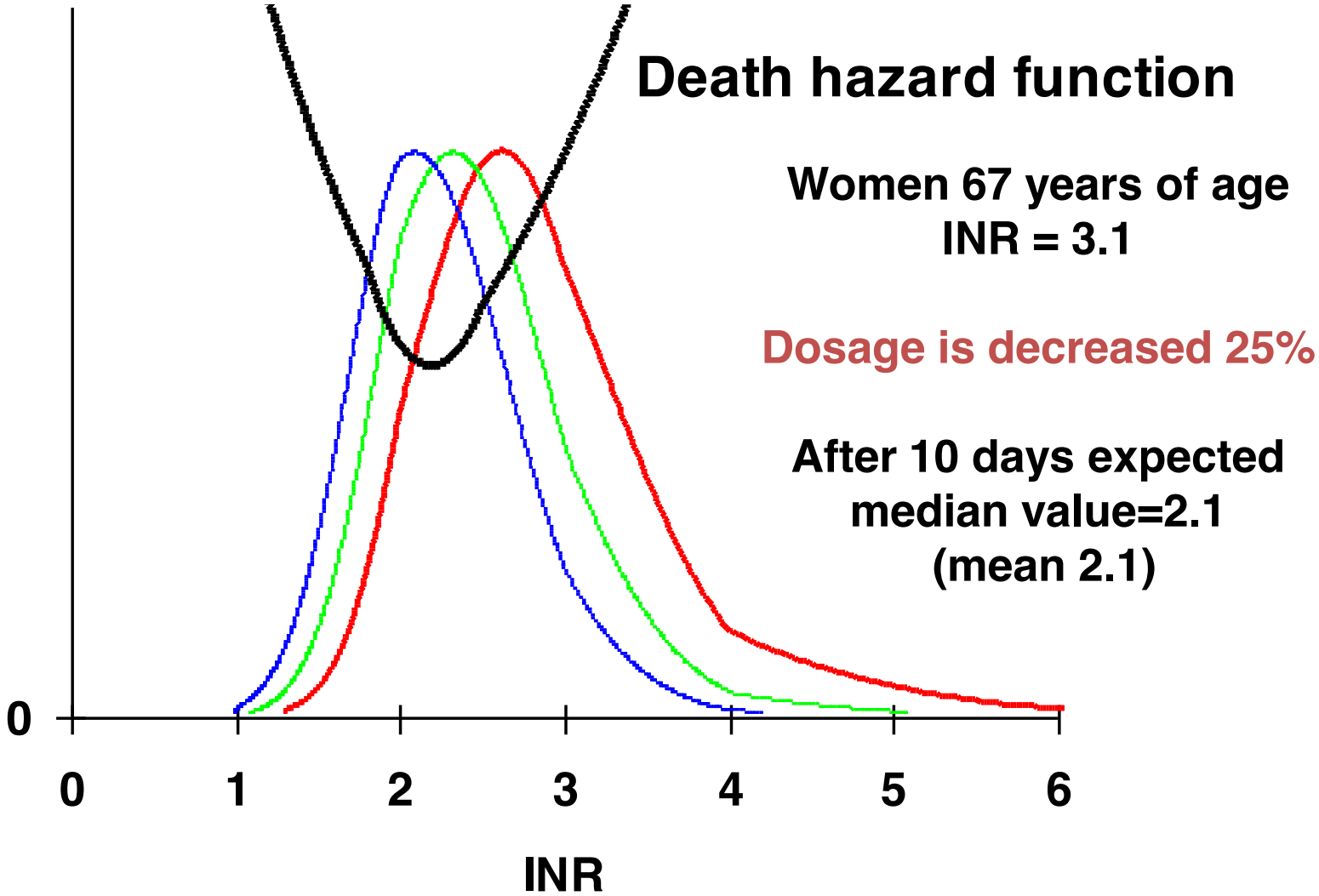
Increase 10 % - algorithm A
Death hazard: 0.0158

Increase 11% - algorithm B
Death hazard: 0.0156

Hazard ratio 1.01


Death hazard function
Women 67 years of age
INR = 3.1
No change of dosage.
After 10 days expected
median = 2.6
(mean = 2.7)
0
0
1
2
3
4
5
6
INR


Death hazard function
Women 67 years of age
INR = 3.1
Dosage is decreased 15%
After 10 days expected median
value=2.3
(mean 2.4)
0
0
1
2
3
4
5
6
INR


Death hazard function
Women 67 years of age
INR = 3.1
Dosage is decreased 25%
After 10 days expected
median value=2.1
(mean 2.1)
0
0
1
2
3
4
5
6
INR

BMJ 2002

42451 Subjects

1.3 Million of INR Measurements

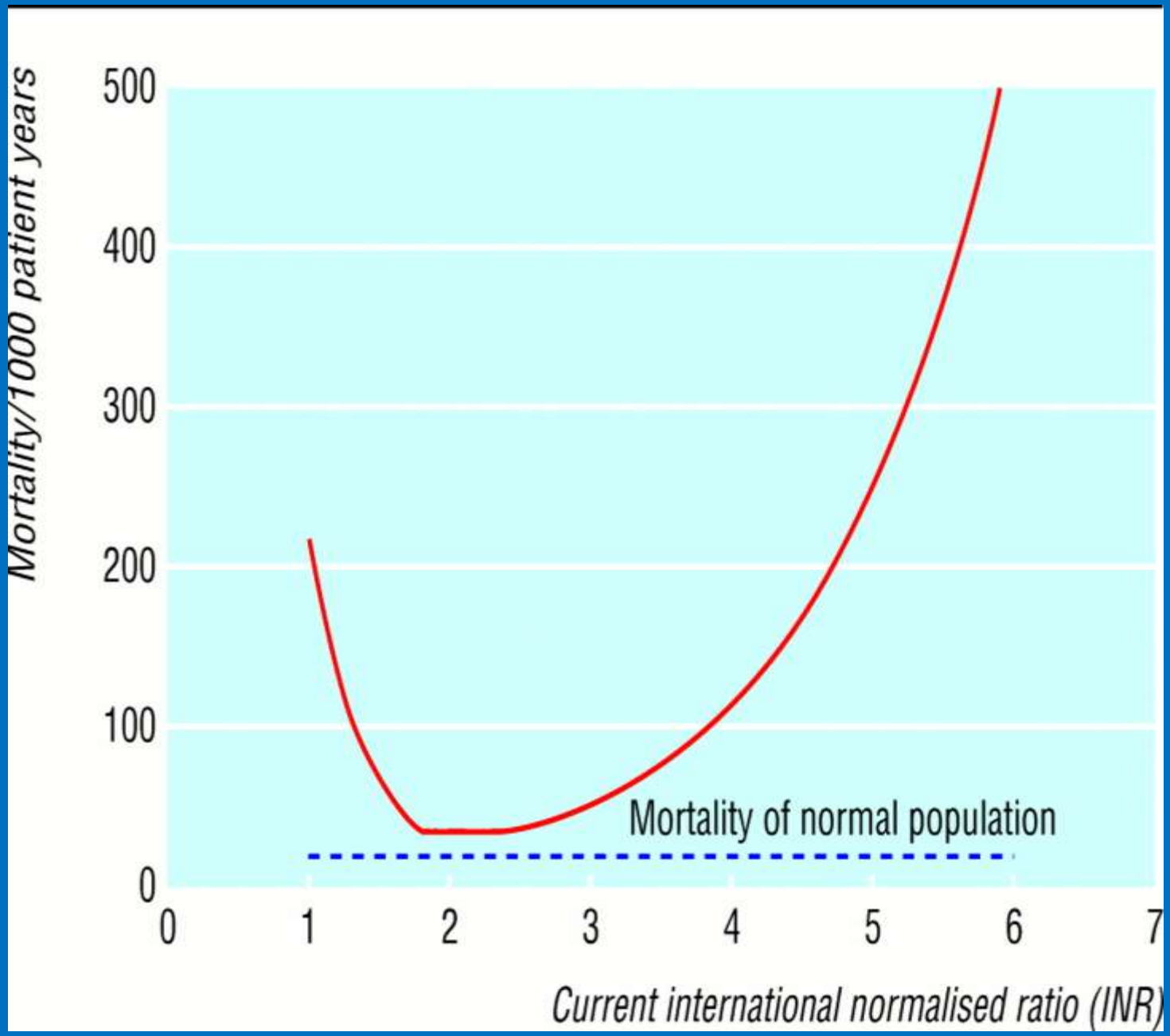
3533 Deaths from a National Register

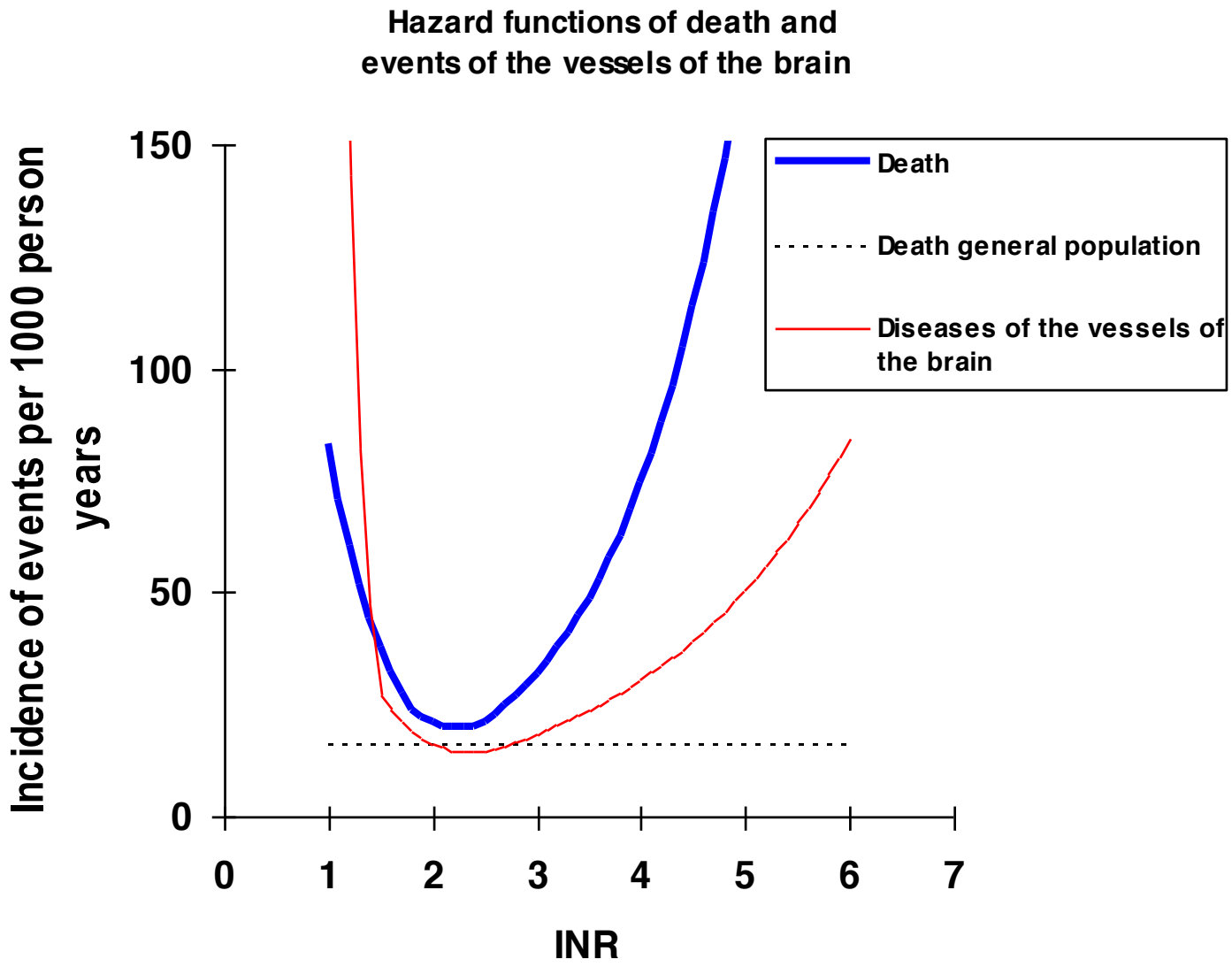
61000 Patient Years

Method

A death hazard function
depending on age, sex and INR.

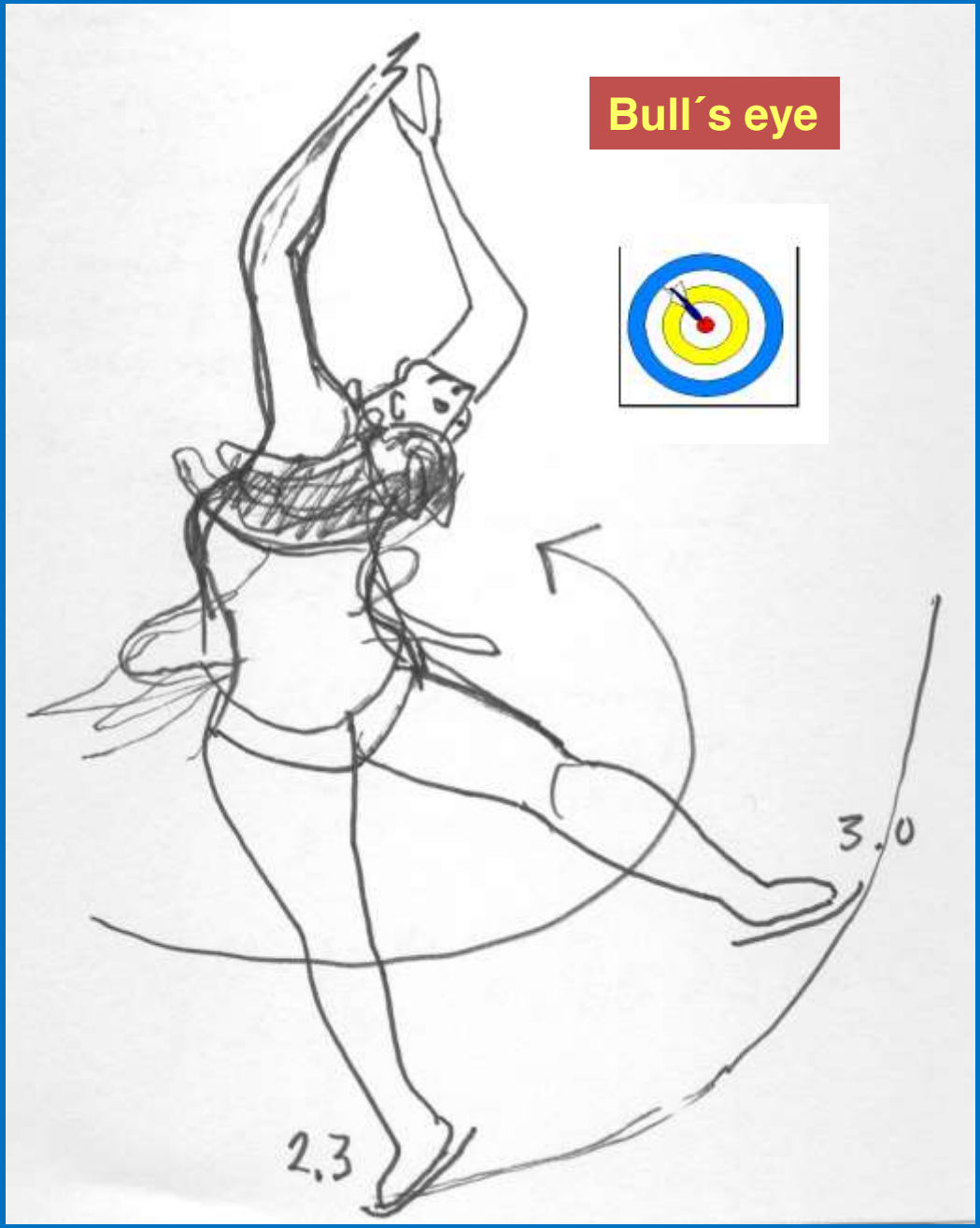
Poisson model – continuous for age and INR
$\exp(\beta_0+\beta_1*x_1+\ldots)$ ß=constants, x=variables


Mortality/1000 patient years
500
400
300
200
100
0
Mortality of normal population
0
1
2
3
4
5
6
7
Current international normalised ratio (INR)


Hazard functions of death and events of the vessels of the brain
Incidence of events per 1000 person years
150
100
50
0
0
1
2
3
4
5
6
7
INR
Death
Death general population
Diseases of the vessels of the brain

Nadir in death hazard function

All indications	2.2
Valve prosthesis	2.3


Bull´s eye
3.0
2,3

On the basis of the existing data, new recommendations regarding lower anticoagulation levels are offered, utilizing a single value goal rather than the traditional therapeutic range.

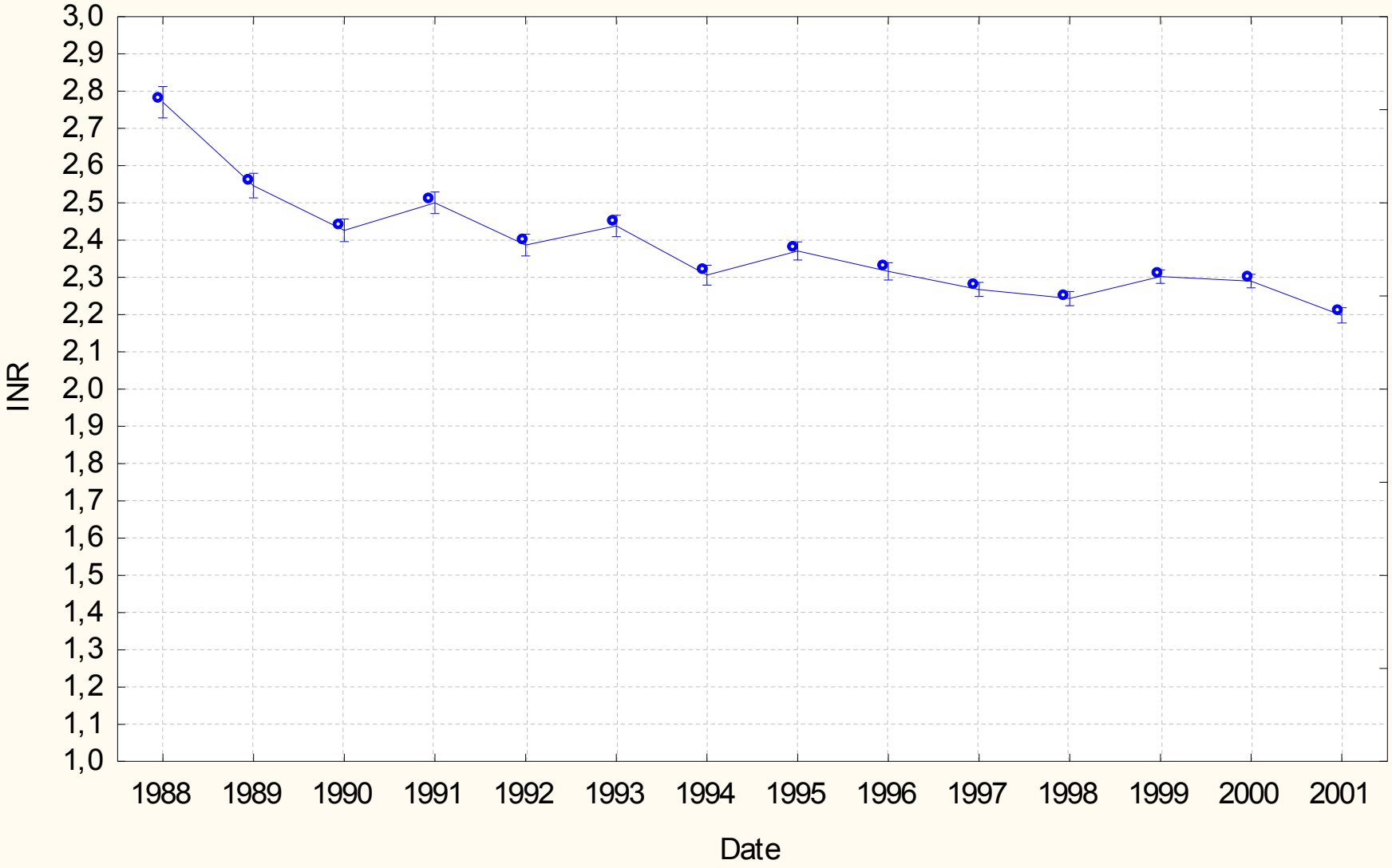
Mayo -98

The risk of death was significantly higher for those who had an increased dosage.

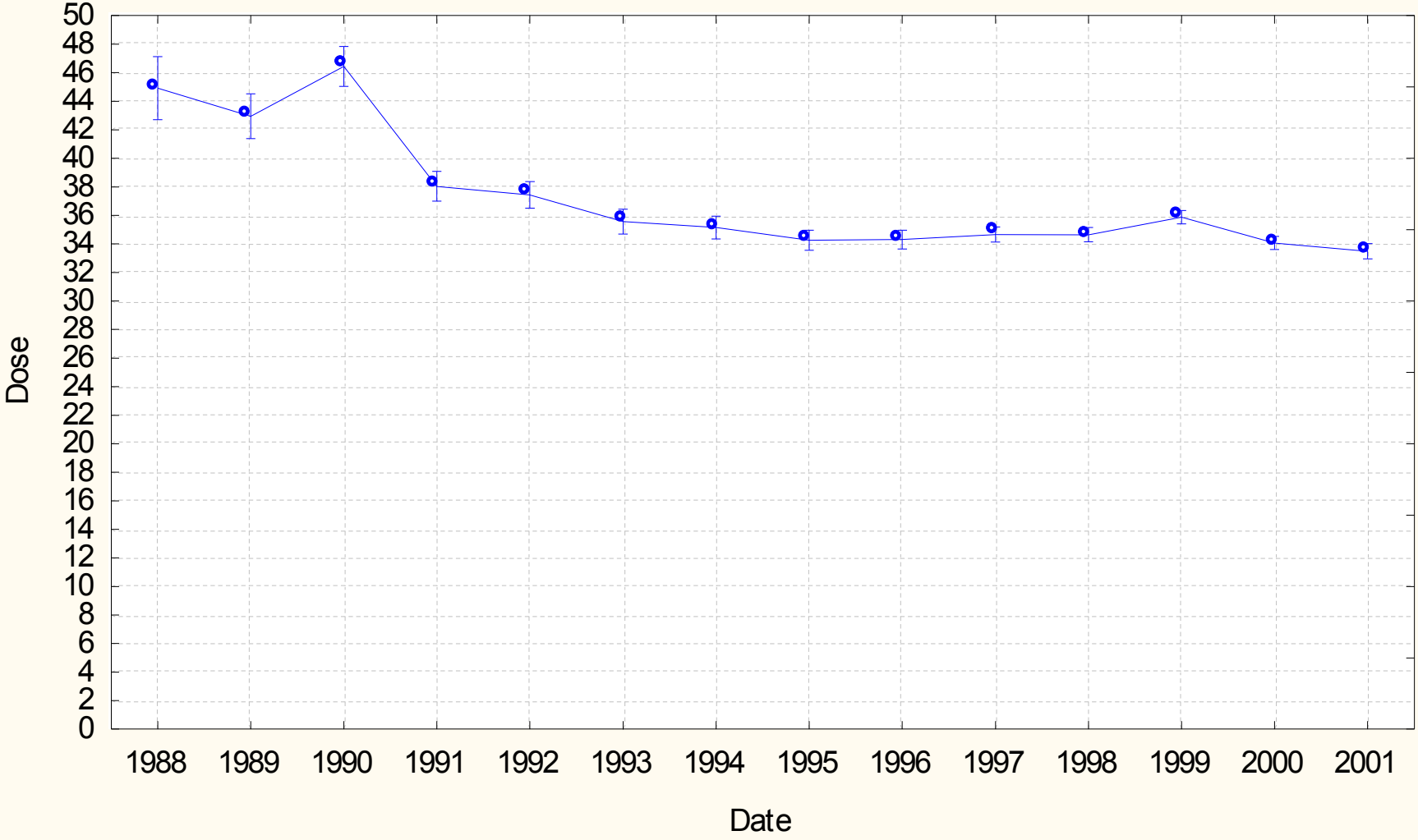
A: A relation to dosage and activities

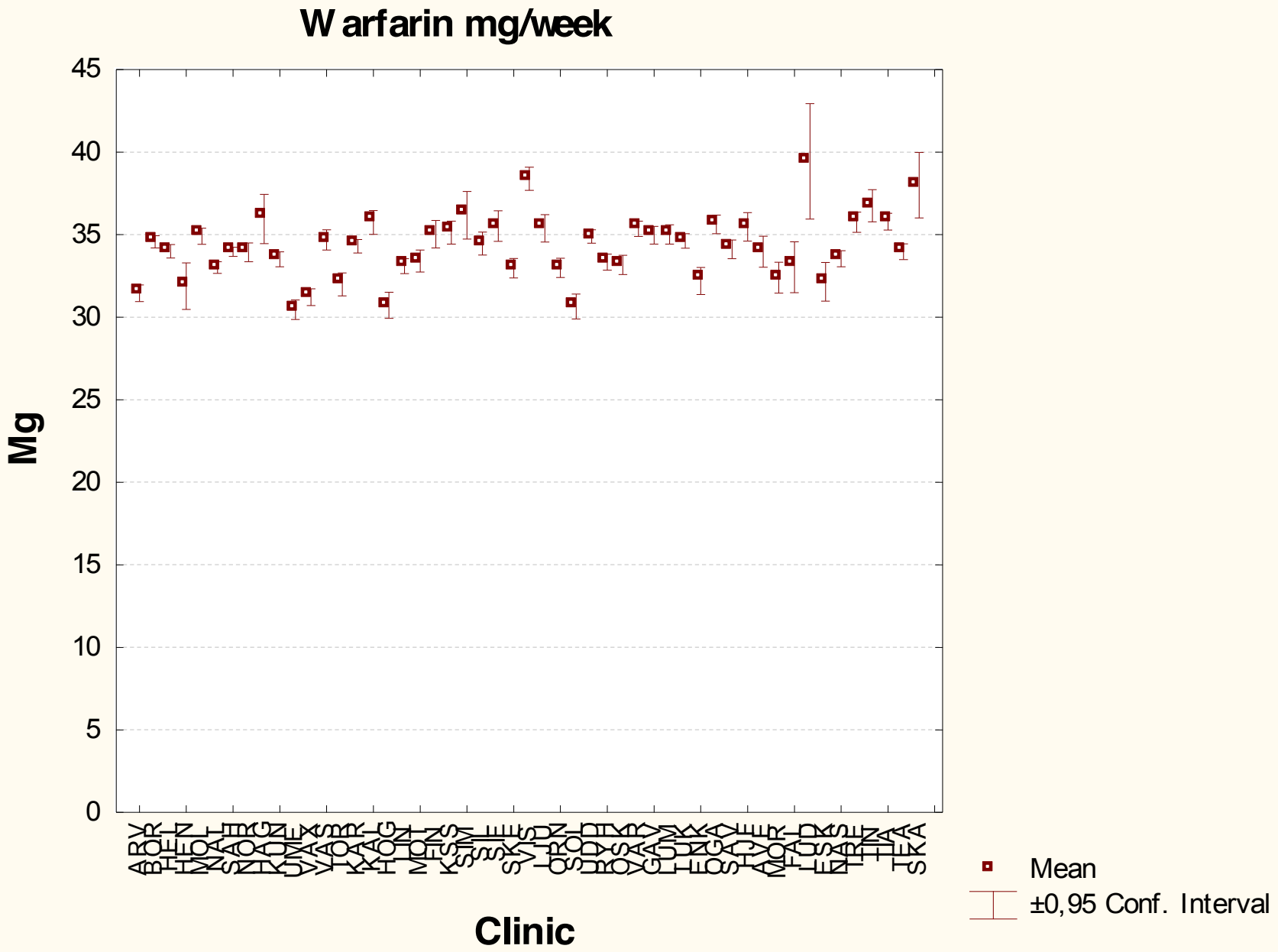
B: We can avoid this. But how?

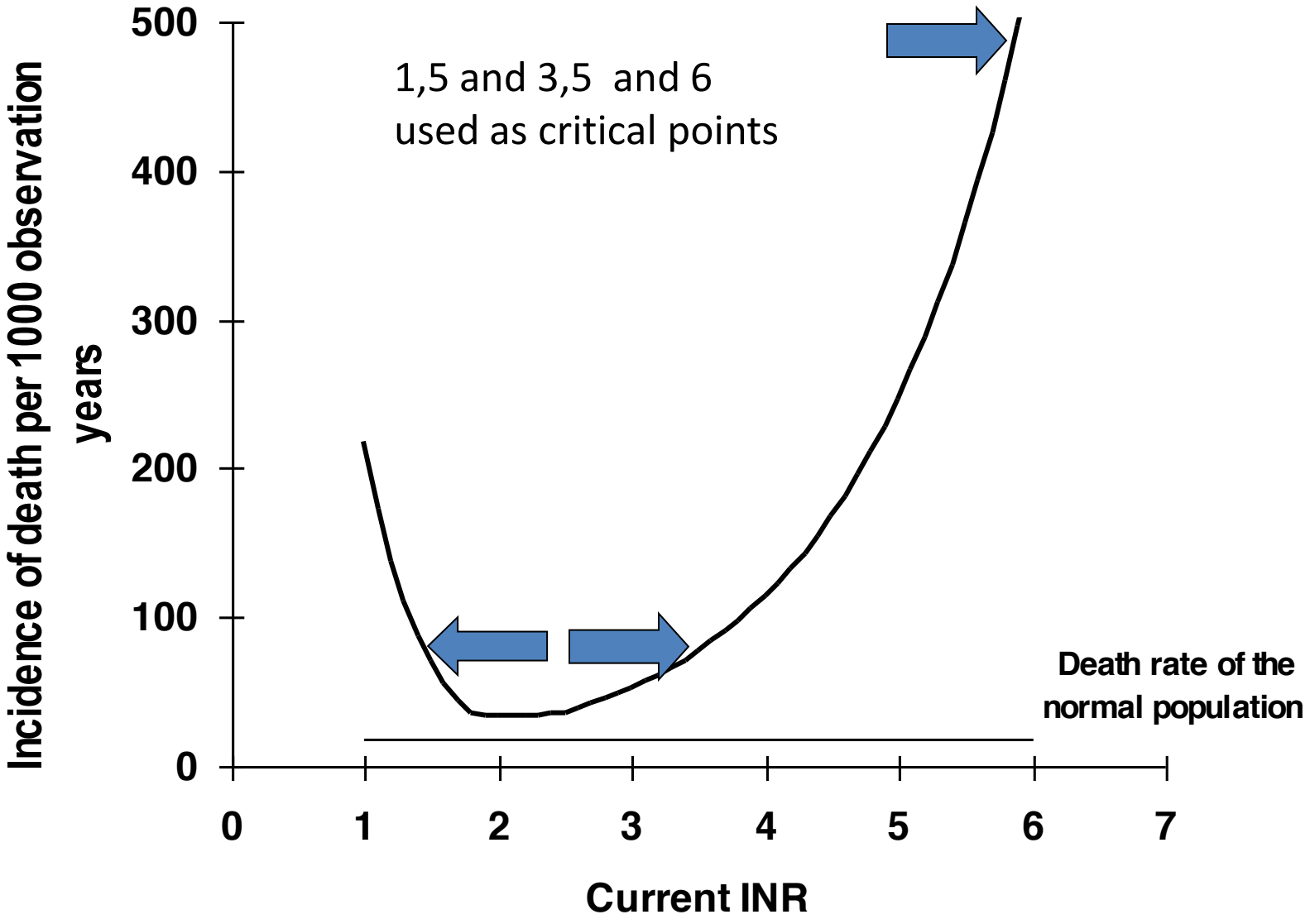
INR in one clinic



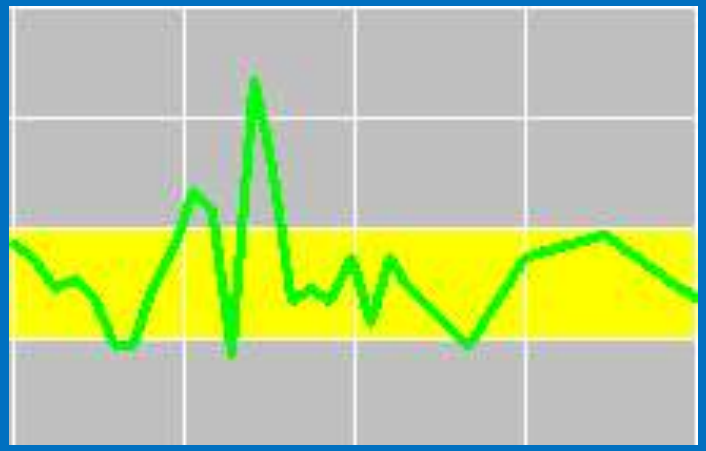
Warfarin mg/week in one clinic (60-70 years of age)




Warfarin mg/week
Mg
45
40
35
30
25
20
15
10
5
0
Clinic
Mean
±0,95 Conf. Interval


1,5 and 3,5 and 6
used as critical points
Incidence of death per 1000 observation years
500
400
300
200
100
0
Death rate of the normal population
0
1
2
3
4
5
6
7
Current INR

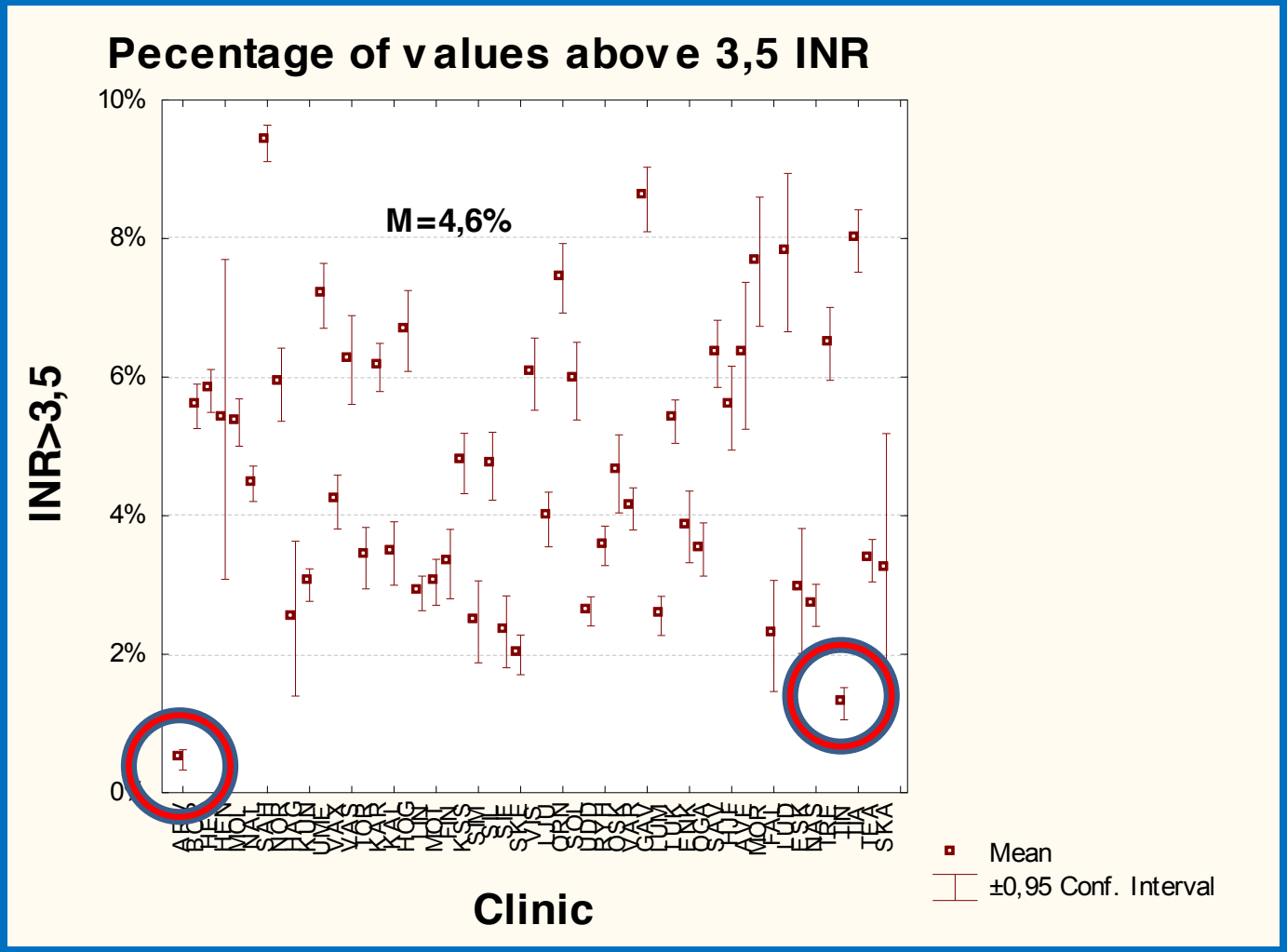
Why outside?



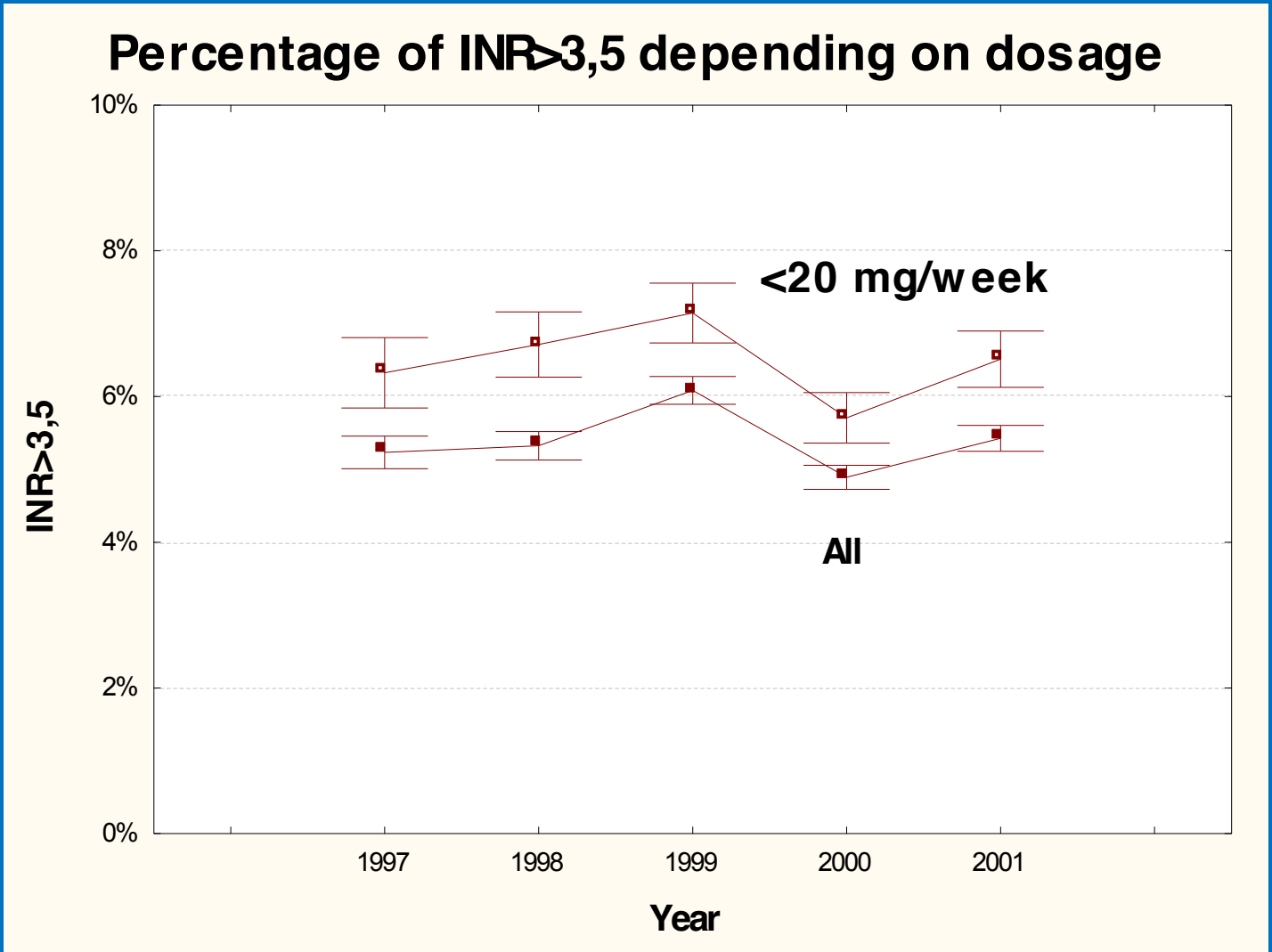
Why inside?

Information? Proportion, TTR and SD.

Patchy care I
High INR-values and different clinics

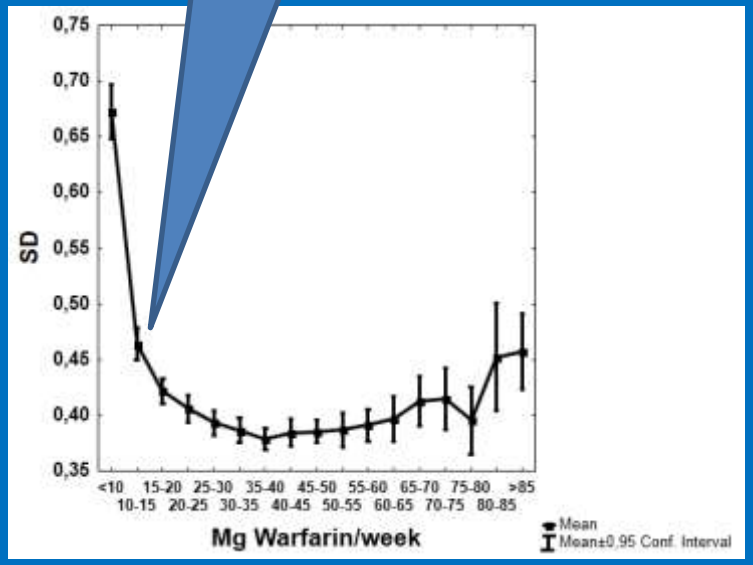


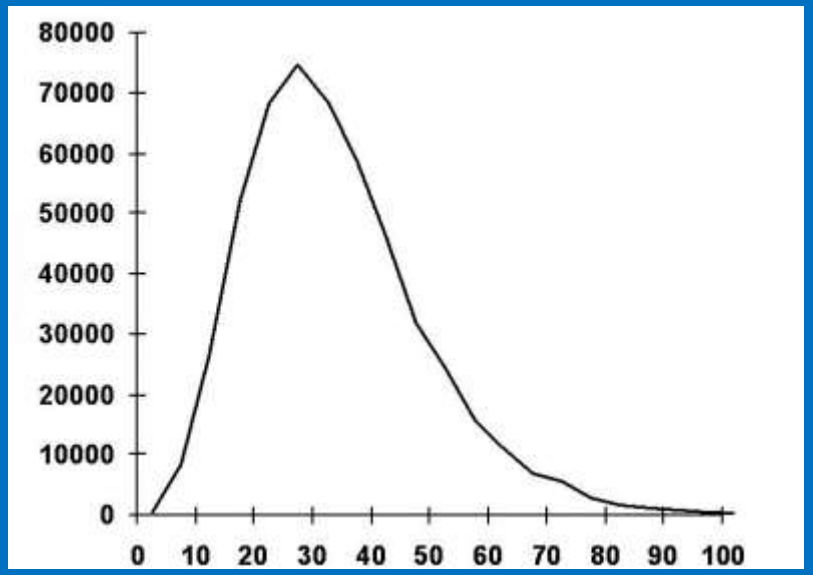
High INR-values and small dosages



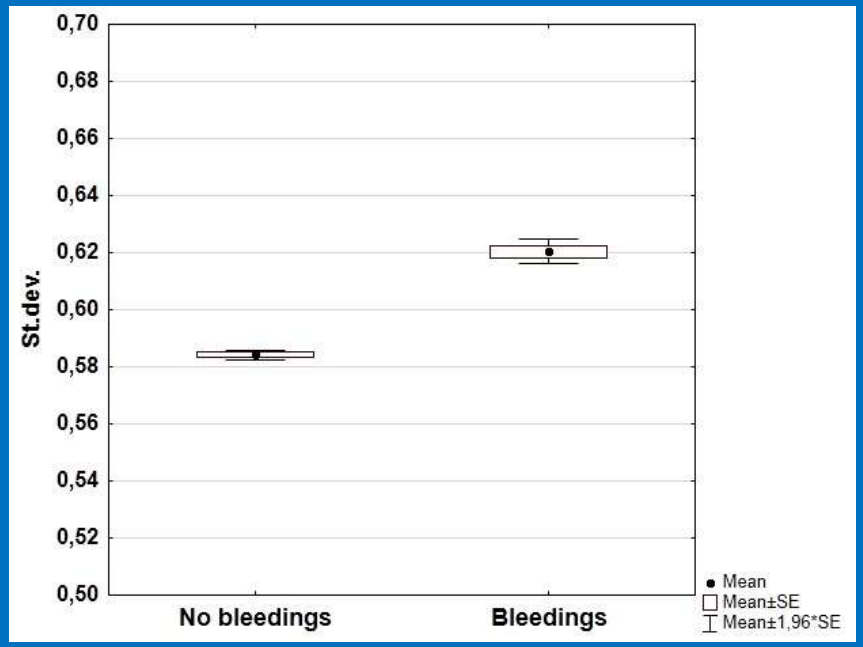
SD and its relation to dosage

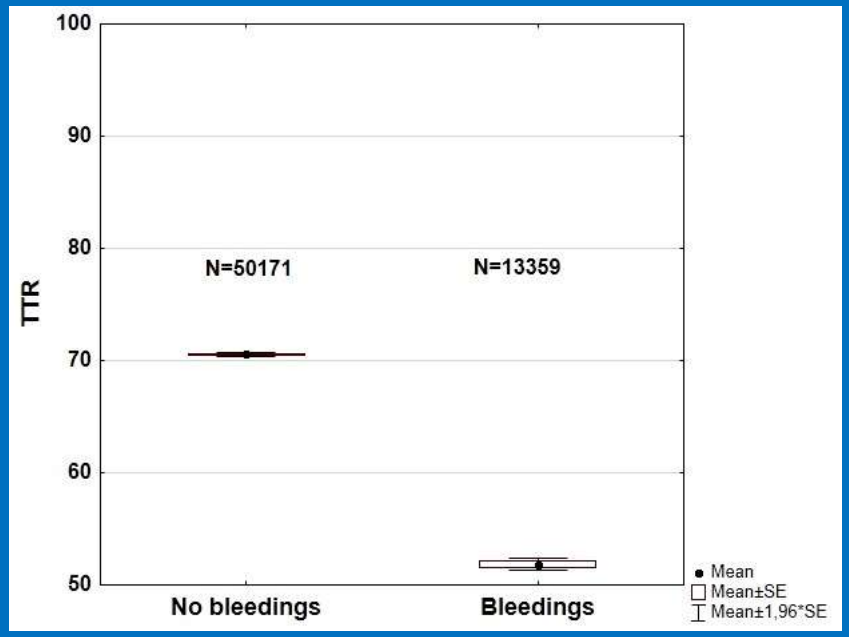
Vitamin K ?



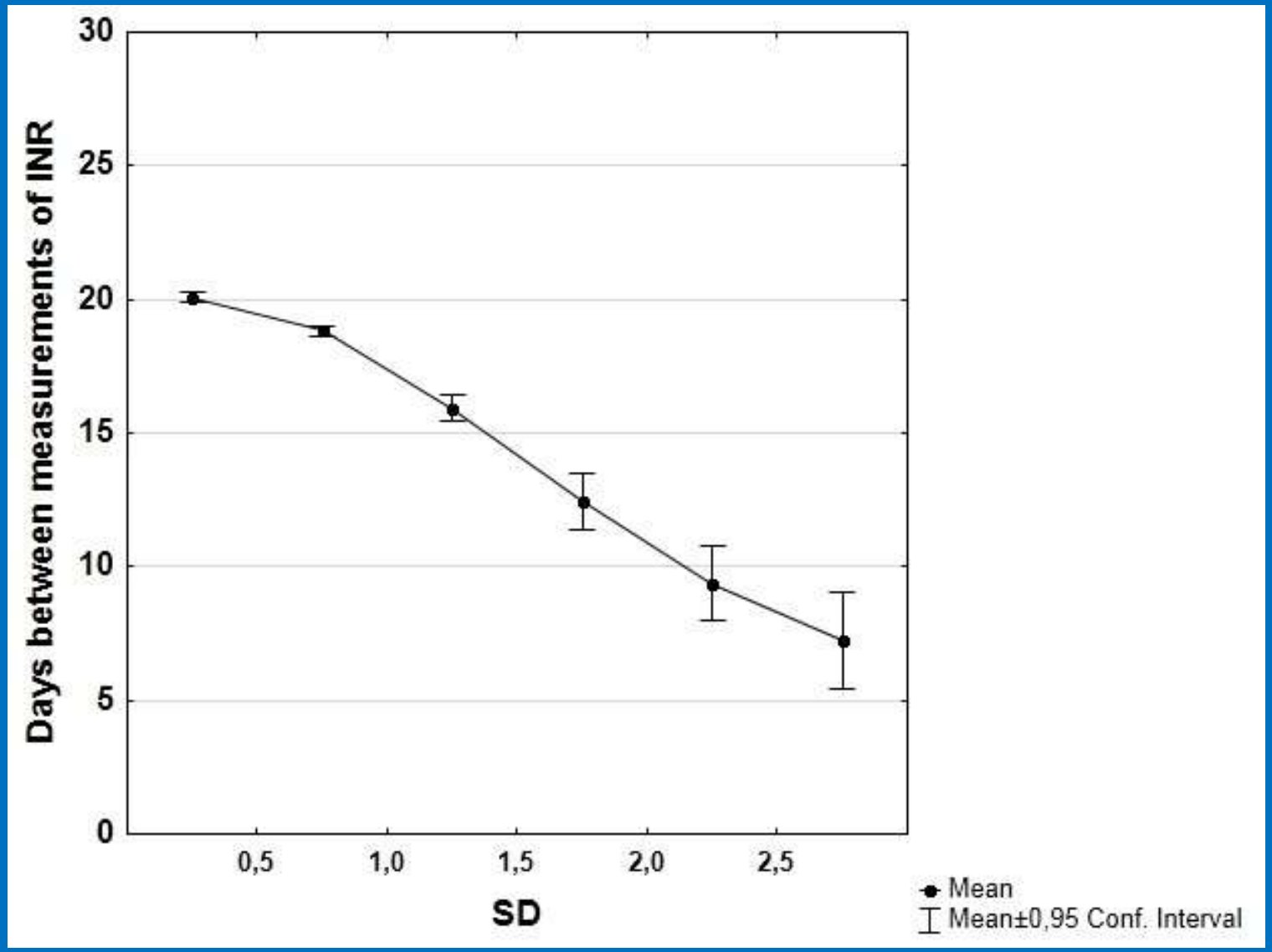


SD is high and TTR low in patients at risk.





SD is high and we want to see the patient earlier



Hamilton General Warfarin Dosing Nomogram

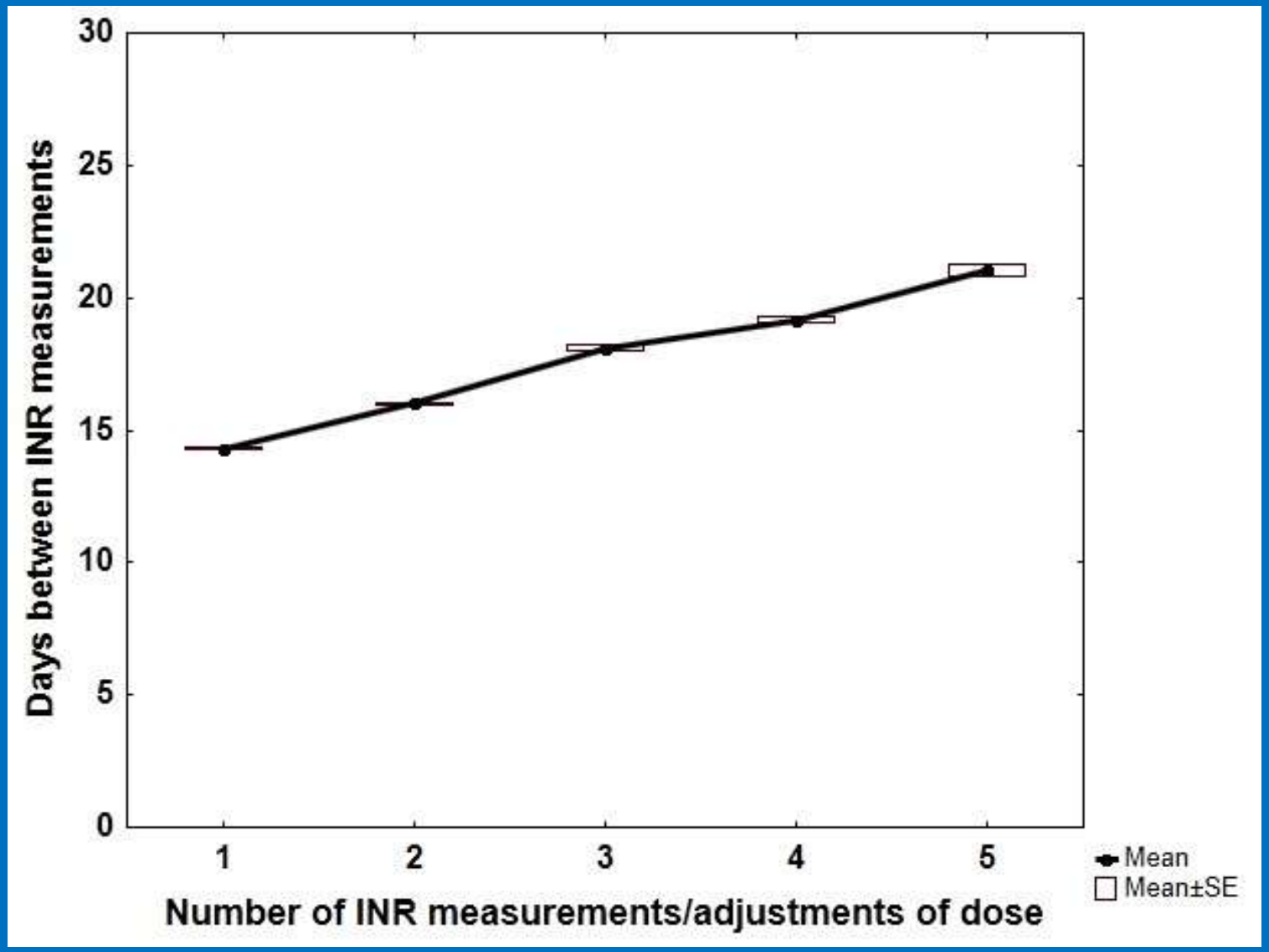
Return Visits:

INR	Checkup
<=1.5	7-10 days
1.51-1.99	1-2 weeks
2.00-3.00	3-4 weeks
3.01-3.99	1-2 weeks
>4.00	7-10 days

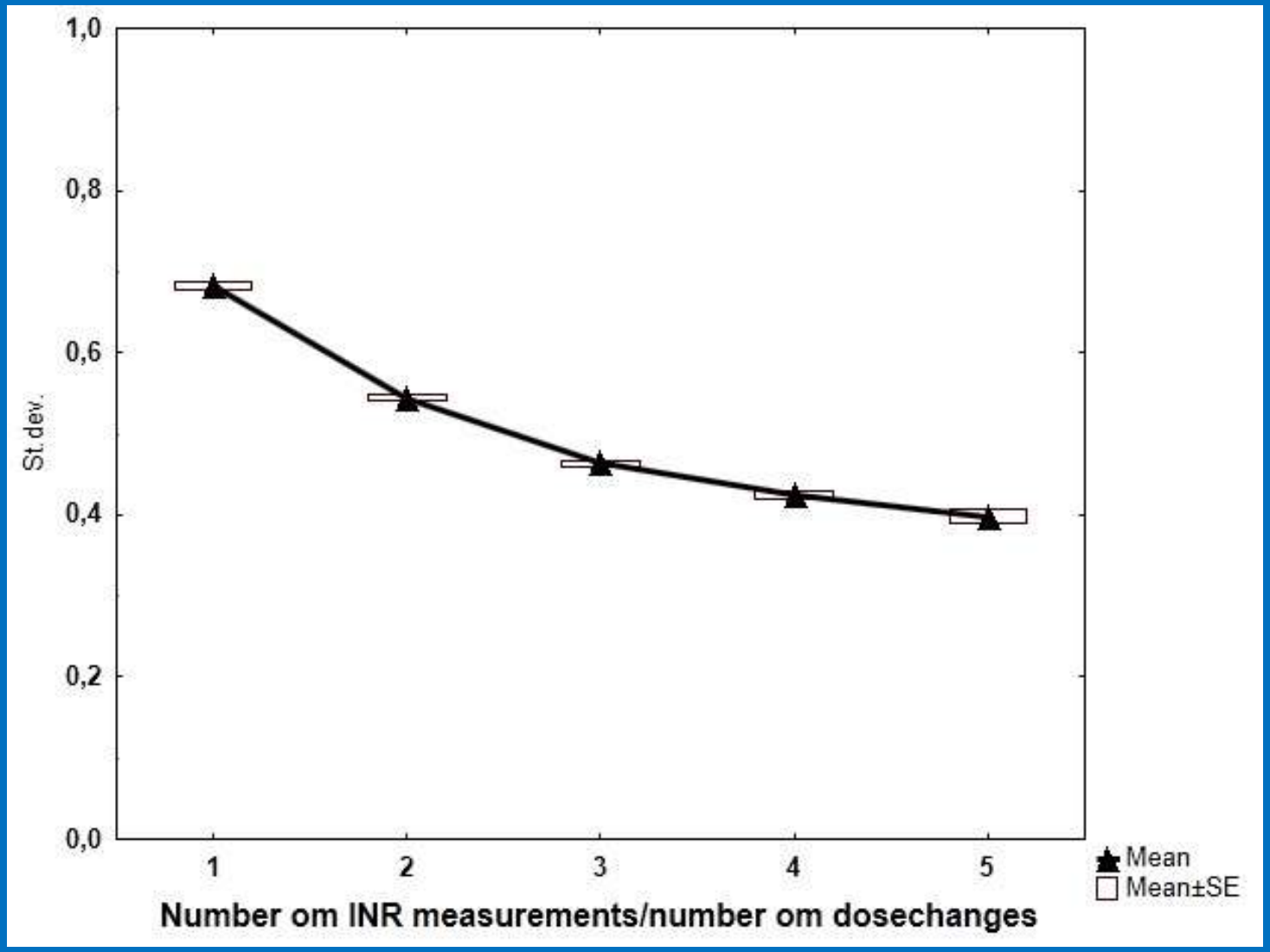
Sweden

5 days
2 weeks
4 weeks
2-3 weeks
10 days

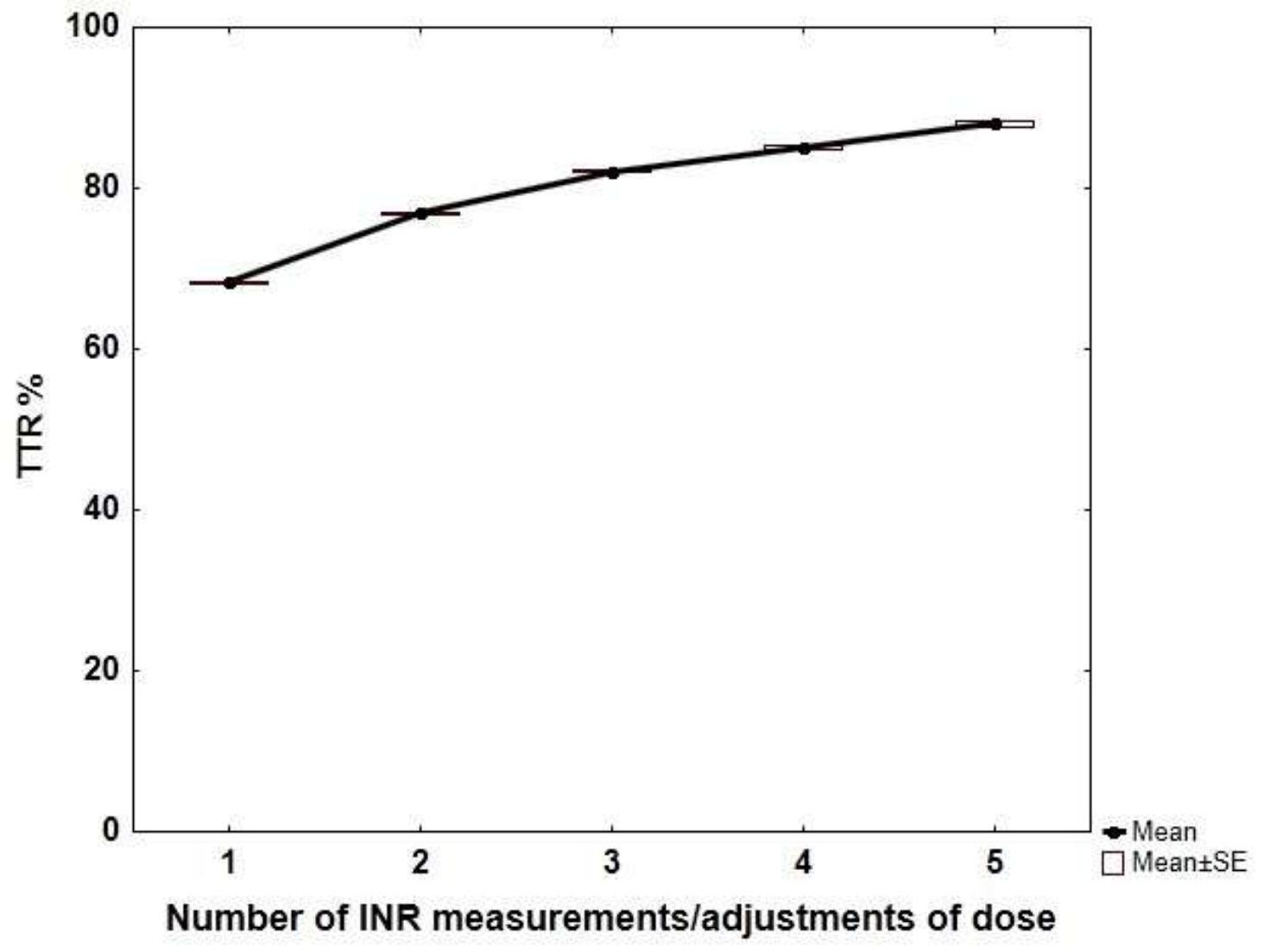
…and change the dose more often



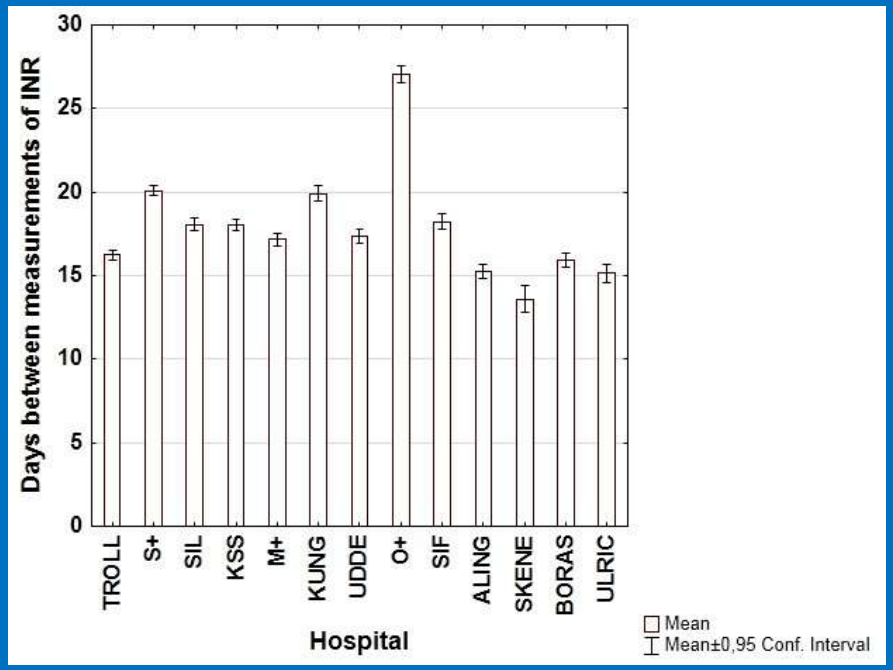
…we have to individualize more to reduce SD

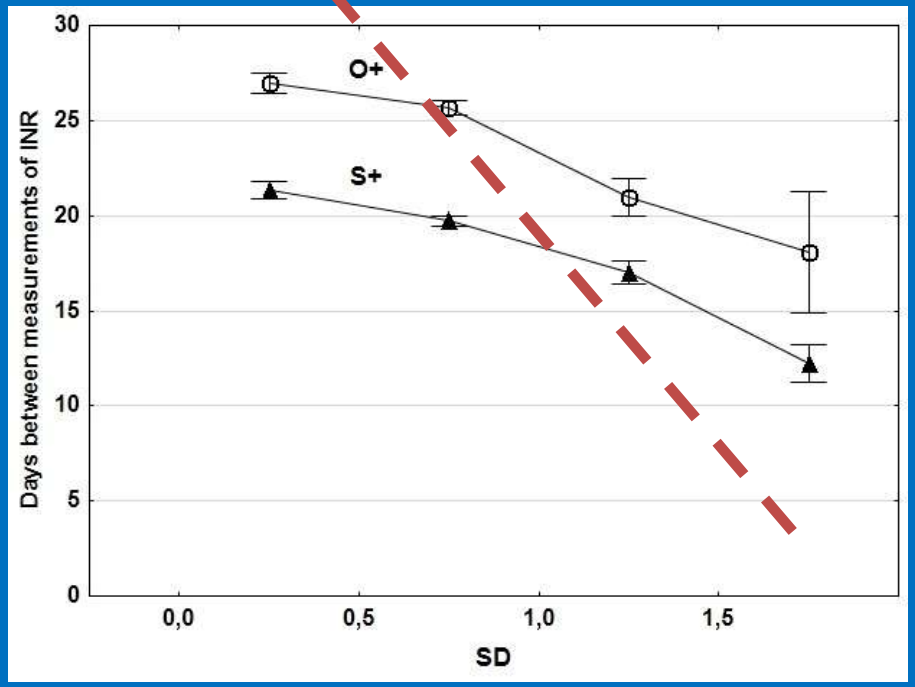


…there is not just one TTR



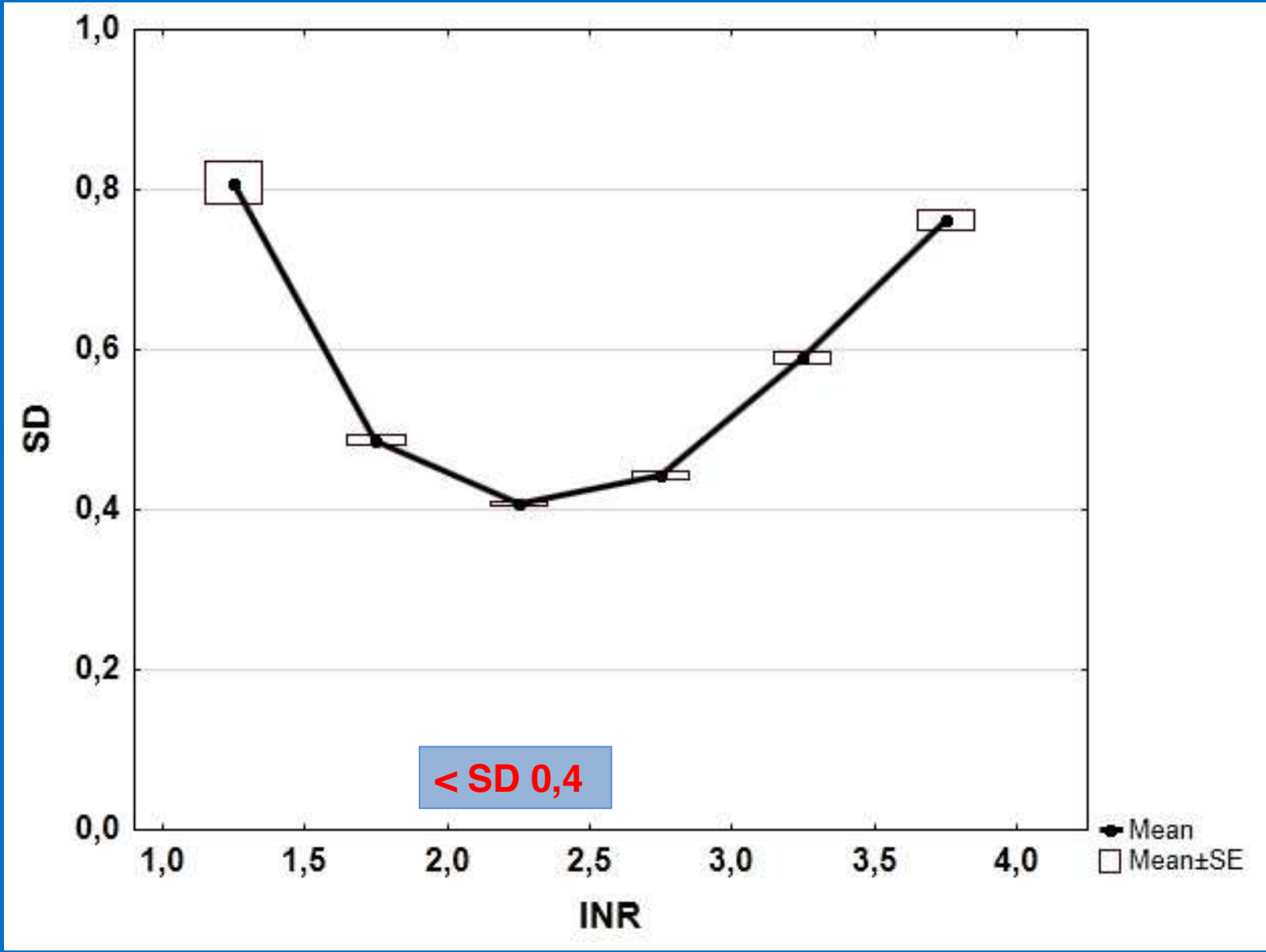
Patchy care II
Individualisation of a hospital or of a patient?





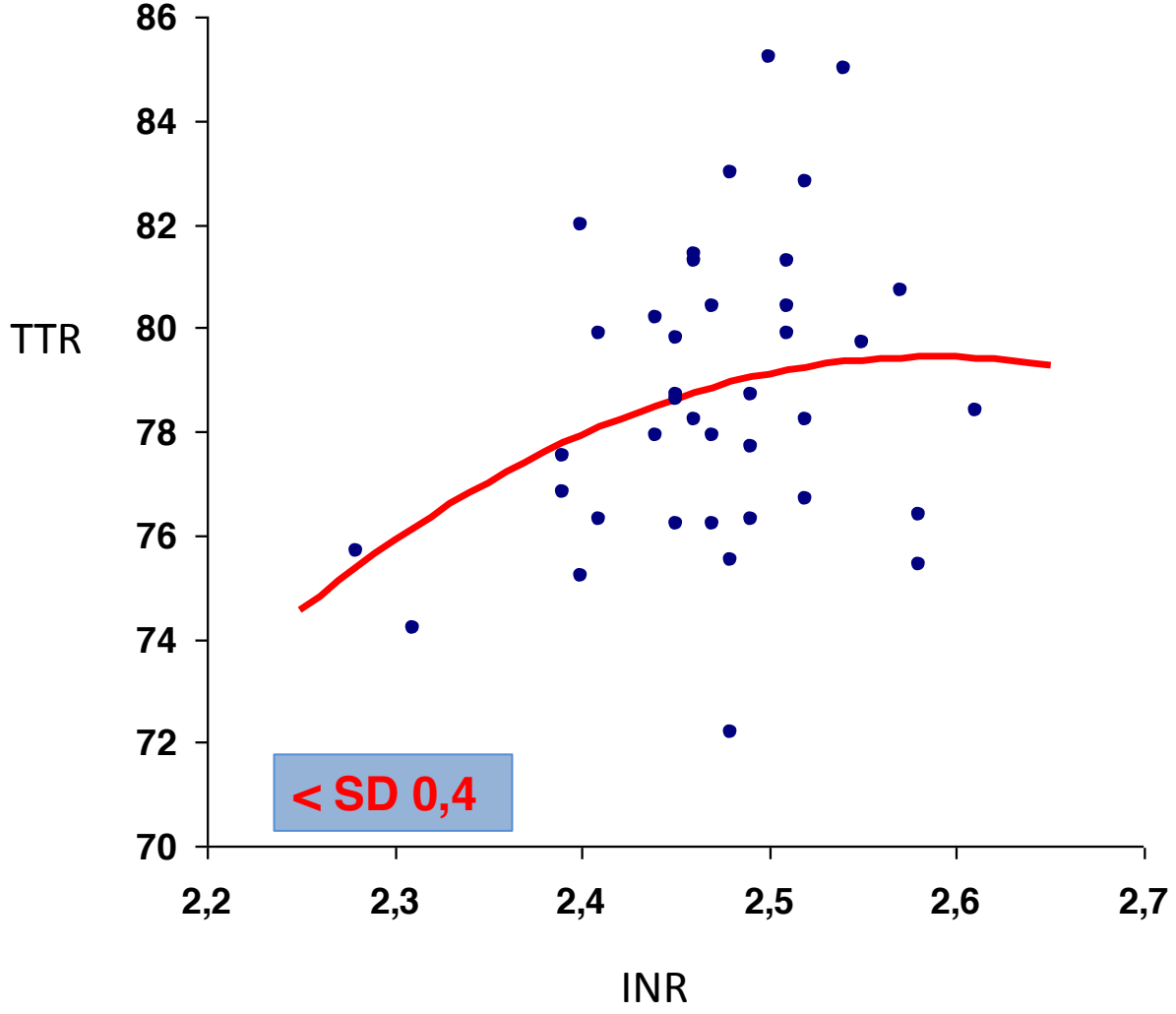
Do the things right or do the right things?

SD and its relation to the last INR

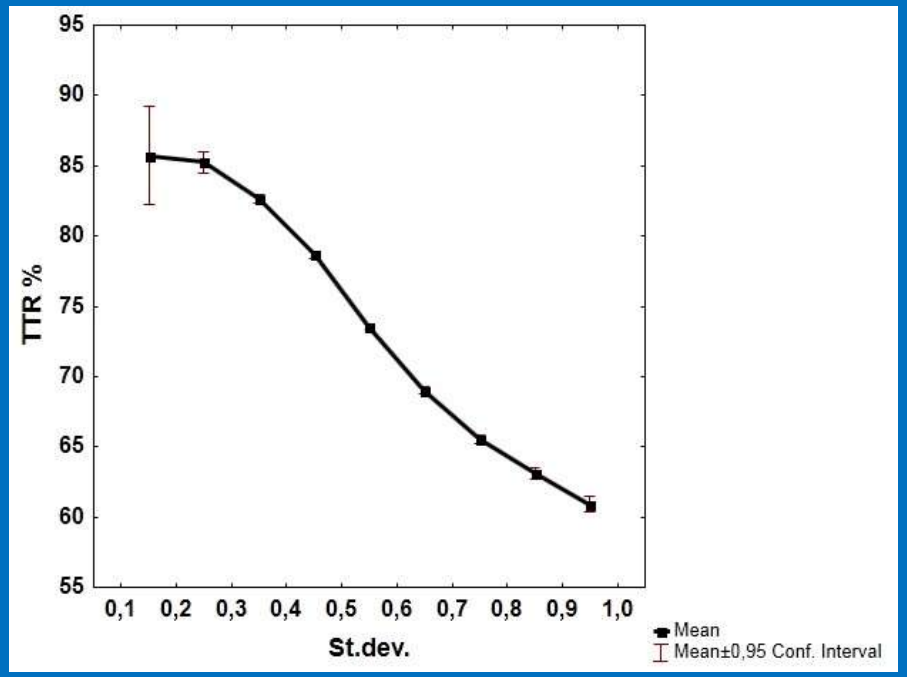


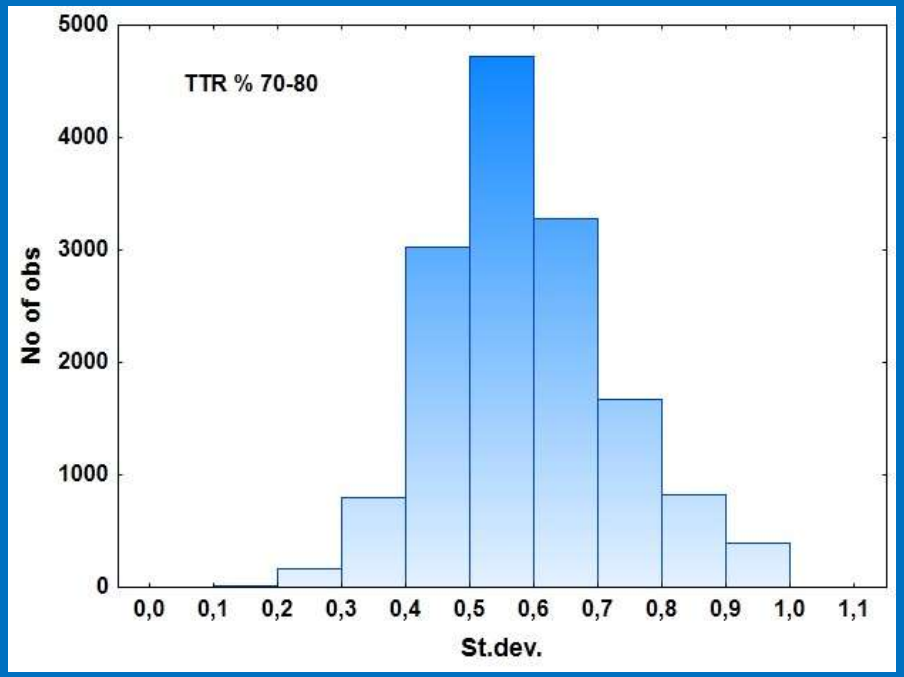

Bull´s eye
3.0
< SD 0,4
2,3

TTR highest value at 2,5. Is >80% to prefer?

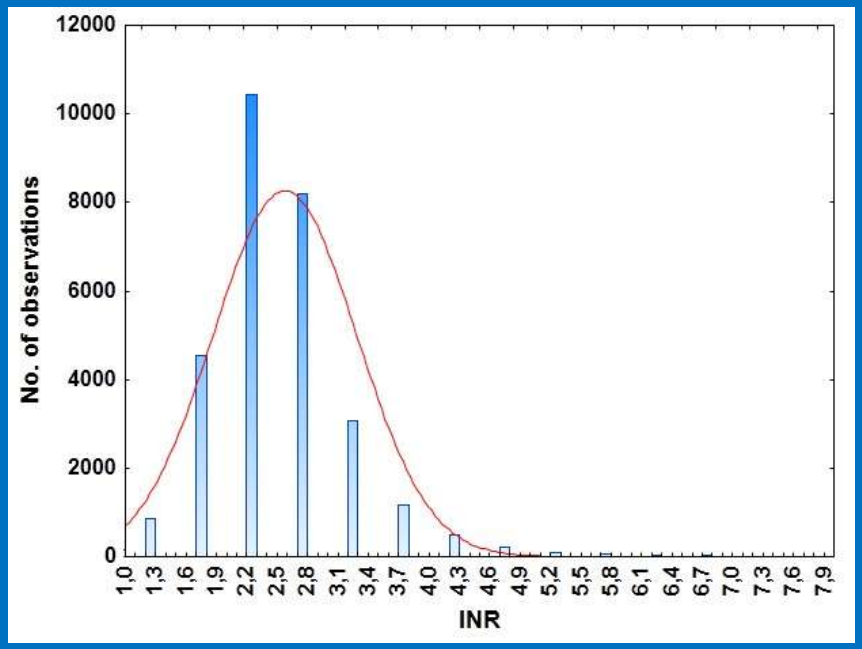


TTR SD-INR are related but R= -0,27





Transformation of INR to sharpen the tool



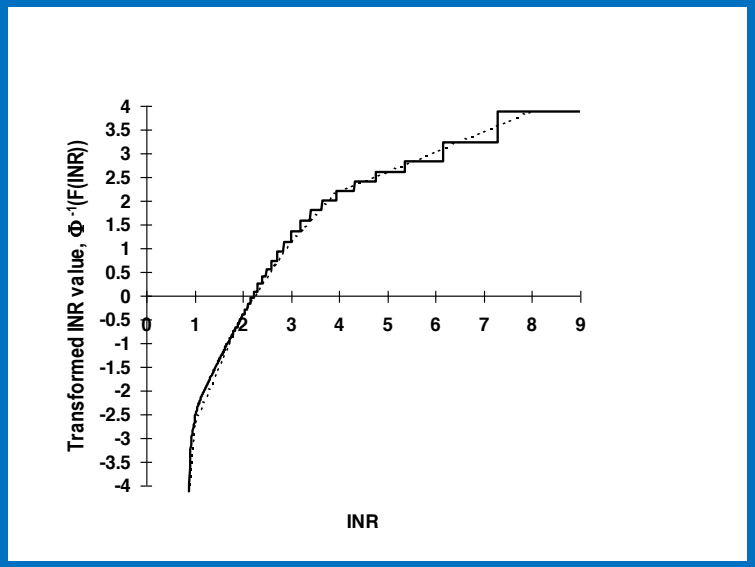
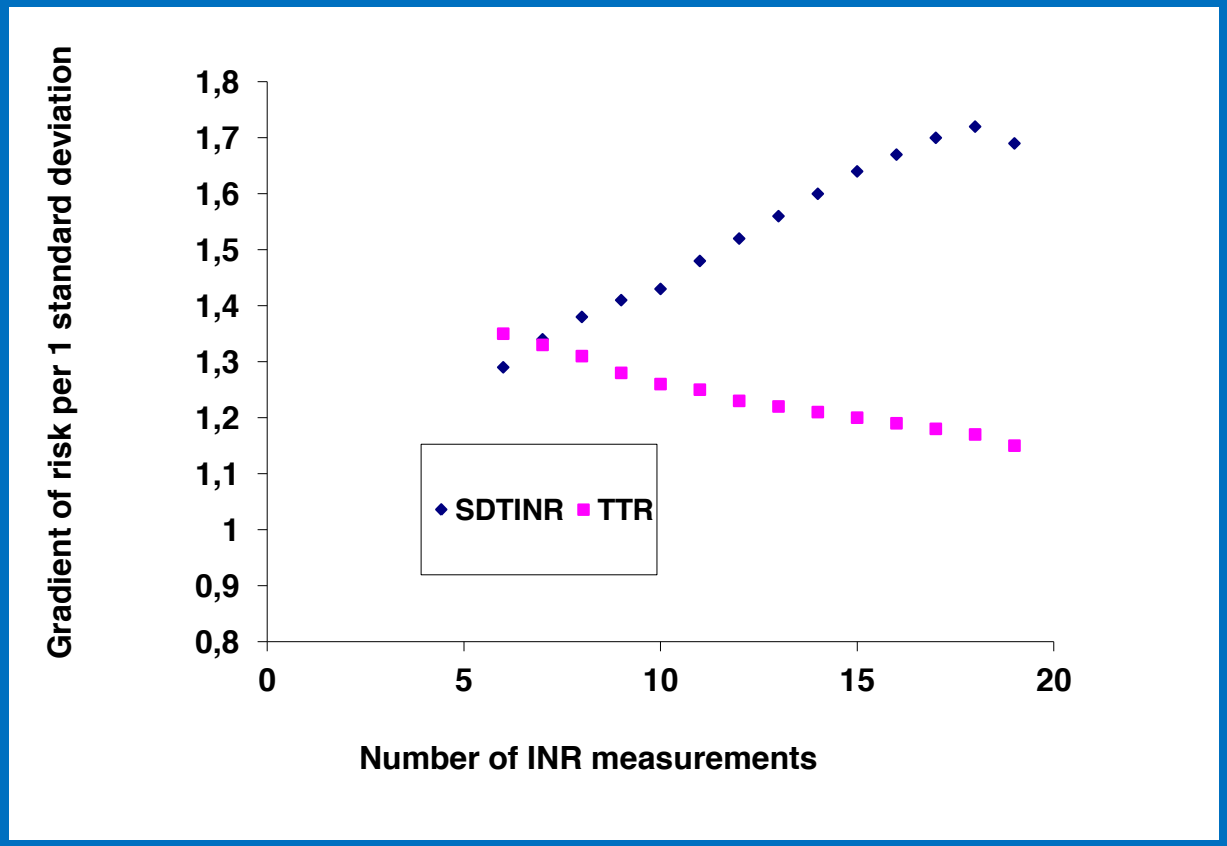


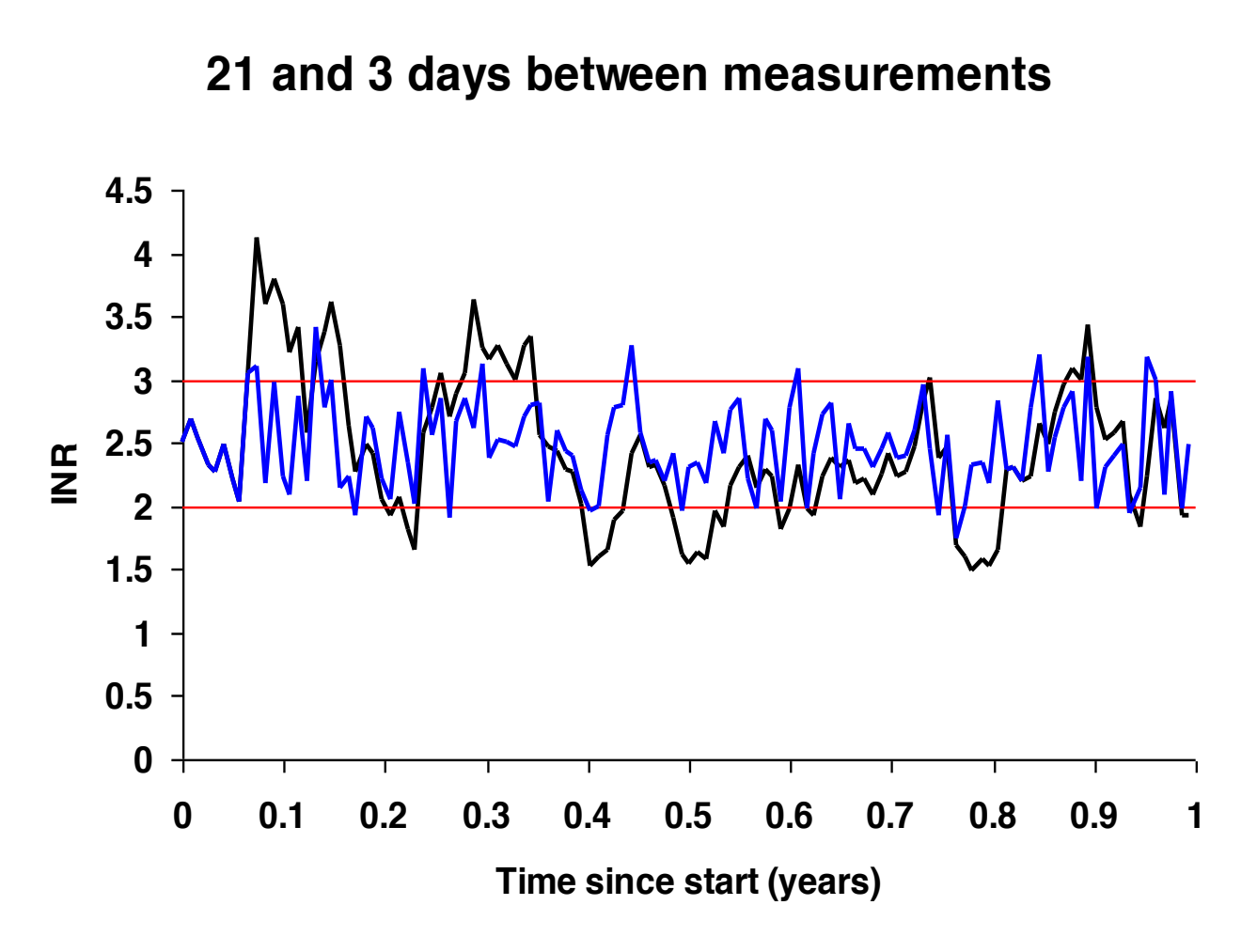
Table 2 Piecewise linear transformation, TR(x) = kx + l, carrying the INR value x to a normally distributed variable.

k	l	Interval
13.03	-15.701	$x \leq 1$
2.276	-4.947	$1 < x \leq 2$
1.525	-3.445	$2 < x \leq 3$
1.077	-2.101	$3 < x \leq 4$
0.403	0.595	$4 < x \leq 5$
0.422	0.500	$x > 5$

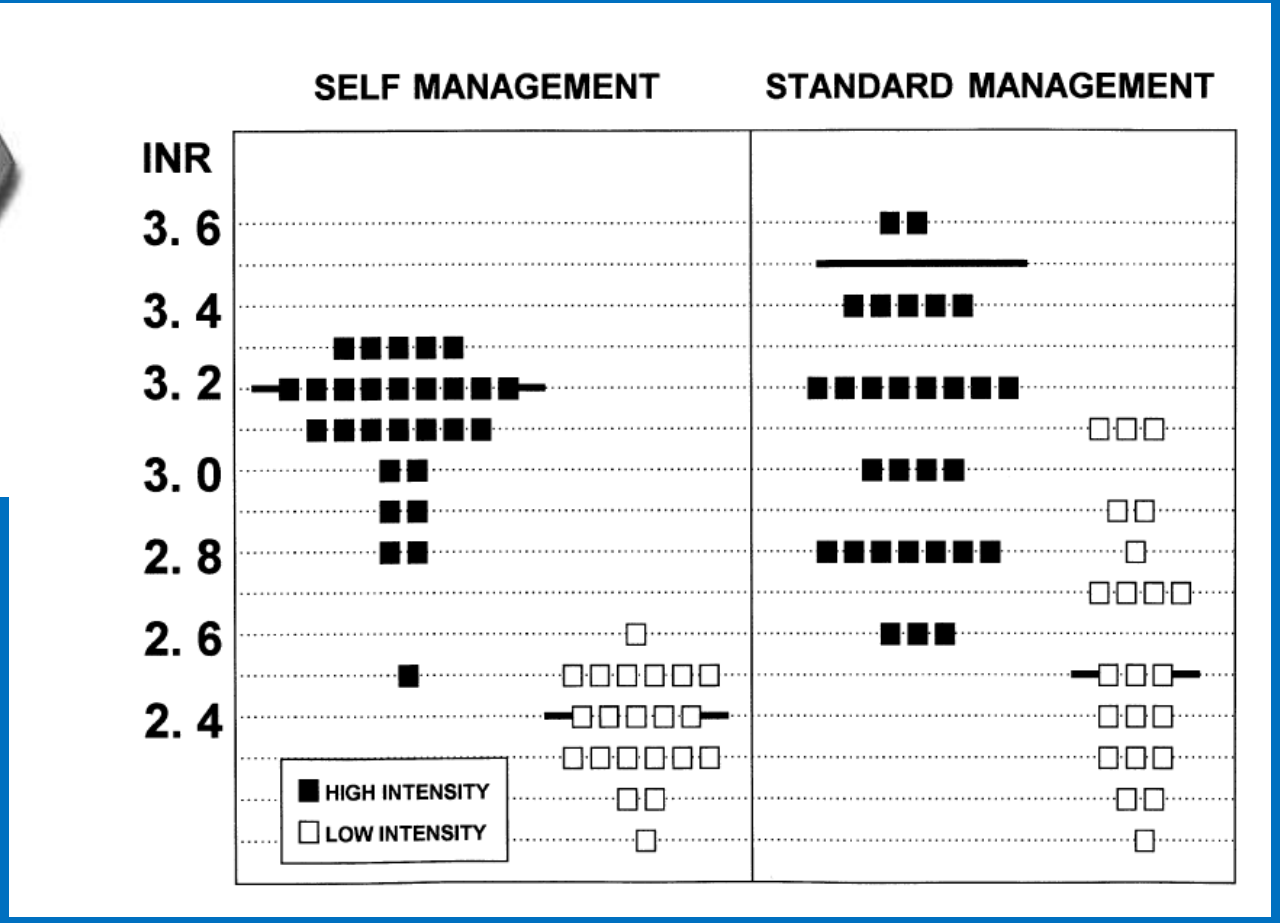
SD is so far the best predictor for death
How much can it be reduced?



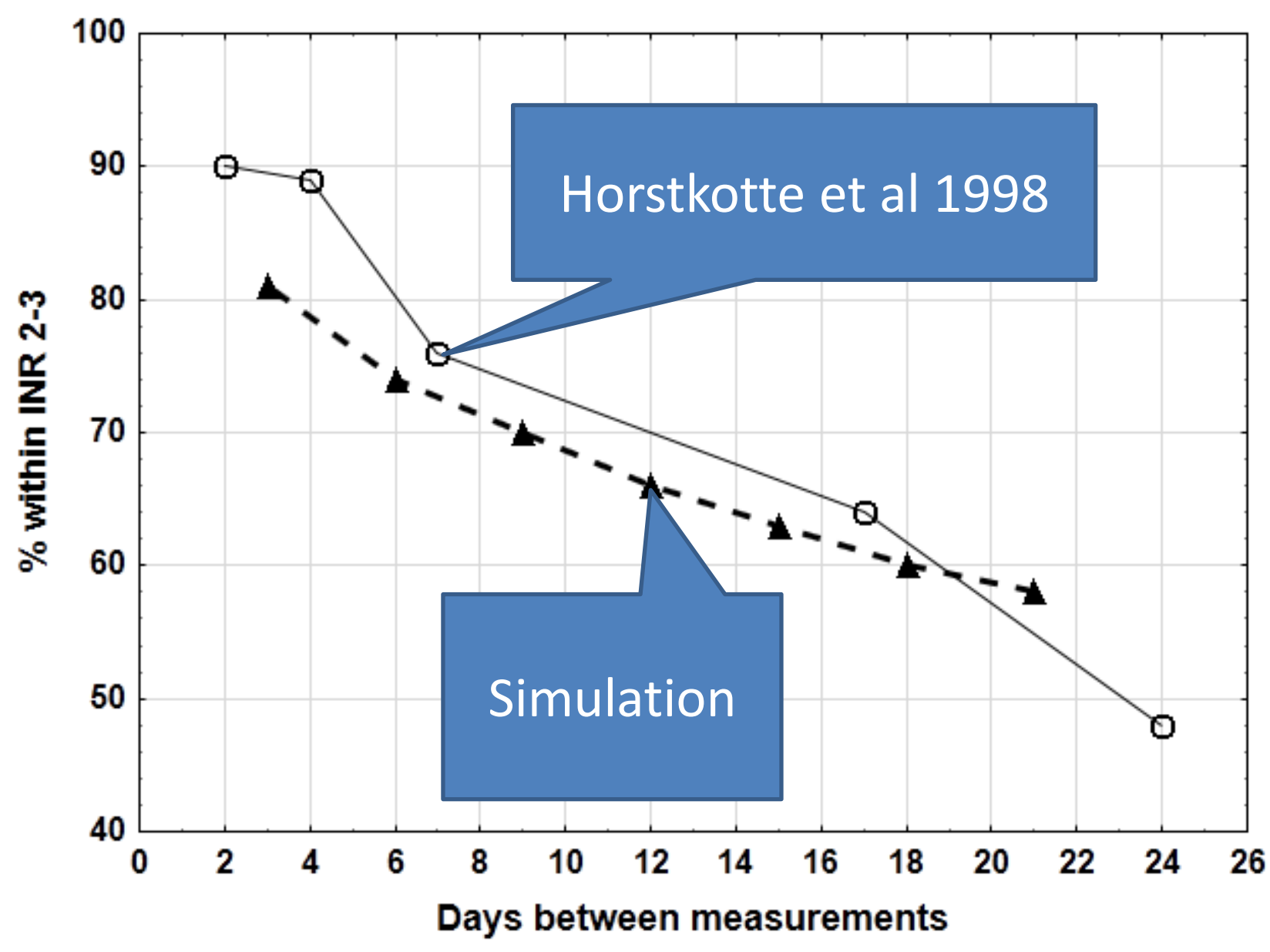
Simulation- Days between measurements



Home-monitoring and stability



Watzke et al 2000 Thromb Haemost vol 83:661-5


Horstkotte et al 1998
Simulation
% within INR 2-3
Days between measurements
100
90
80
70
60
50
40
0
2
4
6
8
10
12
14
16
18
20
22
24
26

Simulation - Risk reduction based on reduction of SD from 21 to 3 days.

Type of end-point	Gradient of risk per 1 SD	Calculated reduction of risk
Death	1.59	39%
Stroke	1.30	25%
Bleed	1.27	23%
Admit to Hospital	1.47	34%

Feedback loop - patient empowerment

Control of a change of dose just in time

Control of interaction caused by a new medication

Control of a change of vitamin-K intake

Control during illness, diarrea, fewer.

Control of bleeding

…

– quality of life

Feedback loop
and timing

Coming research on home-monitoring

1. How much can we individualize and reduce SD?

2. How much can we reduce complications?

3. Implementation of a new ”model” based on timing.

4. Role of K-vitamin, genes etc…