ECAT Symposium 2012

European Organisation For External Quality Assurance Providers in Laboratory Medicine

Interpretation and management of INR results: a case history based survey in 13 countries

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Countries and project-coordinators

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Norway	Kristoffersen AH, Thue G, Sandberg S
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Sweden	Nilsson E
The Netherlands	Meijer P and van der Meer FJ

Aims of the study:

- Evaluate practical performance of VKA monitoring
  - By clinicians in primary and secondary care
  - In 12 different countries in Europe + Australia

- Evaluate if…
  - …the practice is according to guidelines.
    - Are the guidelines appropriate for practical management?
  - …standardized and evidence-based algorithms are used for VKA maintenance dosing.

Method

- Two case histories
  - Two patients treated with VKA
    - A: Atrial fibrillation – stable anticoagulation
    - B: Pulmonary embolism – unexpected high INR result
- Questions to each case history
- Questions about the practice of the doctors

Different phases in laboratory medicine

- Pre-pre analytical
- Preanalytical
- Analytical
- Postanalytical
- ***Post-post analytical***

Favaloro EJ et al. Preanalytical and postanalytical variables: the leading Causes of diagnostic error in hemostasis? Sem Thromb Haemost 2008

Results

- Sent to about 14 000 in primary and secondary care
  - 3159 responded
  - Median response rate 25% (Range 8 – 38%)
  - 143 excluded
    - nurses, pharmacists
    - or did not state profession
- 62 – 267 respondents from each country
- .. and 1385 respondents from Norway

Type of care	Handled VKA patients > 1 time per week
Primary care: 79%	88%
Secondary care: 18%	93%

Case history A

- 76-year-old man with permanent atrial fibrillation and hypertension
- Treated with VKA* and antihypertensives

- Therapeutic interval INR 2.0 – 3.0 (target 2.5)
- Stable INR: 2.0 – 2.8 last months.

- **Today INR 2.3**
  - **You decide *not* to change the VKA dose.**

***Warfarin, acenocoumarol, phenprocoumon, fluindione**

Number of weeks until next INR: at least ___week(s), but no more than week(s).

Results:

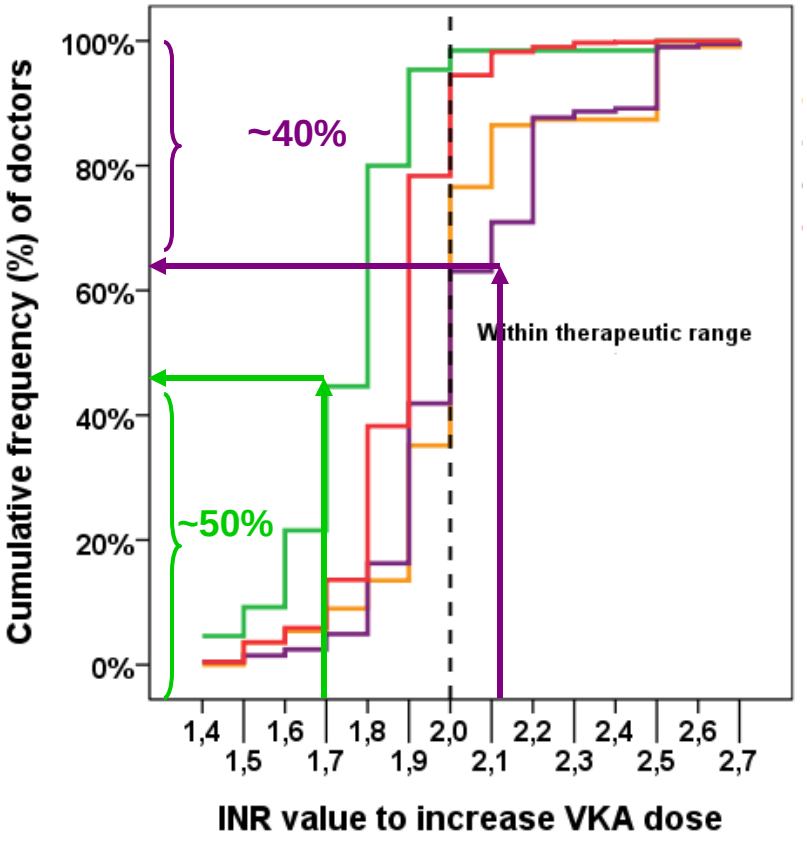
- At least ***4*** and no more than ***6*** weeks (medians)
  - ***England:***
    - GPs (and nurses) at least ***6*** weeks and no more than ***10*** weeks
    - Secondary care at least ***4*** but no more than **8** weeks
    - Larger variation than the other countries

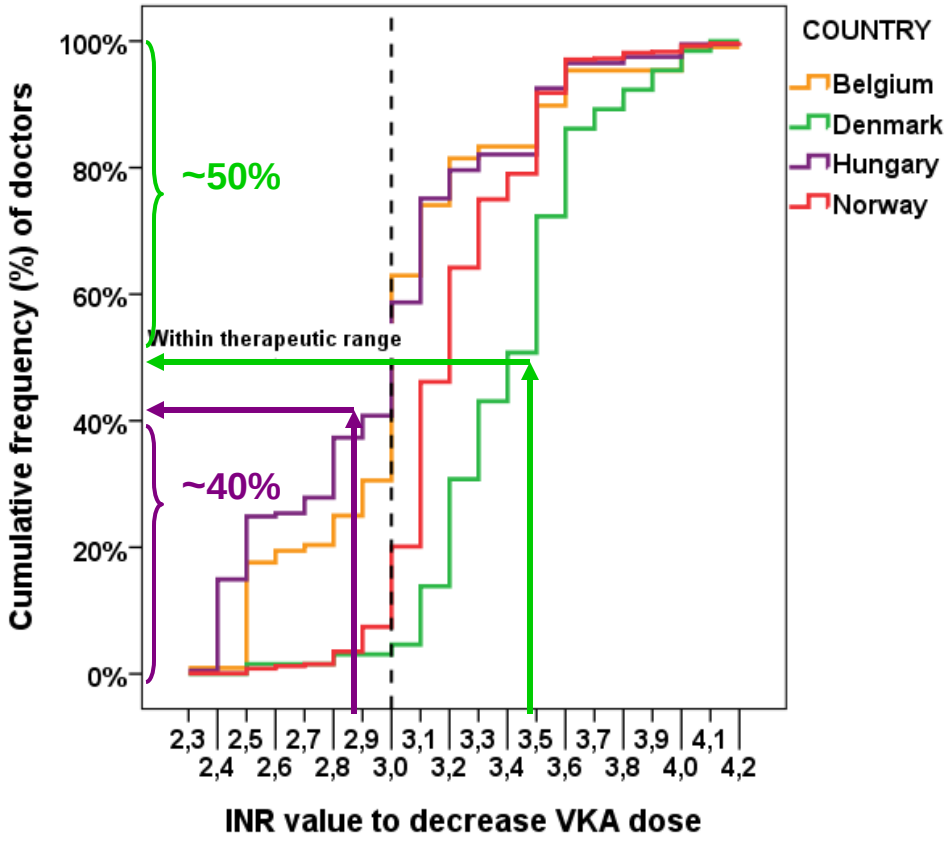
Belgium 3 and 5 weeks
France 3 and 4 weeks

Intervals of INR measurement in stable patients:

Guidelines	Recommendations
ACCP Guideline, Ansell J et al. Chest 2008 ***ACCP Guideline,Holbrook A et al. Chest 2012***	No more than 4 weeks Up to 12 weeks in stable patients
British 3rd ed., BJH 1998	Up to 12 weeks in stable patients
Algorithms	
Norwegian algorithm (Reikvam et al. 2011)	4 – 6 weeks
Danish algorithm (Dalsgaard 2011)	Up to 4 weeks
Studies	**Results**
Horstkotte D et al. J Thromb Thromb 1998 ***Samsa GP et al. J Thromb Thromb 2000***	More frequent intervals => TTR↑ Mostly from studies on patient-self monitoring
Rose AJ et al. Thromb Haemost 2008 ***Witt DM et al. Blood 2009??*** ***Witt DM et al. J Thromb Haemost 2010***	Less frequent intervals in stable patients => TTR ↑
Schulman S et al. Ann Int Med 2011	Randomized study of stable patients (1/3 of all): 12 weeks not inferior to 4 weeks.

INR value to increase and decrease VKA dose - last INR 2.3





INR value to increase and decrease VKA dose

Guidelines	Recommendations
ACCP Guideline, Ansell J et al. Chest 2008 ***ACCP Guideline, Holbrook A et al. Chest 2012***	No reduction in dose when minimally above. No change when INR ≤ 0.5 below or above.
Algorithms	
Norwegian algorithm (Reikvam et al. 2011)	Do not change dose when inside (< 5-8% when outside)
Danish algorithm (Dalsgaard 2011)	Change dose with 5 – 10% when INR is 0.1 – 0.3 outside the range.
Kim YK et al. (J Thromb Haemost 2010) ***Algorithm validated in a pilot study***	About 10% change right outside range.
Studies	**Results**
Banet GA et al. Chest 2003	No reduction in dose when INR is 3.2 - 3.4
Rose AJ et al. J Thromb Haemost 2009	No change until INR is 0.3 INR units outside limits => TTR↑
Sculman S et al. Thromb Res 2010	2 weeks after INR 1.5 – 4.4: 44% versus 40% INRs outside range if dose change versus not.

In your opinion, what is this patient's probability in the next year of having:

	Estimated risk (%) Median (range)		Actual risk (%)
	GPs	Secondary care	From studies
...an ischemic stroke if he is not treated with warfarin? _____%	**20 (6 – 50)**	**6 (5 – 21)**	**~4***
…an ischemic stroke while being treated with warfarin? _____%	**5 (2 – 10)**	**2 (1.4 – 4)**	**~1.3-1.5 (62-68% reduced risk)***
…a serious bleeding event with admission to hospital while treated with warfarin? _____%	**3 (1.5 – 5)**	**2 (1 – 5)**	**~1.3 – 1.9****

***Singer DE et al. Chest 2008, Hart RG et al. Ann Intern Med 2007**
****Schulman S et al. Chest 2008**

Case history B

- 62-year-old woman with pulmonary embolism
- Treated with VKA

- Therapeutic interval INR 2.0 – 3.0 (target 2.5).
- Last INR results: 2.4 and 3.0

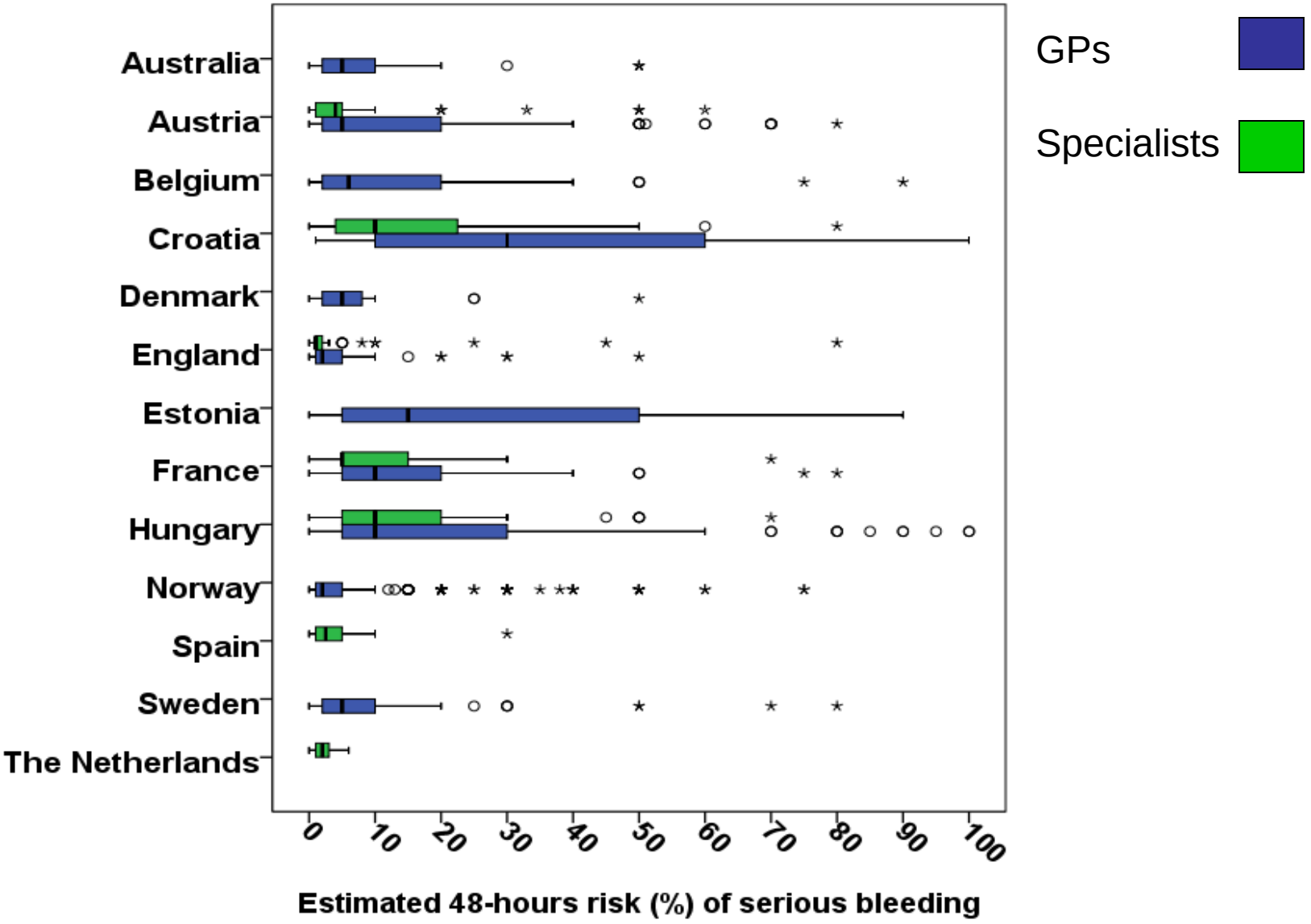
- Today (on a Monday) INR 4.8

Questions:

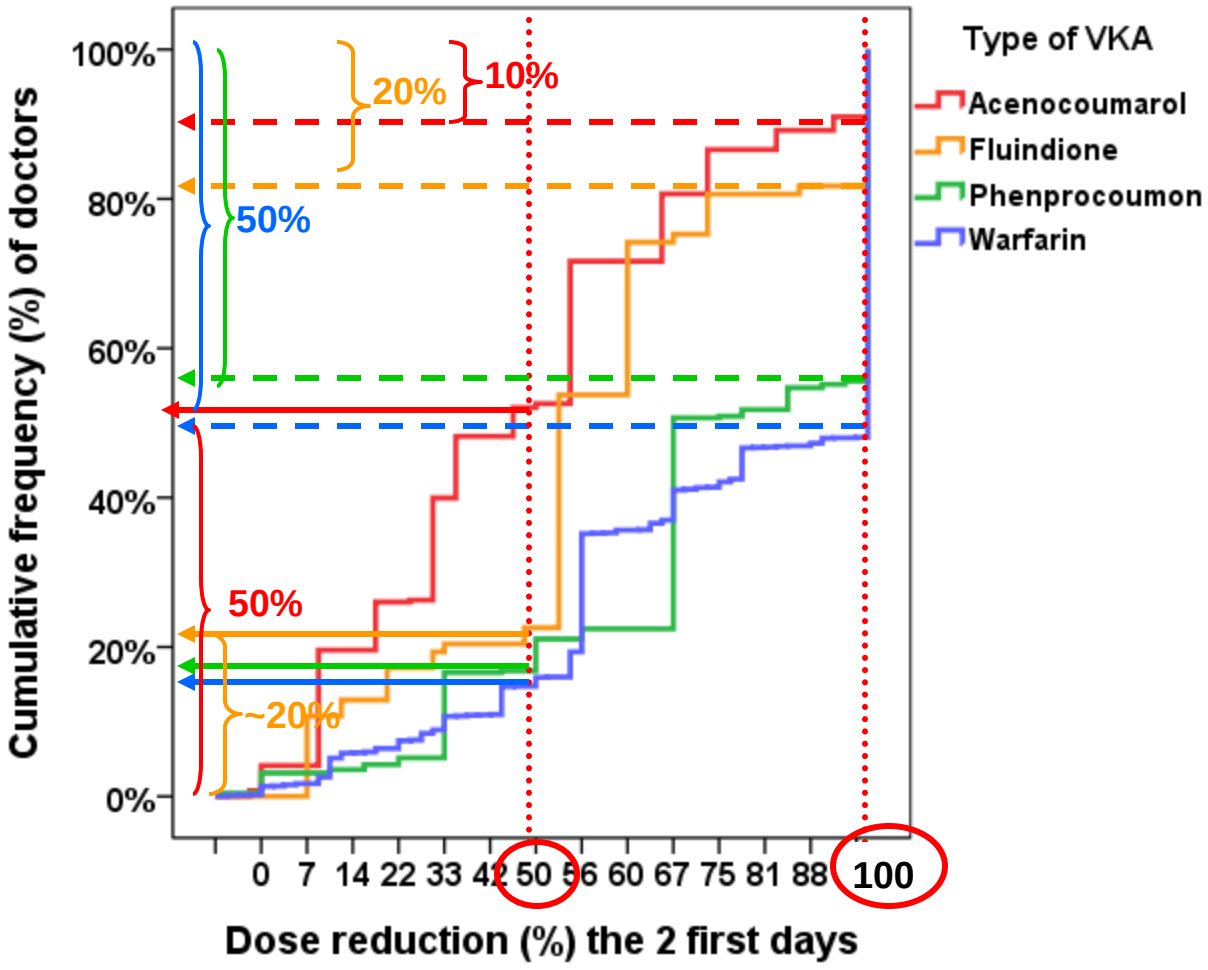
- Estimate the bleeding risk the next 2 days
- Fill in the dosing schedule until the day for a new INR measurement

Weeks ago	INR	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly dose
7	**2.4**	**10 mg**	**12**	**12**	**12**	**10**	**12**	**12**	**80 mg**
3	**3.0**	**10 mg**	**12**	**12**	**12**	**10**	**12**	**12**	**80 mg**
Today	**4.8**								

Bleeding risk the next 48 hours:



Dose reduction the two first days:



Acute dose reduction:

Guidelines	Recommendations
ACCP Guideline, Ansell J et al. Chest 2008	INR < 5.0 1) omit one dose **or** 2) reduce VKA dose
Algorithms	
Norwegian algorithm (Reikvam et al.) **1st edition 2005** **2nd edition 2011**	1st edition: omit 2 doses of VKA therapy 2nd edition: reduce dose or omit 1 dose of VKA therapy (ref ACCP 2008)
Danish algorithm (Dalsgaard 2011)	omit 0 – 2 doses of VKA therapy: low weekly dose => omit 2 days intermediate dose => omit 1 day large dose => only reduction of dose
Kim YK et al. (J Thromb Haemost 2010) ***Validatet in a pilot study***	Omit 1 dose

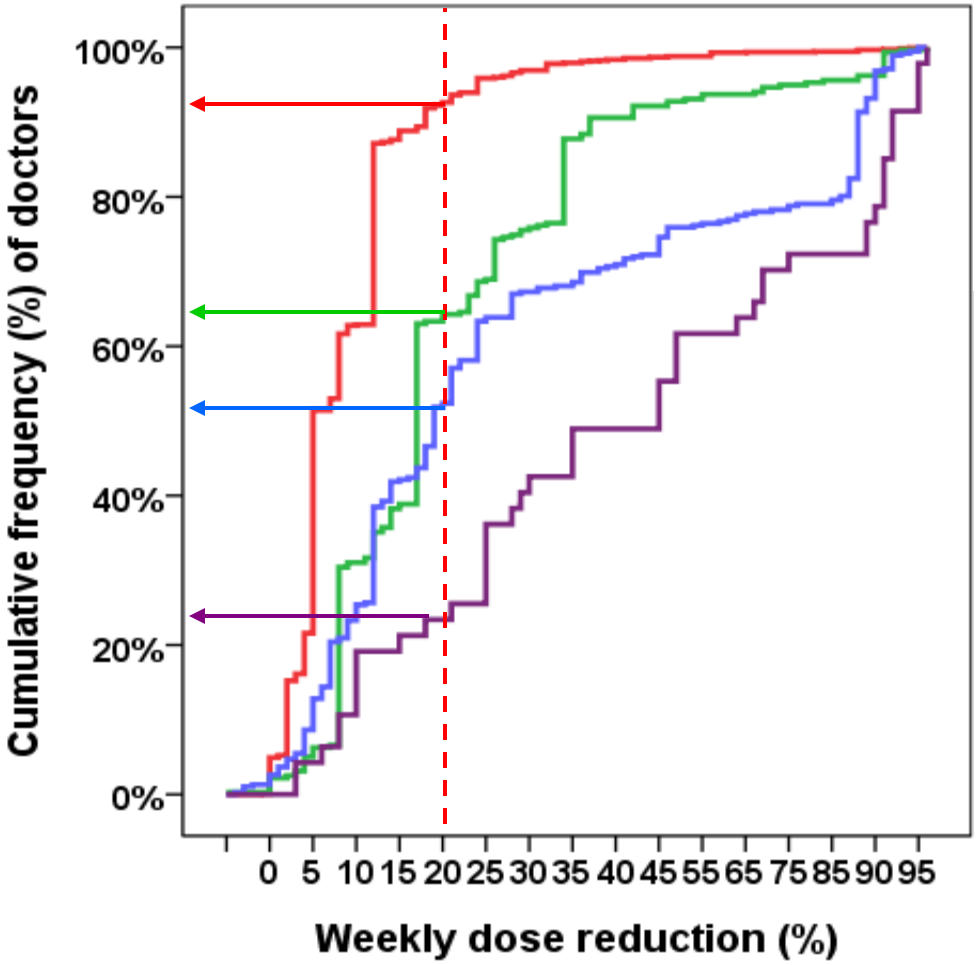
Number of days until a new INR measurement after an INR of 4.8.

- The median number of days until a new INR measurement: 7 days
  - range of medians 2 – 7
  - Considerable variability within each country
  - No difference between primary or secondary care
  - Not dependent on type of VKA used
- The estimated bleeding risk did ***not*** influence on
  - Number of days until a new INR measurement
  - Dose reduction the 2 first days

Days until INR measurement after a supra-therapeutic INR:

Guidelines	Recommendations
ACCP Guideline, Ansell J et al. Chest 2008	Monitor more frequently
Algorithms	
Norwegian algorithm (Reikvam et al.) **1st edition 2005** **2nd edition 2011**	Frequent INR monitoring
Danish algorithm (Dalsgaard 2011)	No specific advice
Kim YK et al. (J Thromb Haemost 2010)	Repeat measurement in 7 – 14 days
Studies	**Results**
Rose AJ et al. Circ Cardiovasc Qual Outcomes 2011	Repeat measurement within 7 days (higher TTR than less frequent INR measurements)

After your initial changes - INR 2.9: Estimate new weekly dose (in mg).



Group 1: Australia, Denmark, England spec., Norway, Spain, Sweden, The Netherlands

Group 2: England GP, Austria spec., Austria GP, Belgium GP, Estonia GP, Hungary spec

Group 3: Croatia GP, France, Hungary

Group 4: Croatia spec.

Weekly dose reduction after a supra-therapeutic INR

	Suggested weekly dose reduction
Guideline	
ACCP Guideline, Ansell J et al. Chest 2008	5 – 20%
Manual dosing algorithms	
Norwegian algorithm (Reikvam et al. 2011)	5 – 8%
Danish algorithm (Dalsgaard 2011)	10%
Kim YK et al. (J Thromb Haemost 2010)	10%
Franke CA et al. (Ann Fam Med 2008)	15 – 20%
Wilson SE et al. (J Thromb thromb 2007)	33%

Do you use clinical experience, manual dosing algorithms or computer dosing programs?

- 83% from Primary Care
- 71% from Secondary Care

} Only **clinical experience**

- **Manual dosing algorithms**
  - prevalent only in Norway and Denmark
    - used by about 50%

- **Computer dosing programs**
  - prevalent only in England and the Netherlands
    - used by 79% of GPs and 58% of specialists in England, 78% in the Netherlands

Underuse of evidence-based warfarin dosing methods for atrial fibrillation patients☆

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Thrombosis Research 125 (2010) e128–e131

- Canadian survey – Questionnaire – 300 doctors responded (~55%)
- ~75% of doctors in primary care and 83% of doctors in secondary care used only clinical experience when dosing.
- ~ 40% of dosing nurses used only clinical experience
- Conclusion:
  - Standardized methods for VKA management were underused

Which approach to follow to increase TTR?

Guideline	Recommendation
ACCP Guideline, Holbrook A et al. Chest 2012	Maintenance therapy: Validated paper nomograms or computer dosing programs - rather than no decision support
British guideline on oral anticoagulation – fourth edition. Keeling D et al. BJH 2011	Self monitoring Computer dosing programs

Time in therapeutic range (TTR) in different countries in RE-LY trial.

We found very large variations in dosing schedules in the different countries – and we have studied some of the ”better” countries.

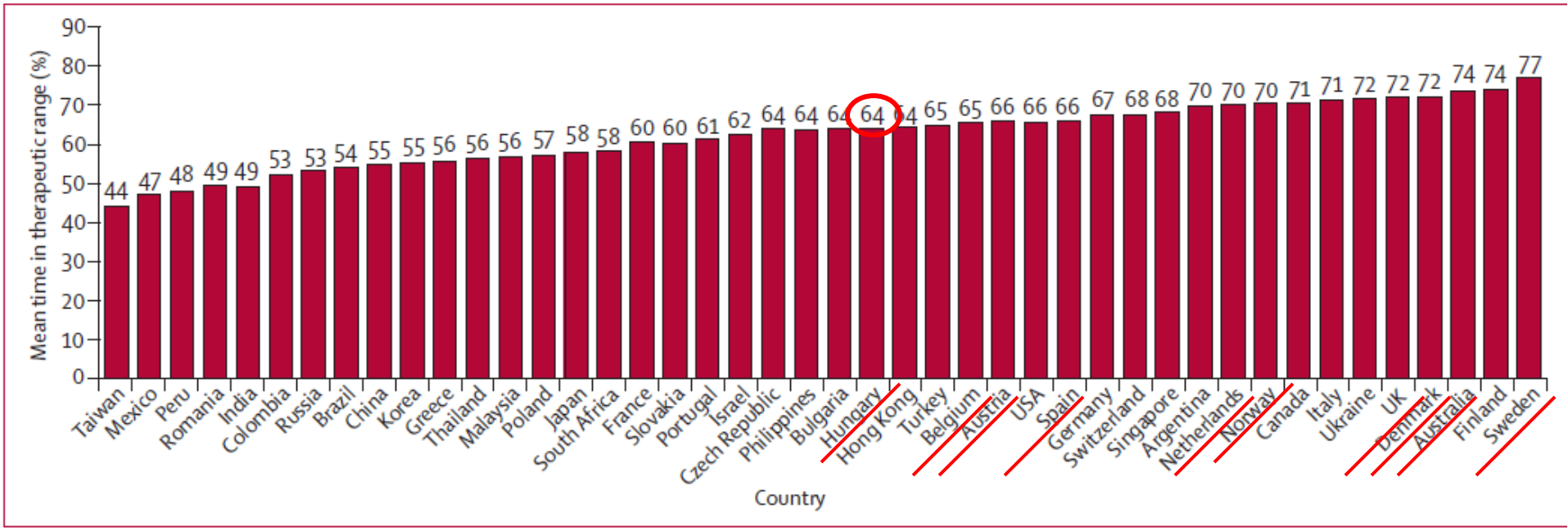

Figure 1: Country distribution of mean time in therapeutic range in the RE-LY trial

No information on Croatia and Estonia.

Summary

- Considerable variations for all results.
  - Both within-country and between-countries.
- Standardized methods for VKA maintenance dosing are used by a limited number of respondents in this survey.
- Efforts to standardize VKA monitoring are still needed.

Thanks to

- The coordinators in the different countries
- Thomas Ellingsen
  - for development of the web database and generating feedback reports
- Nina Christensen and others at NOKLUS
  - for helping with practical issues and with the distribution of the questionnaires
- Sivagowry Kanesamoorthy
  - for entering questionnaires into the web database

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