2°CONVEGNO DI ANTICOAGULAZIONE.it
scienza e pratica clinica per il management dei pazienti anticoagulati
AGGIORNAMENTI 2017

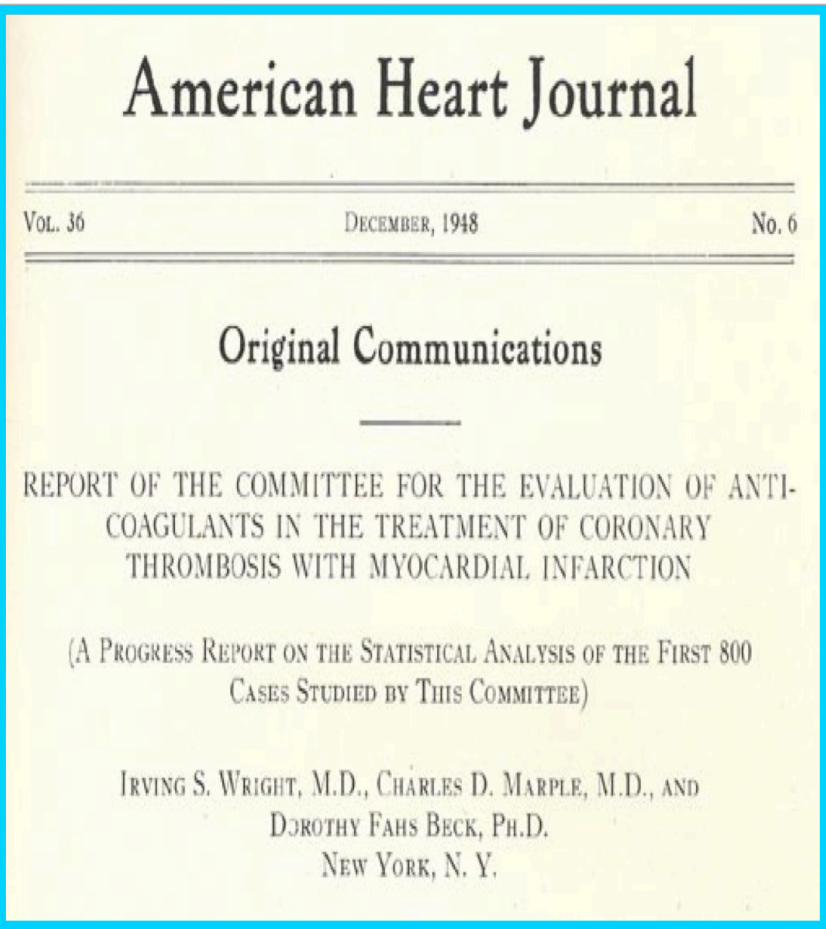
Problemi del Laboratorio per l'anticoagulazione (AVK e NAO)

Moderatori: Armando D'Angelo (Milano), Cristina Legnani (Bologna)

La qualità della terapia con AVK (TTR o altri criteri): problemi e modi per migliorare

Oltre il TTR: nuovi indicatori della qualità terapeutica

Cesare Manotti (Parma)



American Heart Journal

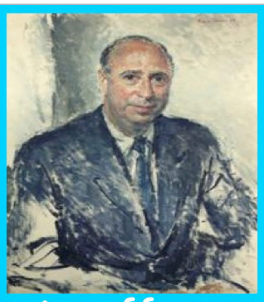
VOL. 36 DECEMBER, 1948 No. 6

Original Communications

REPORT OF THE COMMITTEE FOR THE EVALUATION OF ANTI-COAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

(A PROGRESS REPORT ON THE STATISTICAL ANALYSIS OF THE FIRST 800 CASES STUDIED BY THIS COMMITTEE)

IRVING S. WRIGHT, M.D., CHARLES D. MARPLE, M.D., AND DOROTHY FAHS BECK, PH.D.
NEW YORK, N. Y.



"Non basta affermare che ad un paziente sono stati somministrati farmaci anticoagulanti. Le domande alle quali bisogna rispondere sono: in che quantità, per quanto tempo, quali livelli di efficacia sono stati ottenuti, quanto a lungo tali livelli sono stati mantenuti. Queste informazioni sono necessarie per stabilire se un insuccesso è stato provocato dalla terapia stessa o se la responsabilità ricade su coloro che la somministrano".

Il controllo della qualità terapeutica : un nuovo impegno della FCSA (2000)

OBIETTIVI

FCSA

Valutare la qualità del trattamento nei Centri Federati

Conoscere l'attività del Centri Federati

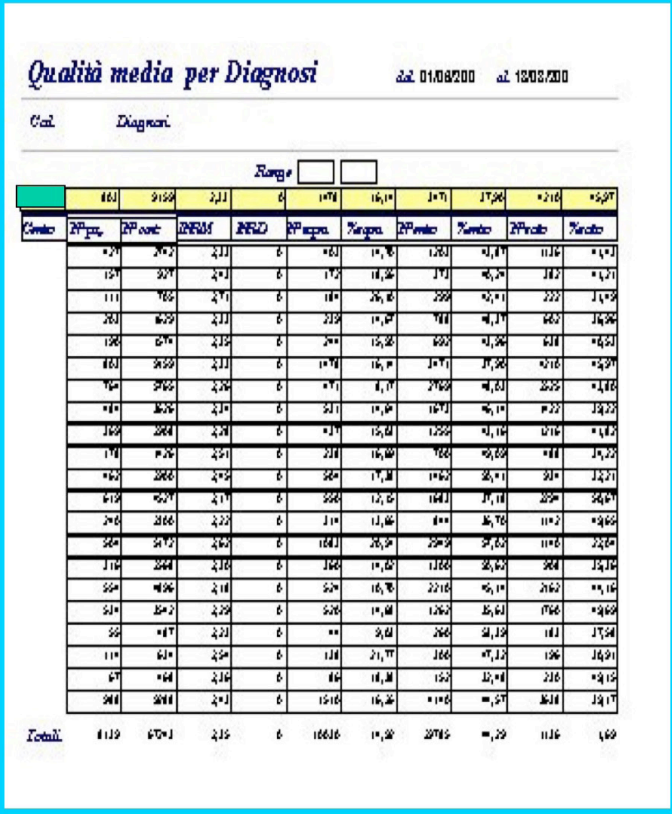
SINGOLI CENTRI

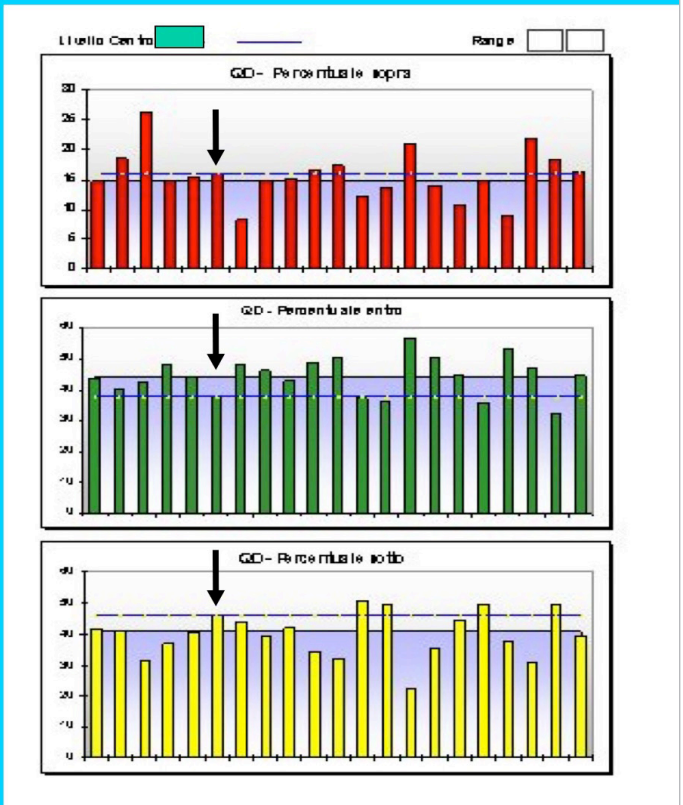
Verificare la Qualità' Terapeutica del CENTRO **confrontandola** con quella degli altri CENTRI partecipanti.

Migliorare la Qualità del Trattamento nei singoli pazienti

Qualificare le prestazioni del Centro

CONTROLLO della QUALITA' TERAPEUTICA (tipo 2)
ANALISI PER SINGOLO CENTRO





Il controllo di qualità della TAO

Metodi di analisi

INR oriented

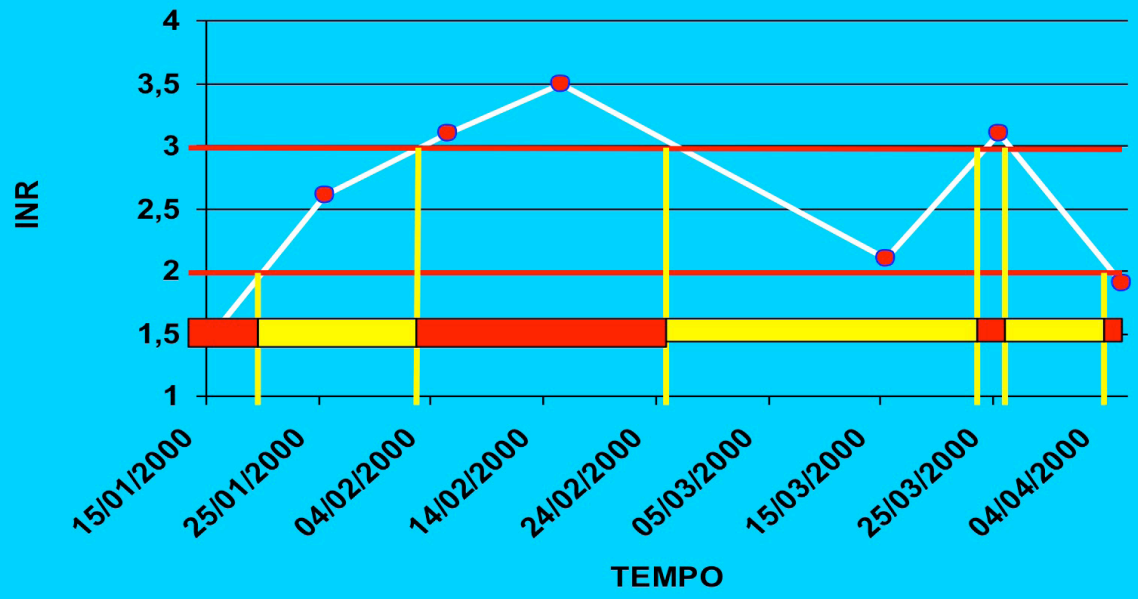
Cumulative INR
Cross section of the files

Patient-time oriented

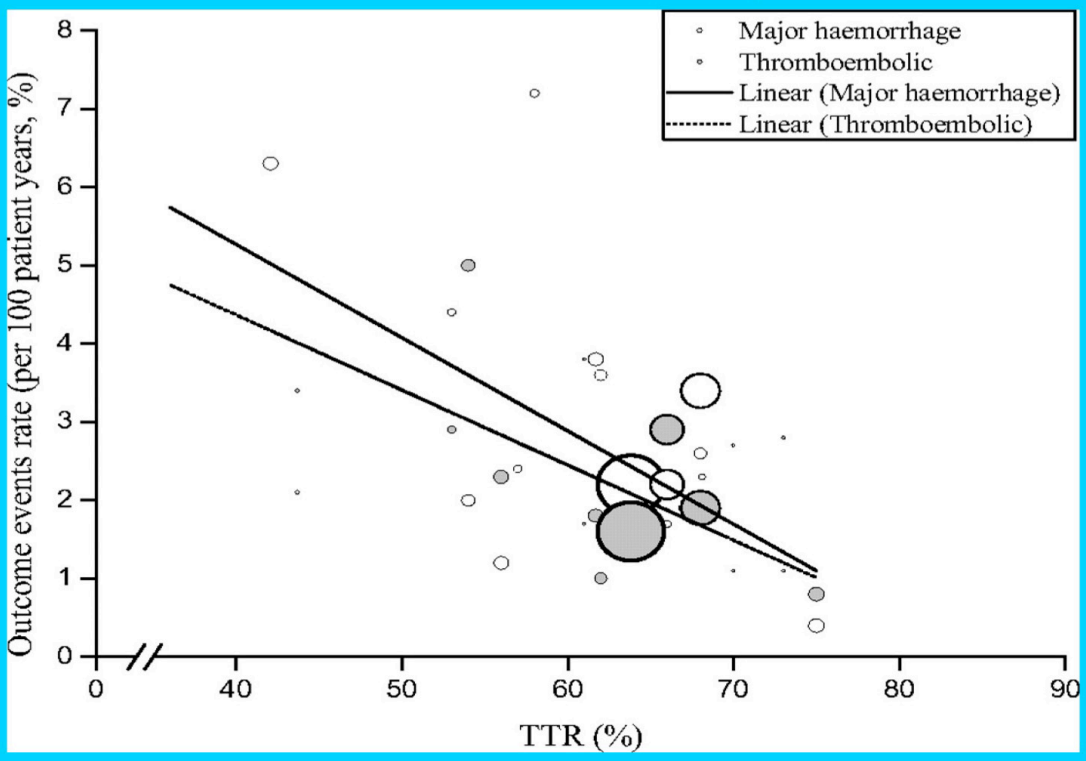
Linear interpolation change (TTR)
(Rosendaal, 1993)

Il controllo di qualità della TAO

INTERPOLAZIONE LINEARE (TEMPO IN RANGE)



TTR versus adverse events (weighted by sample size) for all studies



Qualità ottimale > 60% TTR

Wan, Y. et al. Circ Cardiovasc Qual Outcomes 2008;1:84-91

IMPIEGO TTR nella PRATICA CLINICA :

1) Analisi qualità del trattamento in studi clinici rispetto all'incidenza eventi avversi (mTTR)

2) Verifica "performance" fra Centri (cTTR)

3) Verifica qualità per migliorare efficacia e sicurezza trattamento nel singolo paziente (iTTR)

4) Indicatore per decisione di variazione farmaco (cut off TTR 60%-70%)

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Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lars Wallentin, Salim Yusuf, Michael D Ezekowitz, Marco Alings, Marcus Flather, Maria Grazia Franzosi, Prem Pais, Antonio Dans, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul A Reilly, Sean Yang, Stuart J Connolly, on behalf of the RE-LY Investigators

	110 mg dabigatran			150 mg dabigatran			Warfarin			110 mg dabigatran vs warfarin		150 mg dabigatran vs warfarin	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR (95% CI)	p (interaction)	HR (95% CI)	p (interaction)
Stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, and major bleeding													
<57·1%	1497	220	7·65	1509	199	6·83	1504	285	10·13	0·74 (0·62–0·89)	..	0·67 (0·56–0·80)	..
57·1–65·5%	1524	239	7·84	1526	217	7·09	1514	241	8·03	0·97 (0·81–1·16)	..	0·87 (0·73–1·05)	..
65·5–72·6%	1474	205	6·88	1484	220	7·41	1487	212	7·13	0·97 (0·80–1·17)	..	1·05 (0·87–1·27)	..
>72·6%	1482	200	6·85	1514	212	7·07	1509	192	6·42	1·07 (0·87–1·30)	0·036	1·11 (0·91–1·35)	0·0006
Total death													
<57·1%	1497	120	4·17	1509	112	3·85	1504	161	5·72	0·73 (0·58–0·92)	..	0·67 (0·53–0·85)	..
57·1–65·5%	1524	121	3·97	1526	115	3·75	1514	123	4·09	0·97 (0·75–1·24)	..	0·92 (0·71–1·18)	..
65·5–72·6%	1474	95	3·19	1484	108	3·64	1487	110	3·70	0·86 (0·65–1·13)	..	0·98 (0·75–1·28)	..
>72·6%	1482	105	3·60	1514	99	3·30	1509	91	3·04	1·18 (0·89–1·57)	0·066	1·08 (0·81–1·44)	0·052

HR=hazard ratio.

Table 4: Composite cardiovascular events and total mortality according to centres' mean time in therapeutic range

Lancet 2010; 376: 975-83

IMPIEGO TTR nella PRATICA CLINICA :

1) Analisi qualità del trattamento in studi clinici rispetto all'incidenza eventi avversi (mTTR)

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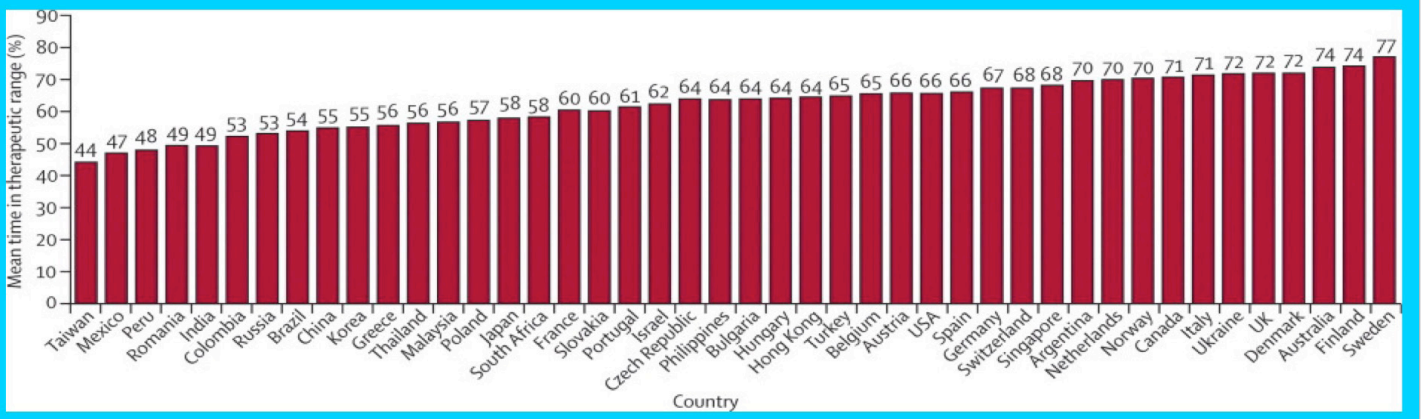


Lancet 2010; 376: 975-83

Center-Related Determinants of VKA Anticoagulation Quality: A Prospective, Multicenter Evaluation

Alberto Tosetto[1]*, Cesare Manotti[2], Francesco Marongiu[3], Italian Federation of Anticoagulation Clinics (FCSA) clinical quality study group[¶]

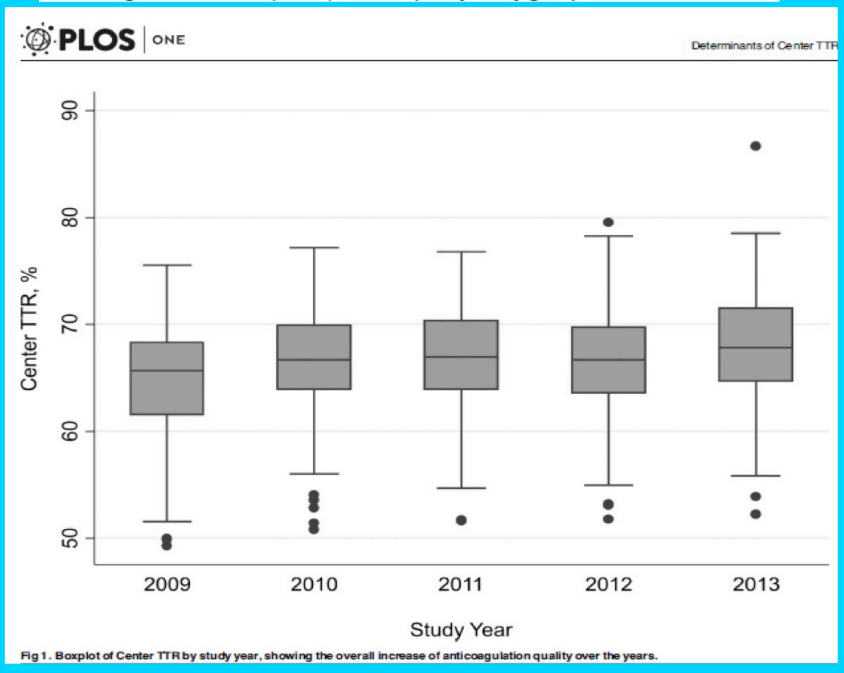


Fig 1. Boxplot of Center TTR by study year, showing the overall increase of anticoagulation quality over the years.

PLOS ONE | DOI: 10.1371/journal.pone.0144314 December 4, 2015

IMPIEGO TTR nella PRATICA CLINICA :

1) Analisi qualità del trattamento in studi clinici rispetto all'incidenza eventi avversi (mTTR)

2) Verifica "performance" fra Centri (cTTR)

3) Verifica qualità per migliorare efficacia e sicurezza trattamento nel singolo paziente (iTTR)

4) Indicatore per decisione di variazione farmaco (cut off TTR 60%-70%)

Quality of Vitamin K Antagonist Control and 1-Year Outcomes in Patients with Atrial Fibrillation: A Global Perspective from the GARFIELD-AF Registry

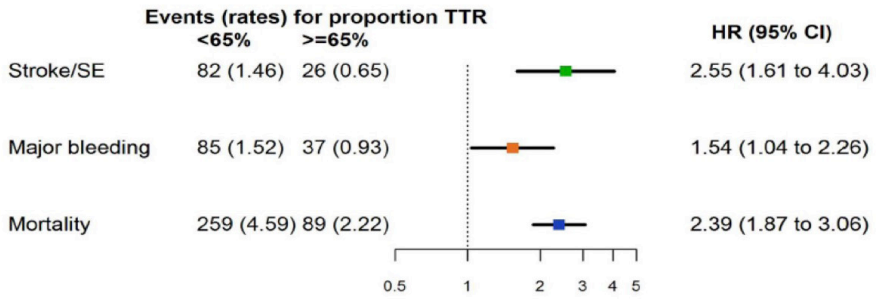


Fig 1. Incidence rates and adjusted hazard ratios for 1-year clinical outcomes according to proportion of time in therapeutic range. Reference group: TTR≥65%. Incidence rates are per 100 person-years. CI, confidence interval; HR, hazard ratio; SE, systemic embolism; TTR, time in therapeutic range. HRs were controlled for the following potential confounders: age group (≤64, 65–69, 70–74, ≥75 years), gender, smoking (no, ex, current), congestive heart failure, vascular disease, moderate-to-severe chronic kidney disease, diabetes mellitus, hypertension, previous stroke (not included in the model for major bleeding events), previous bleeding (not included in the model for stroke/SE), antiplatelet treatment, type of atrial fibrillation, and area (Europe, Asia, other countries).

Conclusion

A large proportion of patients with AF had poor VKA control and these patients had higher risks of stroke/SE, major bleeding, and all-cause mortality. Our data suggest that there is room for improvement of VKA control in routine clinical practice and that this could substantially reduce adverse outcomes.

PLOS ONE | DOI:10.1371/journal.pone.0164076 October 28, 2016

CARATTERISTICHE IMPIEGO TTR :

VANTAGGI

CALCOLO NON COMPLESSO

RISULTATO DI INTUITIVA INTERPRETAZIONE

CONSIDERA L' INTESITA' ' DEL LIVELLO INR RISPETTO AI GIORNI

PERMETTE DI CORRELARE INTESITA' TRATTAMENTO CON L'INCIDENZA DEGLI EVENTI AVVERSI

LIMITI

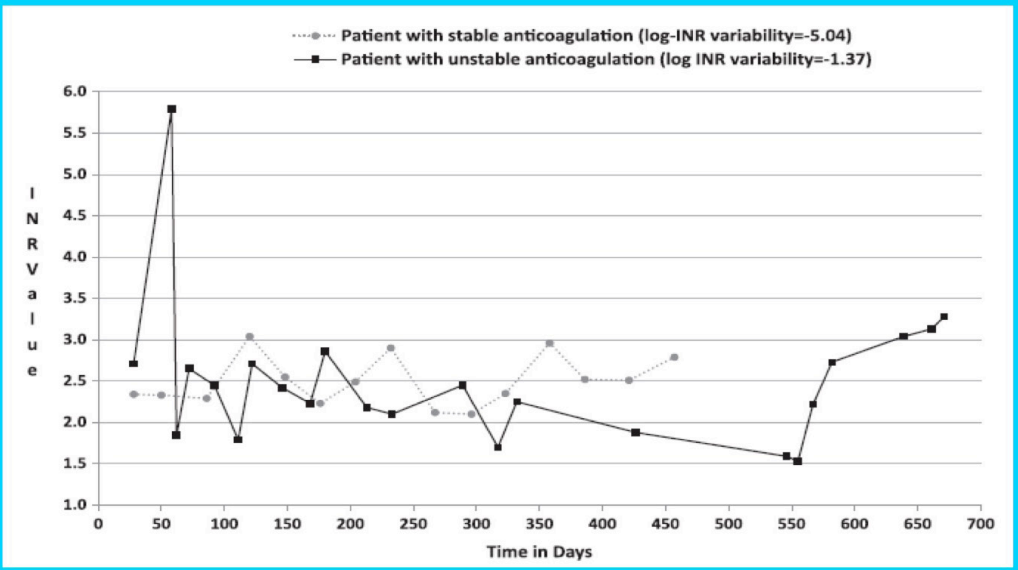
SCARSA DISTINZIONE FRA VALORI OLTRE IL RANGE (MOLTO OLTRE VS POCO OLTRE)

NECESSITA' DI STANDARDIZZAZIONE (TEMPI ESECUZIONE, CRITERI DI ESCLUSIONE INR)

VIENE CONSIDERATA UNA VARIAZIONE LINEARE DELL'INR FRA UN CONTROLLO E L'ALTRO NON CONSIDERADO VARIABILITA' E LA STABILITA' ENTRO IL RANGE DELL' INR o RISPETTO AL PRECEDENTE CONTROLLO NEL SINGOLO PAZIENTE

L'INTERPOLAZIONE NON CONSIDERA LA RELAZIONE FRA CAMBIO DOSE E VARIAZIONE INR

VARIABILITA' INDIVIDUALE DELL'INR



Alternative Calculations of Individual Patient Time in Therapeutic Range While Taking Warfarin: Results From the ROCKET AF Trial

Daniel E. Singer, MD; Anne S. Hellkamp, MS; Zhong Yuan, MD, PhD; Yuliya Lokhnygina, PhD; Manesh R. Patel, MD; Jonathan P. Piccini, MD, MHS; Graeme J. Hankey, MD; Günter Breithardt, MD; Jonathan L. Halperin, MD; Richard C. Becker, MD; Werner Hacke, MD, PhD; Christopher C. Nessel, MD; Kenneth W. Mahaffey, MD; Keith A. A. Fox, MB, ChB; Robert M. Califf, MD for the ROCKET AF Investigators

Background—In the ROCKET AF (Rivaroxaban–Once-daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) trial, marked regional differences in control of warfarin anticoagulation, measured as the average individual patient time in the therapeutic range (iTTR) of the international normalized ratio (INR), were associated with longer inter-INR test intervals. The standard Rosendaal approach can produce biased low estimates of TTR after an appropriate dose change if the follow-up INR test interval is prolonged. We explored the effect of alternative calculations of TTR that more immediately account for dose changes on regional differences in mean iTTR in the ROCKET AF trial.

Methods and Results—We used an INR imputation method that accounts for dose change. We compared group mean iTTR values between our dose change–based method with the standard Rosendaal method and determined that the differences between approaches depended on the balance of dose changes that produced in-range INRs ("corrections") versus INRs that were out of range in the opposite direction ("overshoots"). In ROCKET AF, the overall mean iTTR of 55.2% (Rosendaal) increased up to 3.1% by using the dose change–based approach, depending on assumptions. However, large inter-regional differences in anticoagulation control persisted.

Calculation of iTTR in the Face of Dose Changes

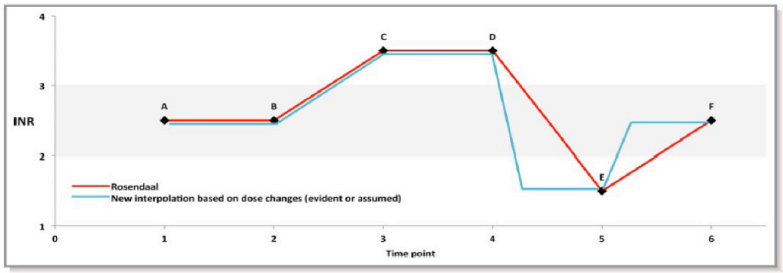


Figure 1. Schematic diagram comparing imputation of international normalized ratio (INR) values between pairs of INR tests using the Rosendaal linear interpolation approach (in red) versus a dose change–based approach (in blue). In this diagram, the target INR range is 2.0 to 3.0 and is highlighted in gray. Points A to F represent INR test results. Points A and B are both in range, and points C and D are both out of range. Since point B is in range, there will be no dose change between B and C. As a result, the 2 imputation approaches do not differ between points A through D. At point D, the INR is above range and a dose change is made resulting in the below-range INR at point E (an "overshoot"). The imputation of INR values will differ by algorithm as illustrated (see Methods), with the result that the individual patient time in the therapeutic range (iTTR) (time in the gray range) will be lower using the dose change-based algorithm. The path from point E to point F illustrates an out-of-range to in-range transition (a "correction"). For such transitions, the dose change–based algorithm will impute a larger iTTR. Across a group of individuals, the difference in mean iTTR according to the 2 imputation approaches will depend on the net effect of corrections versus overshoots.

Il controllo di qualità della TAO
NUOVI Metodi di analisi proposti

INR Variability Variance Growth Rate(VGR)
(Fihn, 1993;Cannagetier, 1999;Fihn, 1996)

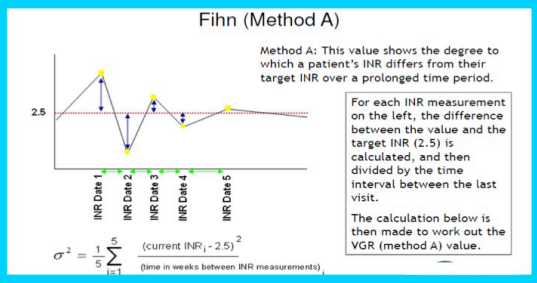
Deviazione Standard INR rispetto linea regressione (SDT_{inr})
(Lind, 2011)

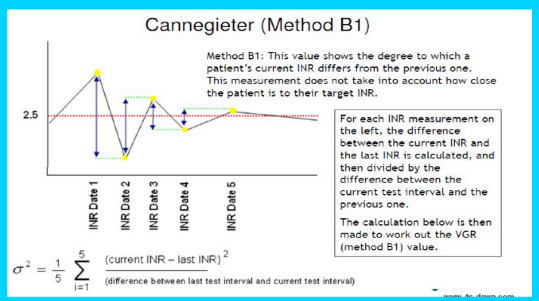
Patterns longitudinali INR (Cluster analisys)
(van den Ham, 2012)

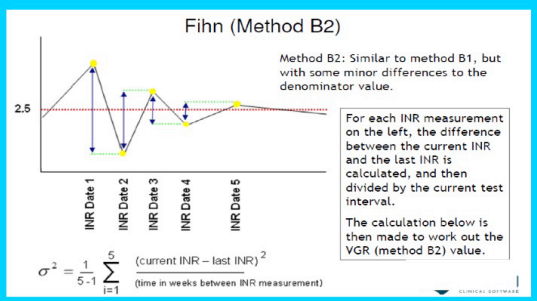
Warfarin Composite Measure (WCM)
(Razouki, 2015)

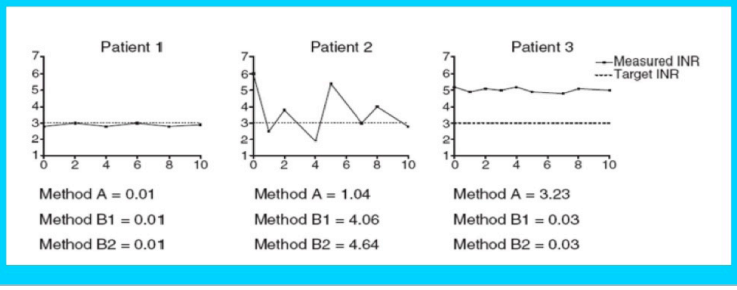
TTR con calcolo variazione INR in base a VARIAZIONE dose
(Singer,2015)

VARIANCE GROWTH RATE VGR









The clinical evaluation of International Normalized Ratio variability and control in conventional oral anticoagulant administration by use of the variance growth rate

S. IBRAHIM,* J. JESPERSEN,† L. POLLER* and ON BEHALF OF THE EUROPEAN ACTION ON ANTICOAGULATION

Summary. *Introduction:* The time in target International Normalized Ratio (INR) range (TIR) is used to assess the control and intensity of oral anticoagulation, but it does not measure variation in the INR. *Objectives:* The value of assessing INR variability by use of the variance growth rate (VGR) as a predictor of events was investigated in patients treated with warfarin. *Methods:* Three different methods of VGR determination (A, B1, and B2) together with the TIR were studied. Method A measures both INR variability and control, but methods B1 and B2 measure variability only. The VGR and TIR were determined over three time periods: overall follow-up to an event, and 6 months and 3 months before an event.

J Thromb Haemost 2013; 11: 1540–6.

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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.

J Thromb Haemost 2013; 11: 1540–6.

The clinical evaluation of International Normalized Ratio variability and control in conventional oral anticoagulant administration by use of the variance growth rate

S. IBRAHIM,* J. JESPERSEN,† L. POLLER* and ON BEHALF OF THE EUROPEAN ACTION ON ANTICOAGULATION

Results: Six hundred and sixty-one control patients were matched to 158 cases (bleeding, thromboembolism, or death). With all VGR methods, the risk of an event was greater in unstable patients at 6 months before an event than in stable patients. Method A demonstrated the greatest risk 3 months before an event in the unstable VGR group as compared with the stable group (odds ratio 3.3, 95% confidence interval 1.9–5.7, $P < 0.005$). The risk of an event was 1.9 times greater in patients with a low TIR (< 39%) than in those with a high TIR (> 80%) in the 3-month period ($P = 0.02$). Risk of bleeding was significantly greater in the 3-month period in patients with unstable VGR, with the greatest risk found with method B2 ($P < 0.01$).

J Thromb Haemost 2013; 11: 1540–6.

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S. IBRAHIM,* J. JESPERSEN,† L. POLLER* and ON BEHALF OF THE EUROPEAN ACTION ON ANTICOAGULATION

The present findings demonstrate the predictive ability and the possible increased safety of using the VGR, and show that unstable patients defined by a high VGR have an increased risk of clinical events while receiving warfarin or alternative conventional oral anticoagulants. The use of VGR method A, taking both INR control and variability into consideration, also ensures that the TIR is still considered to be an important contributory factor in the monitoring of oral anticoagulation.

INR monitoring with a measure such as the VGR on a shorter-term basis (i.e. 3 or 6 months before the current INR measurement) may help in detecting and isolating patients who may be at increased risk of possible adverse episodes. Computer-assisted dosage programs are now widely used in oral anticoagulant control, and the VGR could therefore be incorporated in such programs, thereby giving a 'V-score' instantly to a clinician and offering the possibility of identifying accurate safety cut-off points for the VGR, which could provide an additional safety marker for adverse clinical events. This could potentially aid clinicians by identifying patients who may be at increased risk of clinical events. It would also help in identifying any potential underlying comorbid medical conditions, together with primary diagnoses such as AF and deep vein thrombosis that increase the risk of clinical events.

J Thromb Haemost 2013; 11: 1540–6.

Improving Quality Measurement for Anticoagulation

Adding International Normalized Ratio Variability to Percent Time in Therapeutic Range

Zayd Razouki, MD; Al Ozonoff, PhD; Shibei Zhao, MPH; Guneet K. Jasuja, PhD; Adam J. Rose, MD, MSc

WHAT IS KNOWN

- Percent time in therapeutic range (TTR) and international normalized ratio (INR) variabilities measure different aspects of warfarin anticoagulation control. TTR is a measure of anticoagulation intensity, whereas INR variability is a measure of anticoagulation stability.
- TTR and INR variability have each been shown to predict warfarin-related adverse events, but little is known about whether using both measures would predict such events better than only 1 of them.

WHAT THE STUDY ADD

- Patients with unstable anticoagulation (ie, high INR variability) had an increased hazard for warfarin-related adverse effects, despite similar levels of TTR.
- Achievement of high TTR may not protect patients unless stability of INR (ie, low INR variability) is also achieved.

Circ Cardiovasc Qual Outcomes. 2014;7:664-669

Improving Anticoagulation Measurement

Novel Warfarin Composite Measure

Zayd Razouki, MD, MSc; James F. Burgess, Jr, PhD; Al Ozonoff, PhD; Shibei Zhao, MPH; Dan Berlowitz, MD, MPH; Adam J. Rose, MD, MSc

Background—Percent time in therapeutic range (TTR) and international normalized ratio (INR) variability both measure warfarin control and are associated with outcomes independently. Here, we examine the advantages of a warfarin composite measure (WCM), which summarizes the 2 when measuring patient outcomes. We also examine how the measure chosen would affect anticoagulation clinic performance rankings.

Table 3. Hazard Ratios for Fatal Bleeding Comparing 3 Anticoagulation Measures, TTR, Log INR Variability, and WCM

Quintiles Measurements	TTR	Log INR Variability	WCM
Poorest control	2.18 (1.57–3.03)	2.49 (1.79–3.47)	3.04 (2.16–4.28)
Poor control	1.49 (1.06–2.10)	1.45 (1.02–2.08)	1.67 (1.16–2.42)
Fair control	1.19 (0.84–1.70)	1.18 (0.81–1.72)	1.45 (0.99–2.11)
Good control	0.92 (0.68–1.23)	1.18 (0.81–1.71)	1.18 (0.79–1.75)
Excellent control	Reference	Reference	Reference

Effect across each column was statistically significant at the $P<0.001$ level. Effects across rows cannot be directly compared using a statistical test, as the samples are not independent. INR indicates international normalized ratio; TTR, therapeutic range; and WCM, warfarin composite measure.

Circ Cardiovasc Qual Outcomes. 2015;8:600-607

Improving Anticoagulation Measurement
Novel Warfarin Composite Measure

Zayd Razouki, MD, MSc; James F. Burgess, Jr, PhD; Al Ozonoff, PhD; Shibei Zhao, MPH; Dan Berlowitz, MD, MPH; Adam J. Rose, MD, MSc

WHAT IS KNOWN

- Percent time in therapeutic range (TTR, a measure of anticoagulation intensity) and international normalized ratio (INR) variability (a measure of anticoagulation stability) are 2 different independent measures that are associated with adverse events with warfarin therapy.
- TTR and INR variability together provide more information about risk of warfarin adverse events than each individually.

WHAT THE STUDY ADDS

- Warfarin composite measure is a novel and valid summary score that combines TTR and INR variability, thus accounting for both the intensity and stability of warfarin therapy.
- Warfarin composite measure produces the largest range of risk for warfarin complications, reducing the measurement constrains that limit the use of TTR and INR variability as separate measures.
- Warfarin composite measure, as a performance measure, reconciles the discordance in ranking anticoagulation clinics that occurs when using TTR or INR variability separately.

Circ Cardiovasc Qual Outcomes. 2015:8:600-607

Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation

Marcus Lind [a,b,*], Martin Fahlén [c], Mikhail Kosiborod [d], Björn Eliasson [a], Anders Odén [e]

Background – rationale for study: Atrial fibrillation is associated with an increased risk of stroke and mortality which is reduced by treatment with Warfarin. The most commonly used tool to assess the effectiveness of warfarin therapy is the time in therapeutic Range (TTR) of International Normalised Ratio (INR) 2.0-3.0. Our aim was to study whether INR variability, as assessed by the standard deviation of transformed INR (SDT_{INR}) is more prognostically important than the TTR.

Methods and Results: We studied 19,180 patients with atrial fibrillation on warfarin therapy to evaluate the association of TTR and that of SDT_{INR} with all-cause mortality, stroke, bleeding and hospitalisation.

The SDT_{INR} was more prognostically important than the TTR. One standard deviation (SD) higher of SDT_{INR} had a hazard ratio (HR) of 1.59 (95% CI 1.52-1.66) of mortality compared with 1.18 (95% CI 1.13-1.24) for one SD lower of TTR. For the other 3 events the HR was also higher for the SDT_{INR} than for the TTR (stroke 1.30 (95% CI 1.22-1.39) vs. 1.06 (95% CI 1.00-1.13), bleeding 1.27 (95% CI 1.20-1.35) vs. 1.07 (95% CI 1.01-1.14), hospitalisation 1.47 (95% CI 1.45-1.49) vs. 1.13 (95% CI 1.10-1.15). When both metrics were included in the same analysis only the SDT_{INR} was of significant predictive value.

We measured variability of INR by the standard deviation of transformed INR values (SDT_{INR}). The correlation coefficient between the SDT_{INR} and the TTR was calculated. A low absolute value of the correlation coefficient would indicate a difference in predictive ability of the two metrics. The predictive ability in relation to mortality, stroke, bleeding and hospitalisation of the two metrics was both estimated in separate analyses and included in the same analysis

Thrombosis Research 129 (2012) 32–35

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Table 2
The predictive ability of two variables reflecting variation in INR, the SDT_{INR} and the TTR.

Risk variable	Hazard ratio per a change of 1 SD of the risk variable			
	Death	Stroke	Bleeding	Admission to hospital
SDT_{INR}	1.59	1.30	1.27	1.47
(95% CI)	(1.52 – 1.66)	(1.22 – 1.39)	(1.20 – 1.35)	(1.45 – 1.49)
TTR	1.18	1.06	1.07	1.13
(95% CI)	(1.13 – 1.24)	(1.00 – 1.13)	(1.01 – 1.14)	(1.10 – 1.15)

In conclusion, INR variability (as measured by SDT_{INR}) was a more powerful predictor of clinical outcomes in patients with atrial fibrillation on warfarin therapy than the current standard TTR. These findings suggest that SDT_{INR}, should have a role in monitoring patients with atrial fibrillation on warfarin therapy, assessing the quality and performance of anticoagulation clinics, and as a potential endpoint in clinical trials.

Thrombosis Research 129 (2012) 32–35

The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation

H. A. VAN DEN HAM,* O. H. KLUNGEL,* H. G. M. LEUFKENS* and T. P. VAN STAA*†

Summary. *Background:* Anticoagulation control is often summarized using the percentage of time spent in a therapeutic range (TTR). This method does not describe the timing and severity of fluctuations in the International Normalised Ratio (INR). *Objective:* To evaluate whether the TTR method can be improved by considering the patterns of INR over time. *Methods:* The cohort included adults aged 40+ years with atrial fibrillation (AF) and laboratory records of INR as recorded in the UK Clinical Practice Research Datalink. Statistical clustering techniques based on simple INR measures were used to describe the patterns of INR. Nested case–control studies calculated the odds ratios (ORs) for the risk of stroke, bleeding and mortality with TTR and different INR patterns. It was also evaluated whether cluster analyses improved the prediction of outcomes over TTR.

J Thromb Haemost 2013; 11: 107–15.

The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation

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Table 4 Characteristics of International Normalized Ratio (INR) measures in the six clusters

Measure	Reference cluster (N = 145874 [13.8%]) Mean (SD)	Cluster 1 (N = 198003 [18.8%]) Mean (SD)	Cluster 2 (N = 265821 [25.2%]) Mean (SD)	Cluster 3 (N = 173865 [16.5%]) Mean (SD)	Cluster 4 (N = 90444 [8.6%]) Mean (SD)	Cluster 5 (N = 178724 [17.0%]) Mean (SD)	Cluster 6 (N = 1755 [0.2%]) Mean (SD)
Max $\|\Delta_1\|$*	0.47 (0.21)	0.91 (0.40)	1.06 (0.48)	1.64 (0.71)	2.18 (1.00)	1.88 (0.76)	5.13 (2.17)
Change relative to mean over time	0 (0.15)	0.07 (0.34)	0.04 (0.26)	−0.012 (0.29)	−0.71 (0.38)	0.07 (0.34)	0.12 (0.71)
Percentage below therapeutic range	0 (0)	0.16 (0.17)	0.26 (0.23)	0.04 (0.07)	0.30 (0.20)	0.26 (0.16)	0.20 (0.18)
Percentage above therapeutic range	0 (0)	0.09 (0.11)	0.04 (0.06)	0.40 (0.19)	0.15 (0.12)	0.16 (0.11)	0.43 (0.26)
Mean of INR values above therapeutic range	0 (0)	0.05 (0.07)	0.03 (0.05)	0.23 (0.17)	0.20 (0.18)	0.12 (0.10)	0.98 (0.89)
Slope b of linear line	0 (0)	0 (0.01)	0 (0.01)	0 (0.01)	−0.01 (0.02)	0 (0.01)	−0.01 (0.15)
Number of INR measurements	4.64 (1.66)	7.26 (2.39)	7.46 (2.40)	8.00 (2.84)	11.26 (3.89)	14.94 (3.78)	12.50 (5.90)
Ratio mean $\|\Delta_2\|$/mean $\|\Delta_1\|$†	1.69 (0.49)	1.27 (0.28)	1.87 (0.21)	1.78 (0.27)	1.53 (0.25)	1.63 (0.19)	1.66 (0.31)

*Max $|\Delta_1|$ = Maximum of the absolute difference between two subsequent INR measurements. †Ratio mean $|\Delta_2|$/mean $|\Delta_1|$ = ratio of the mean absolute second differences to the mean of absolute first differences.

J Thromb Haemost 2013; **11**: 107–15.

The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation

H. A. VAN DEN HAM,* O. H. KLUNGEL,* H. G. M. LEUFKENS* and T. P. VAN STAA*†

Results: A number of 27 381 patients were studied with a mean age of 73 years. The OR for mortality was 3.76 (95% confidence interval [CI] 3.03–4.68) in patients with < 30% TTR compared with patients with 100% TTR. INR patterns were found to be best described by six different clusters. The cluster with the most unstable pattern was associated with the largest risk of mortality (OR 10.7, 95% CI 8.27–13.85) and stroke (OR 3.42, 95% CI 2.08–5.63). INR measures that predicted death independent of the TTR-included absolute difference between two subsequent INR measurements and change relative to the mean over time.

J Thromb Haemost 2013; **11**: 107–15.

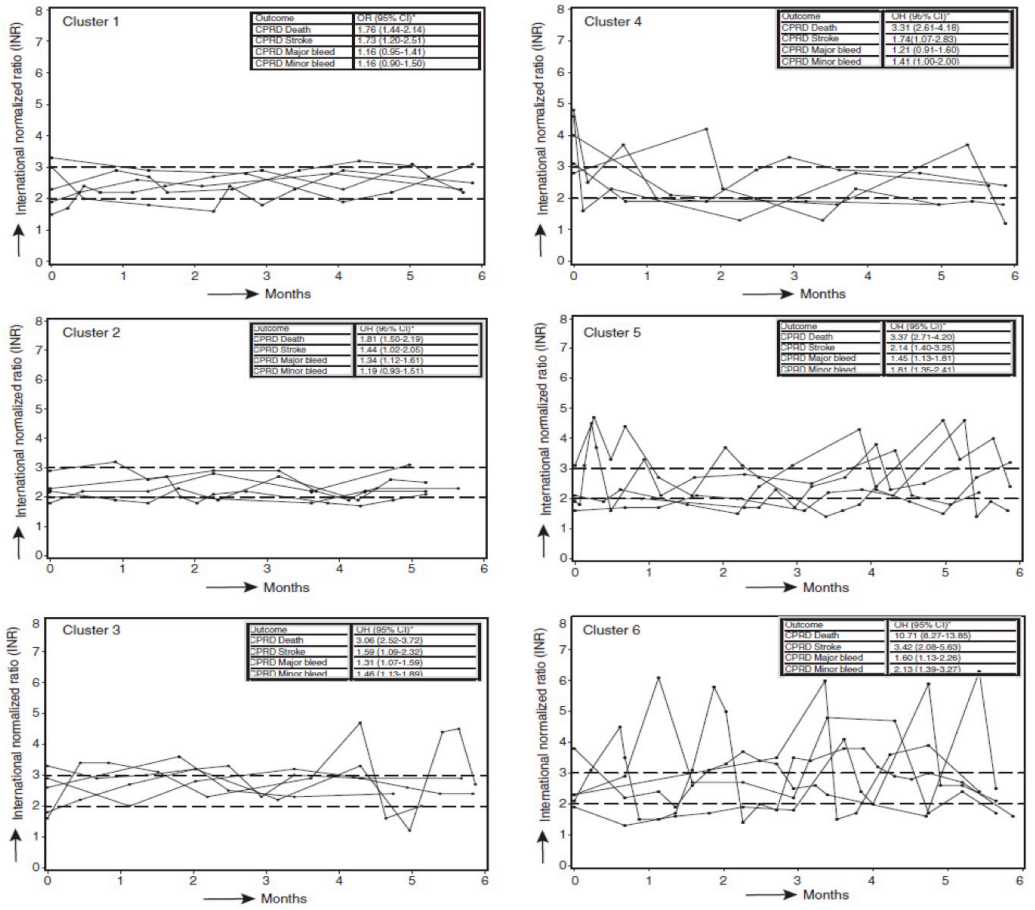
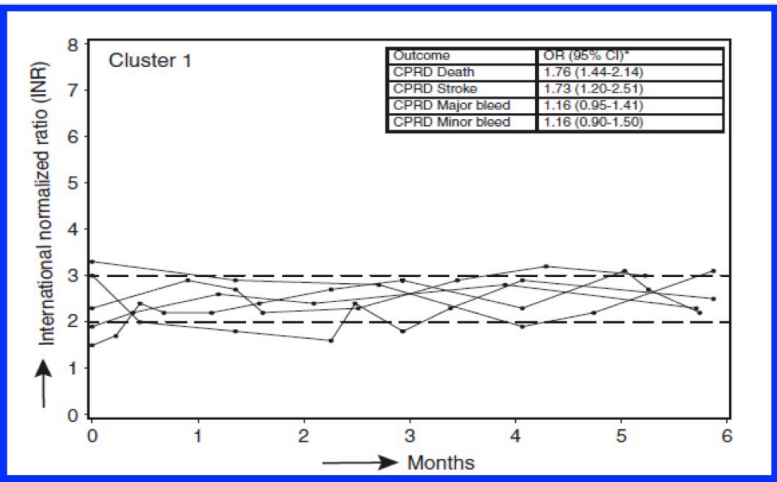
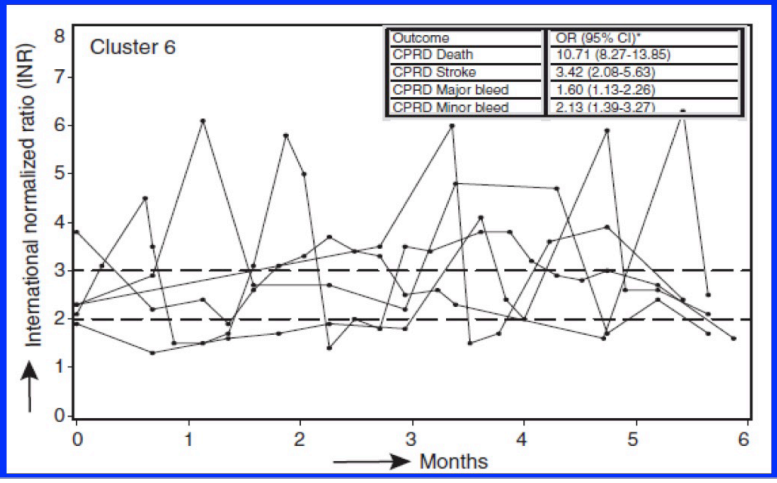


Fig. 2. Clusters with distinct International Normalized Ratio (INR) patterns and adjusted odds ratios (ORs) with each clus minor bleed.

J Thromb Haemost 2013; **11**: 107–15.





The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation

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In conclusion, unstable INR patterns are associated with an increased risk of mortality, stroke and bleeding. We assessed that the Roosendaal method for measuring long-term anticoagulation control can be improved by also measuring the magnitude and timing of deviations of INR values from the reference range. Cluster analysis of INR patterns improved prediction of clinical outcomes over TTR and may help to identify warfarin users who need additional anticoagulation monitoring.

J Thromb Haemost 2013; **11**: 107–15.

Conclusioni (1)

TTR mantiene la sua validità nella valutazione della qualità del trattamento :

Analisi qualità del trattamento in studi clinici rispetto all'incidenza eventi avversi (mTTR)

Verifica "performance" fra Centri (cTTR)

Utile considerare standardizzazione (tempi di esecuzione, criteri di esclusione) e "miglioramento" calcolo interpolazione correlata alla variazione dosaggio

Conclusioni (2)

Miglioramento efficacia e sicurezza trattamento nel singolo paziente (iTTR)

TTR misura esclusivamente l'intensità del livello di anticoagulazione NECESSARIO per migliorare la qualità l'introduzione di strumenti che misurino ANCHE la variabilità INR nel tempo.

Diversi metodi per il calcolo della variabilità sono stati proposti ed hanno dimostrato ottima predittività degli eventi.

Considerando insieme intensità (TTR) e Variabilita WCM si è riscontrato un ulteriore miglioramento della predittività.

I controlli a sei/tre mesi hanno dimostrato maggiore predittività degli eventi rispetto a tempi più lunghi (dodici mesi o più)

Necessari studi osservazionali e prospettici integrando il calcolo di intensità e variabilità

Utile potrebbe essere l'incorporazione anche di indici di rischio già disponibili ed altri dati clinico/sociali.