Can we improve monitoring of INR?

DAWN User Group Meeting 2014

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Good news

- High quality anticoagulant treatment is offered in many countries and in different settings, particularly specialized clinics

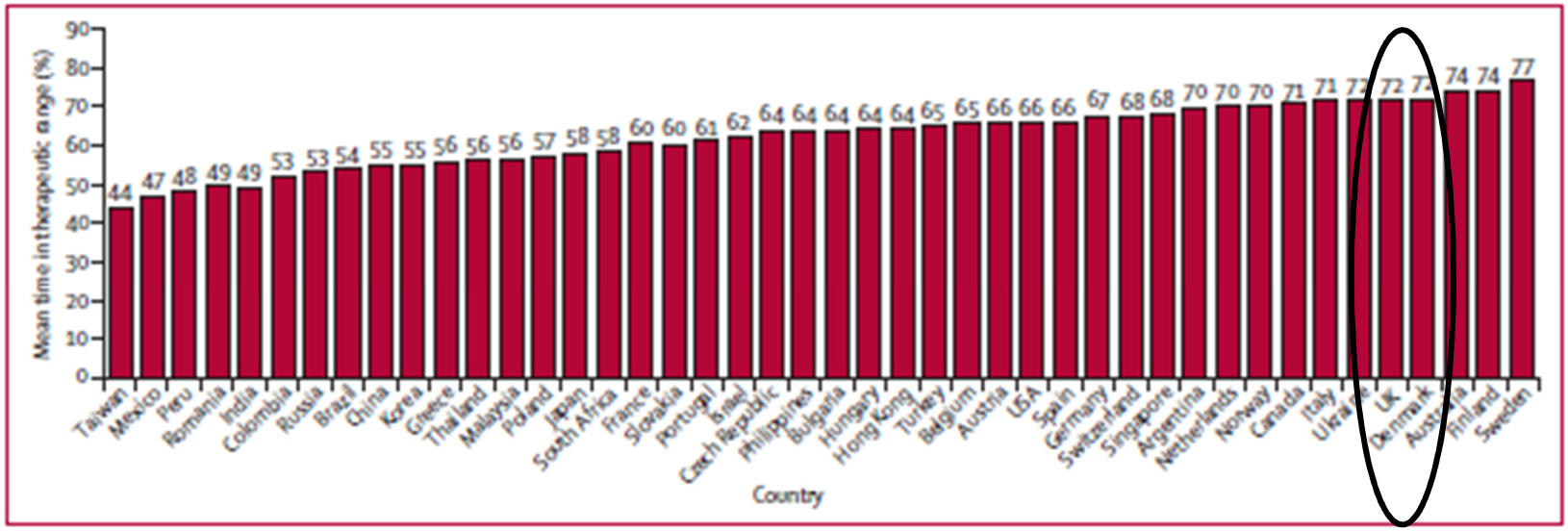


Figure 1: Country distribution of mean time in therapeutic range in the RE-LY trial

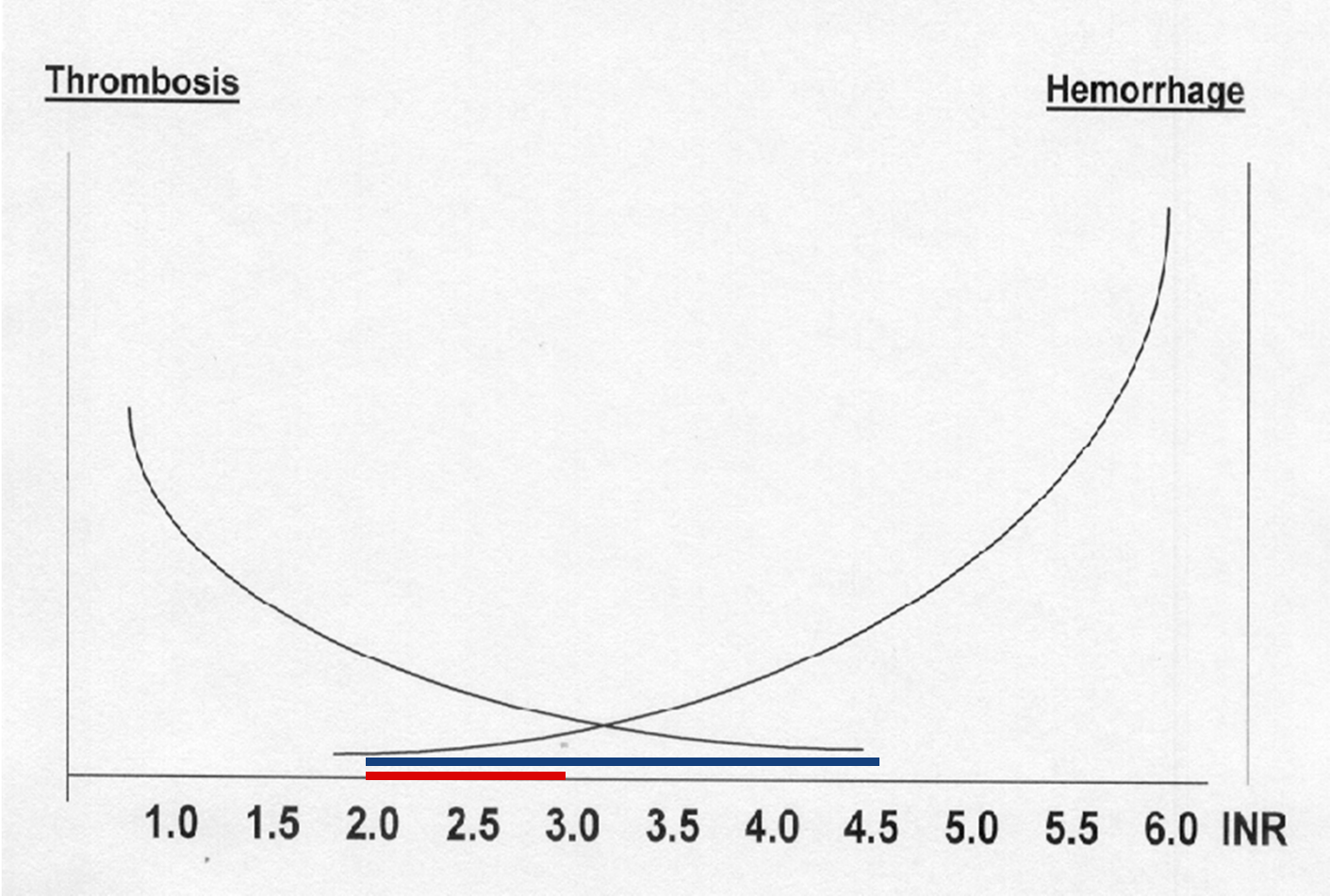
RE-LY trial

Historical background

- Standardization of the prothrombin time began in 1962
- WHO standardization scheme in 1983

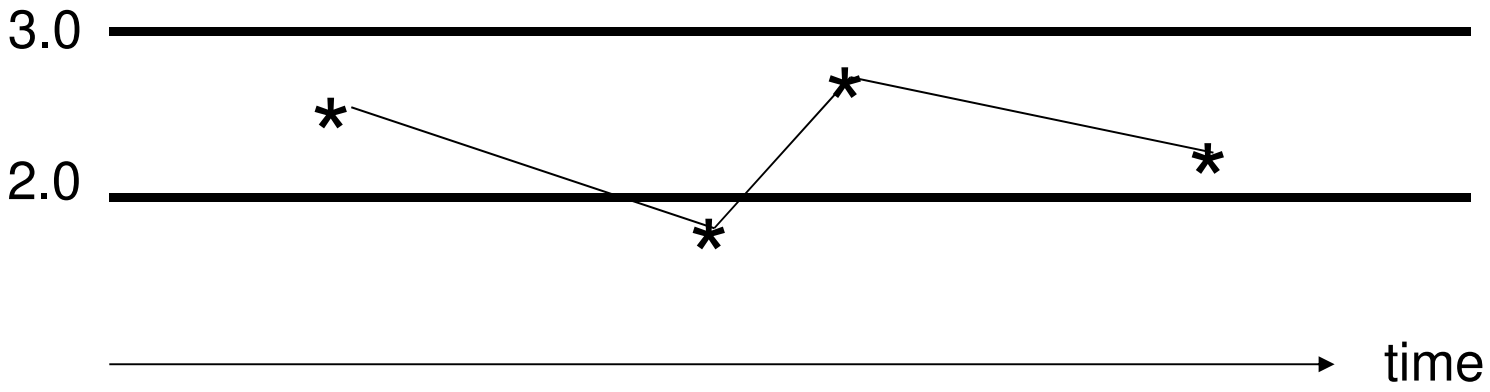
$$\text{INR} = \left[\frac{\text{PT Patient}}{\text{PT Reference Plasma}} \right]^{\text{ISI}}$$

Narrow therapeutic window



Monitoring the quality of anticoagulant treatment

- Rate of clinical events
- Number of INRs in range
- Percentage of INRs in range
- Time in terapeutic range (TIR) by linear interpolation



Computer-assisted dosage
- European Action on anticoagulation

Manual group	All weeks	1 – 3	4 – 9	10 – 21	22+
Number of patients	1,315	1,315	1,153	1,094	909
Patient years	1,599	122	149	240	1,088
Number of INRs	25,575	3,778	2,819	3,880	15,278
Number of clinical events (events/100 patient-years)	92 (5.8)	6 (4.9)	10 (6.7)	23 (9.6)	53 (4.9)
% TIR (Rosendaal)	63.4%	51.1%	58.4%	62.9%	64.4%

DAWN AC	All weeks	1 – 3	4 – 9	10 – 21	22+
Number of patients	1316	1316	1157	1089	894
Patient years	1649	125	146	247	1131
Number of INRs	28819	3694	3092	4377	17656
Number of clinical events (events/100 patient-years)	93 (5.6)	5 (4.0)	14 (9.5)	10 (4.0)	64 (5.6)
% TIR (Rosendaal)	66.8%	51.7%	60.7%	66.2%	69.6%

Poller et al, Thromb Haemost 2009

Clinical events

DAWN program	Manual-dosed (events per 100 patient years)	Computer-assisted dosage (events per 100 patient years)
Number of total events adjudicated	92 (5.8, [95% CI: 4.6–7.0])	93 (5.6, [95% CI:4.6–6.9])
Minor bleeds	*43 (2.7)*	*42 (2.5)*
Major bleeds	*14 (0.9)*	*23 (1.4)*
Thrombotic events	*23 (1.4)*	*15 (0.9)*
Deaths	*12 (0.8)*	*13 (0.8)*
Adjudicated as non-events	*7*	*10*

Number of events by clinical indication		
AF	51 (5.9)	53 (6.1)
DVT / PE	18 (6.4)	9 (3.1)
Mechanical heart valves	9 (5.9)	11 (7.3)
Other indications	14 (4.6)	20 (6.0)

Poller et al, Thromb Haemost 2009

Challenge:

- High quality treatment is already provided by anticoagulant clinics (TIR > 70%)
- About half of all clinical events occur at INR within therapeutic range
- TIR is often considered the ”golden standard”, but is **not** a dependable predictor of clinical events, particularly bleedings
- Room for improvement?

Focus on clinical events:

Table 1 Comparative results with warfarin and dabigatran in the RE-LY and EAA studies

	RE-LY study warfarin	Dabigatran		EAA study warfarin
		110 mg	150 mg	
Patients, total	6022	6015	6076	5939
Patients per centre	6.3			182.5
Average age	72			72
Starting anticoagulants, %	50			79
Overall events (% per year)				
Stroke	1.57	1.44	1.01	0.30
Major bleeding	3.36	2.71	3.11	0.86
Minor bleeding	16.37	13.16	14.84	2.70
Deaths per year	4.13	3.75	3.64	0.75

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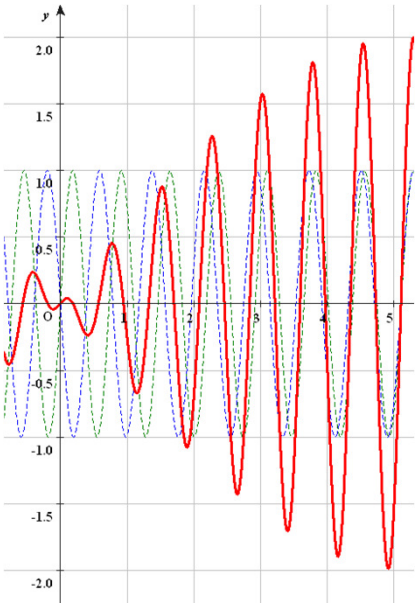
INR fluctuations

- Hypothesis: INR fluctuations (perhaps within therapeutic range or safe range) may cause clinical events



Variance growth rate

- A measure of INR variability and/or control

- Three different measurements of VGR were evaluated retrospectively in 158 cases and 661 controls from the European Action of Anticoagulation study

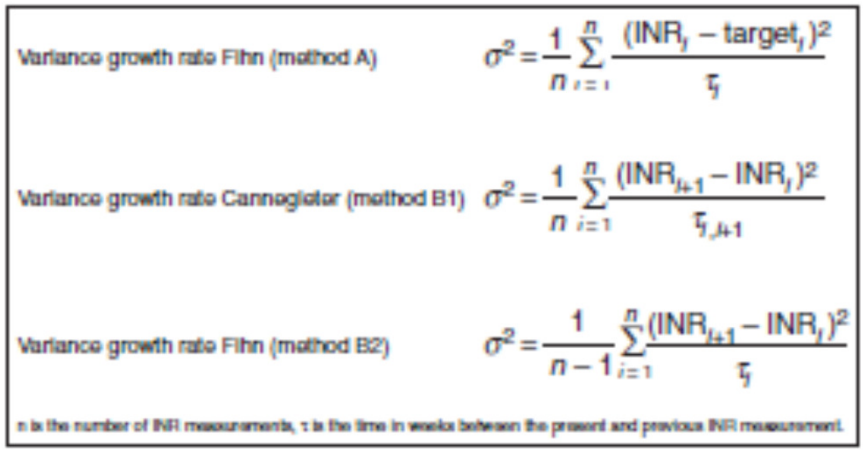


Fig. 1. Calculation formulas for the three variance growth rate methods measuring International Normalized Ratio (INR) variability and control (method A) and INR variability only (methods B1 and B2).

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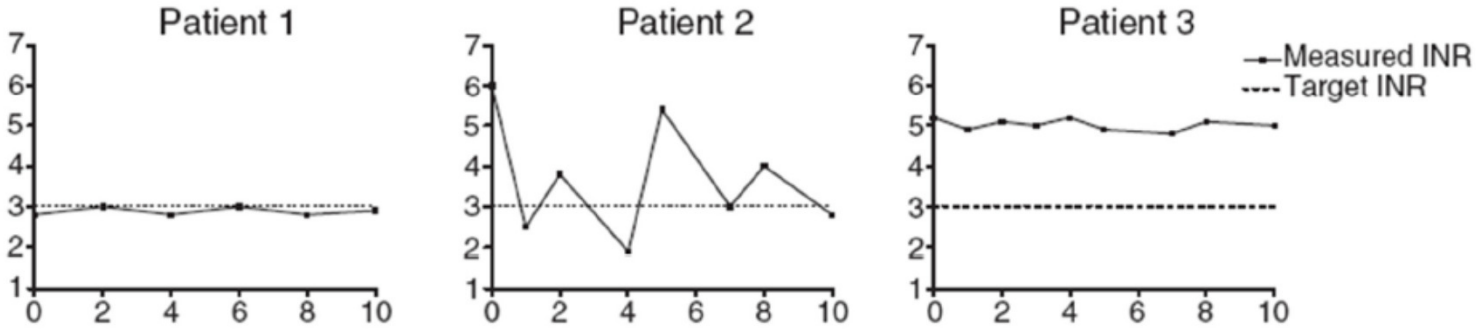
Patient Examples



Patient 1	Patient 2	Patient 3
Method A = 0.01	Method A = 1.04	Method A = 3.23
Method B1 = 0.01	Method B1 = 4.06	Method B1 = 0.03
Method B2 = 0.01	Method B2 = 4.64	Method B2 = 0.03

The above graphs show three different patients with a target INR of 3.0 and how each method for calculating the VGR rate would differ.

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”Predicting clinical events”, presentation by Syd Stewart

All clinical events

Table 2 Results of the regression models for the different categories, using the three variance growth rate (VGR) methods and time in target International Normalized Ratio (INR) range (TIR) for all clinical events

Assessment method – grouped categories	Study entry to event				6 months before event				3 months before event			
	OR	95% CI	*P*-value	C*	OR	9 % CI	*P*-value	C*	OR	95% CI	*P*-value	C*
TIR				0.60				0.61				0.59
Excellent	1.00				1.00				1.00			
Good	1.55	0.8–2.7	0.17		1.75	1.0–3.2	0.07		1.36	0.7–2.6	0.34	
Average	2.03	1.1–3.7	0.02†		2.30	1.3–4.0	< 0.01†		1.44	0.8–2.6	0.21	
Below average	2.15	1.2–3.8	0.01†		2.00	1.1–3.5	0.01†		2.11	1.3–3.6	< 0.01†	
Poor	1.60	0.9–2.9	0.10		1.85	1.1–3.2	0.03†		1.90	1.1–3.2	0.02†	
VGR												
Method A				0.61				0.63				0.64†
Excellent – stable	1.00				1.00				1.00			
Good	0.82	0.5–1.5	0.51		1.66	0.9–3.0	0.09		1.32	0.7–2.6	0.42	
Average	0.87	0.5–1.6	0.65		2.36	1.4–4.0	< 0.01†		2.43	1.4–4.0	< 0.01†	
Below average	0.67	0.4–1.2	0.16		1.93	1.1–3.5	0.03†		2.20	1.3–3.8	< 0.01†	
Poor – unstable	1.58	0.9–2.7	0.10		2.68	1.6–4.6	< 0.005†		3.30	1.9–5.7	< 0.005†	
Method B1				0.60				0.60				0.60
Excellent – stable	1.00				1.00				1.00			
Good	0.92	0.5–1.6	0.78		1.60	1.0–2.7	0.07		1.60	1.0–2.8	0.05	
Average	1.10	0.6–2.0	0.74		2.41	1.4–4.1	< 0.01†		1.51	0.9–2.6	0.15	
Below average	0.69	0.4–1.3	0.24		1.54	0.8–2.9	0.17		2.02	1.1–3.8	0.03†	
Poor – unstable	1.50	0.9–2.6	0.15		1.90	1.2–3.1	0.01†		2.06	1.3–3.4	< 0.01†	
Method B2				0.60				0.61				0.61
Excellent – stable	1.00				1.00				1.00			
Good	0.81	0.4–1.5	0.51		1.19	0.7–2.0	0.54		1.39	0.8–2.4	0.24	
Average	1.23	0.7–2.2	0.48		2.36	1.4–4.0	< 0.01†		2.00	1.2–3.6	0.01†	
Below average	0.79	0.4–1.5	0.46		1.81	1.0–3.2	0.04†		2.07	1.2–3.6	0.01†	
Poor – unstable	1.49	0.8–2.6	0.17		1.81	1.1–3.0	0.02†		2.00	1.2–3.3	< 0.01†	

CI, confidence interval; OR, odds ratio. TIR: excellent, > 80%; good, 80–69%; average, 69–57%; below average, 57–39%; poor, < 39%. VGR method A: excellent – stable, 0.0–0.1; good, 0.1–0.18; average, 0.18–0.32; below average, 0.32–0.67; poor – unstable, > 0.67. VGR methods B1 and B2: excellent – stable, 0.0–0.14; good, 0.14–0.28; average, 0.28–0.50; below average, 0.50–1.0; poor – unstable, > 1.0. *C-statistic from unconditional logistic regression models – all VGR models tested for equality as compared with the TIR C-statistic at their respective intervals. †Significant at 5% level.

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All bleeding events

Table 3 Results of the regression models for the different categories using the three variance growth rate (VGR) methods and time in target International Normalized Ratio (INR) range (TIR) for all bleeding events

Assessment method – grouped categories	Study entry to event				6 months before event				3 months before event			
	OR	95% CI	*P*-value	C*	OR	95% CI	*P*-value	C*	OR	95% CI	*P*-value	C*
TIR				0.59				0.61				0.60
Excellent	1.00				1.00				1.00			
Good	1.57	0.7–3.4	0.26		1.08	0.5–2.5	0.85		1.58	0.7–3.6	0.27	
Average	1.98	1.0–4.1	0.07		2.36	1.2–4.7	0.01†		1.97	0.9–4.1	0.07	
Below average	1.71	0.8–3.5	0.15		1.43	0.7–2.9	0.33		2.42	1.1–5.2	0.02†	
Poor	1.02	0.5–2.2	0.95		1.09	0.5–2.5	0.84		1.53	0.7–3.4	0.3	
VGR												
Method A				0.60				0.62				0.63
Excellent – stable	1.00				1.00				1.00			
Good	0.85	0.4–1.8	0.67		2.32	1.2–4.4	0.01†		1.72	0.6–4.6	0.28	
Average	1.11	0.6–2.2	0.76		2.18	1.1–4.3	0.02†		2.21	0.6–8.9	0.26	
Below average	0.60	0.3–1.3	0.19		1.10	0.5–2.4	0.81		2.88	1.1–7.2	0.02†	
Poor – unstable	1.47	0.8–2.9	0.26		2.66	1.4–5.2	< 0.01†		3.80	1.5–9.8	< 0.05†	
Method B1				0.62				0.60				0.62
Excellent – stable	1.00				1.00				1.00			
Good	1.00	0.5–2.0	0.99		1.42	0.7–2.7	0.3		1.87	0.7–4.7	0.18	
Average	1.19	0.6–2.3	0.62		2.56	1.3–5.0	0.01†		3.35	1.5–7.5	< 0.005†	
Below average	0.60	0.3–1.2	0.14		1.84	0.9–3.7	0.08		3.34	1.5–7.5	< 0.005†	
Poor – unstable	1.76	0.9–3.4	0.1		1.84	1.0–3.5	0.06		3.71	1.6–8.5	< 0.005†	
Method B2				0.61				0.60				0.62
Excellent – stable	1.00				1.00				1.00			
Good	0.90	0.4–1.9	0.78		1.04	0.5–2.0	0.91		1.89	0.7–5.1	0.22	
Average	1.21	0.6–2.4	0.59		2.38	1.2–4.7	0.01†		3.64	1.4–9.3	< 0.01†	
Below average	0.71	0.3–1.4	0.33		1.98	1.0–3.6	0.04†		3.80	1.5–9.7	< 0.01†	
Poor – unstable	1.65	0.8–3.3	0.15		1.61	0.9–3.0	0.14		4.10	1.6–10.6	< 0.01†	

CI, confidence interval; OR, odds ratio. TIR: excellent, > 82%; good, 82–69%; average, 69–57%; below average, 57–39%; poor, < 37%. VGR method A: excellent – stable, 0.0–0.1; good, 0.1–0.17; average, 0.17–0.29; below average, 0.29–0.60; poor – unstable, > 0.60. VGR methods B1 and B2: excellent – stable, 0.0–0.14; good, 0.14–0.27; average, 0.27–0.47; below average, 0.47–1.0; poor – unstable, > 1.0. *C-statistic from unconditional logistic regression models – all VGR models tested for equality as compared with the TIR C-statistic at their respective intervals. †Significant at 5% level.

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Conclusion

- ” …the predictive ability of the VGR methods was shown to be as effective as that of the typically reported precentage TIR, especially for INR monitoring in the short term”
- ”It is recommended that at least two outcome measures should be reported that assess INR and dose determination”

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Conclusion

Although the %TTR is generally reported in studies on the *full follow-up* of oral anticoagulation in patients:

INR monitoring with a measure such as the VGR on a shorter-term basis and %TTR (i.e. 3 or 6 months before the current INR measurement) *may* offer additional safety by detecting and isolating patients who may be at increased risk of possible adverse episodes.

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”Predicting clinical events”, presentation by Syd Stewart

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Final Thoughts

What meaningful actions to reduce the variability of Patient's INRs could you take?

A large prospective trial is needed to confirm the conclusions above?

Novel Oral Anticoagulants - no method of predicting events yet?

Need volunteer DAWN AC users to try out/give feedback on new VGR/%TTR features

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Taking up the challenge

Before a large trial is carried out

… we need to investigate how to implement VGR in daily practice

Feasibility study

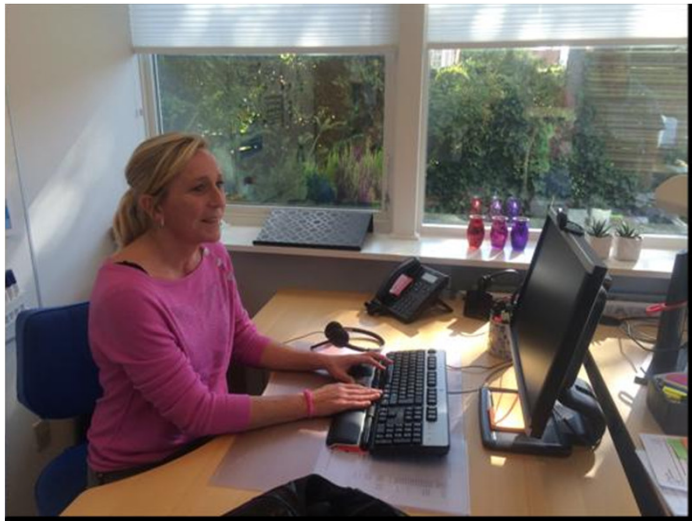
- Which method of VGR has the best *predictive ability* of poor anticoagulant control/clinical events?
- What cut-off of VGR is reasonable?
- How to respond to a rise in VGR?

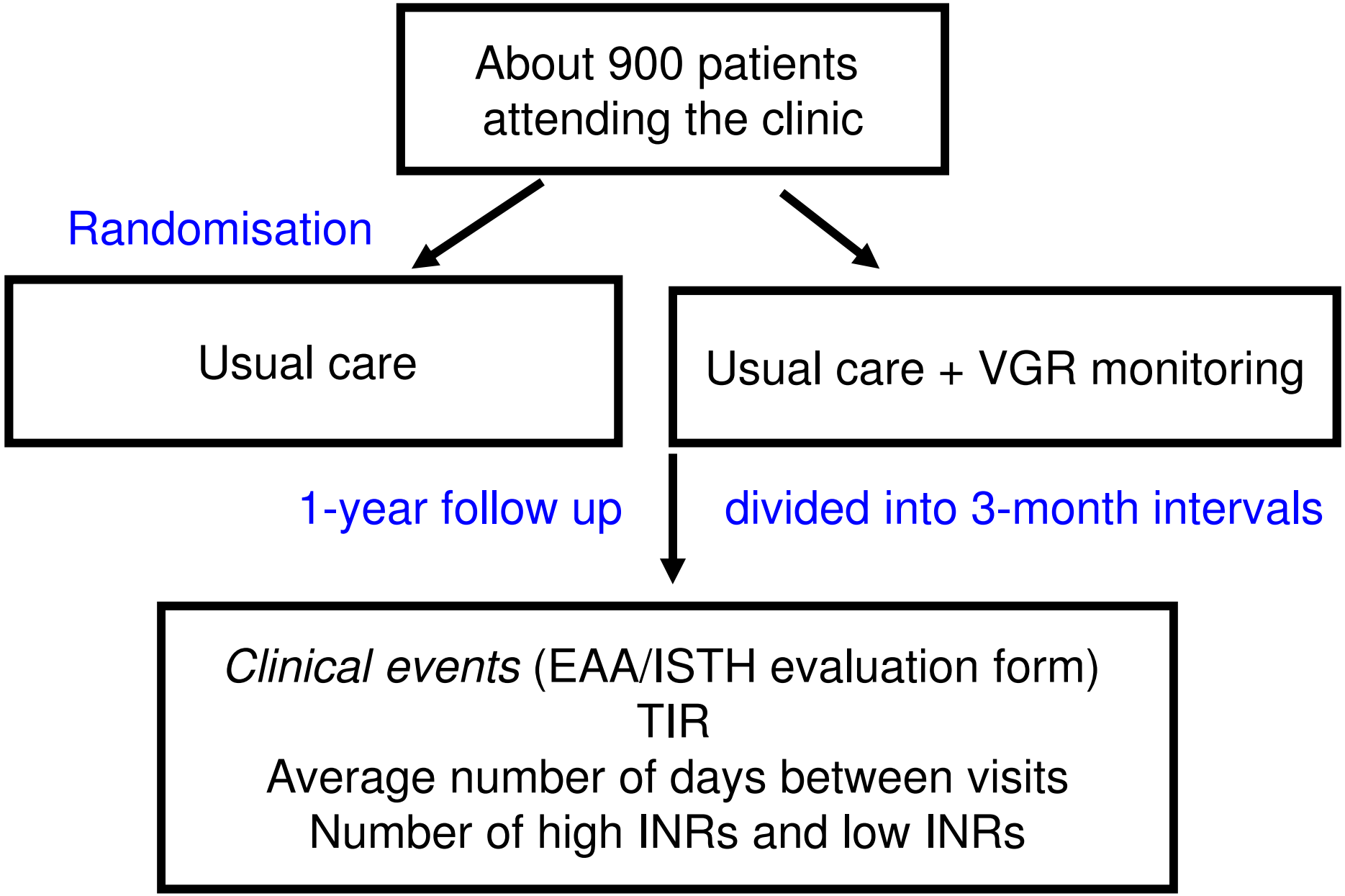
Prospective evaluation of VGR

- Setting: Anticoagulant Clinic, Esbjerg
  - 900 patients monitored in a nurse-managed, physician-supervised clinic
  - Documented high treatment quality (high TIR, low number of clinical events)

- Design
  - Single-site randomised, prospective study

    Larger randomised, prospective study?




About 900 patients attending the clinic
Randomisation
Usual care
Usual care + VGR monitoring
1-year follow up
divided into 3-month intervals
Clinical events (EAA/ISTH evaluation form)
TIR
Average number of days between visits
Number of high INRs and low INRs

Subgroup analysis

- Patients new to anticoagulant treatment and patients in long-term treatment (> 6 months)
- Patients with arterial and venous thrombotic disease
- Younger and older patients

Larger prospective trial

- Project investigating specialized atrial fibrillation clinics
- Collection of data for 3 years
- 250 patients/year are expected to be enrolled at each site

- Possibility to randomise patients to VGR monitoring or usual care

Thank you for listening