

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

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Disclosure

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.
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Disclosure

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Disclaimers

“The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.”

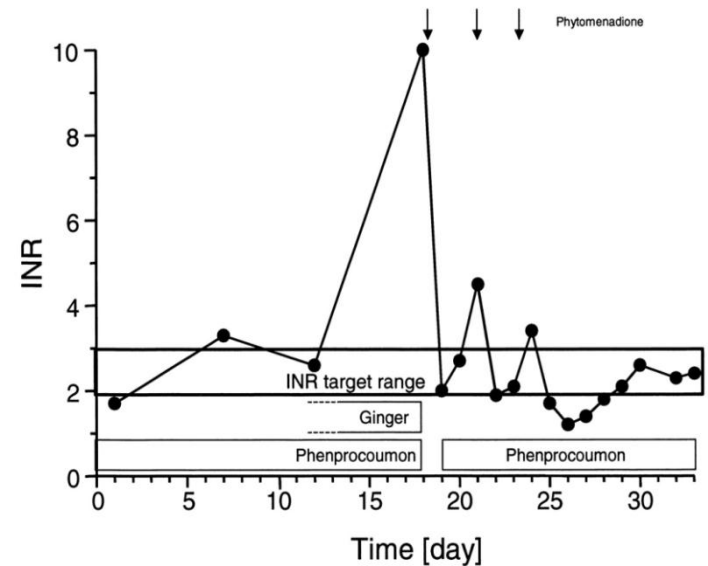
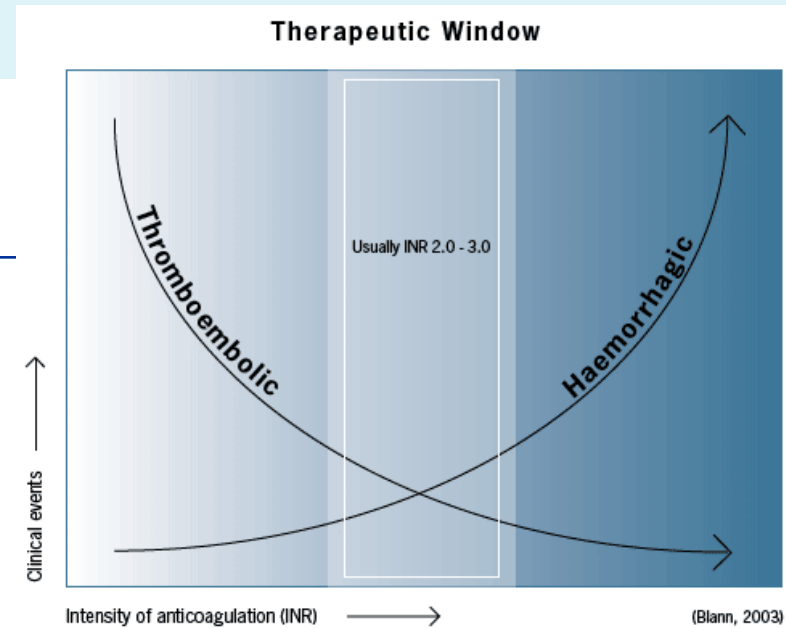
Background

- Atrial fibrillation (AF)
 - common cardiac arrhythmia
 - disturbance of electrical conduction in the heart
 - Risk of thromboembolism → ischaemic stroke
- Warfarin
 - reduces risk with 68% (RCT)
 - narrow therapeutic window
 - drug-drug interaction, food-drug interaction, inter current illness, genetic profile
 - large intra and inter patient variability



INR

- Biomarker effectiveness/safety
- INR monitoring is done by visiting anticoagulation clinic
- Therapeutic range lies between 2.0-3.0.
- Percent Time in Therapeutic range (TTR)
 - Often used in trials
 - Does not capture the timing and impact of fluctuations



Objectives

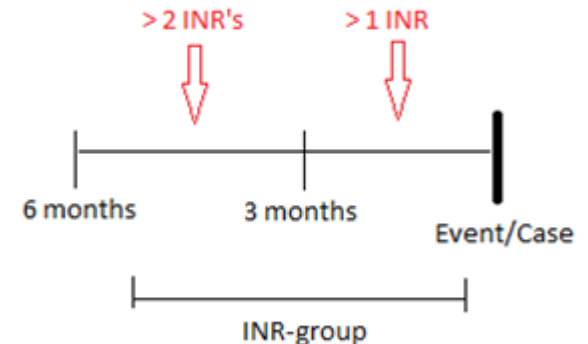
- To associate TTR and clusters of INR patterns with stroke, bleeding and death
- Assess whether prediction of outcomes by TTR method can be improved by considering clusters of patterns of INR over time

Methods

- Data extracted from CPRD (UK)
- Study population
 - patients > 40 year, record of AF
 - first three INR readings within a 6 month period
- Study design: nested case-control study

Methods INR control (exposure)

- Unit of analysis:
 - most recent INR group before event



1. Percentage of time spent in therapeutic range (TTR) (Roosendaal et al. 1993)
2. Clustering of same type of patterns with the help of two stage statistical modelling technique (Leffondré et al. 2004)
 - select measures of change (range from min to max, mean-over-time, standard deviations etc.)
 - classify each INR group into separate clusters

Methods

- Outcomes
 - Death, Stroke/TIA, Major bleed, Minor bleed
- Statistical analysis
 - Conditional logistic regression to estimate OR's; corrected for covariates

Methods

- 1) Matched by practice, gender, age, calendar year, duration of time since first ever-reading
 - effects of TTR and Cluster analysis on outcomes separately
- 2) Additionally matched by percentage of TTR
 - whether the measures of change as identified in the cluster analysis contributed to risk of outcomes

Results

Outcome (CPRD)	INR % Time in range	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Death†	<30%	649	430	4.3 (3.5-5.2)	3.8 (3.0-4.7)
	30-39%	456	190	6.0 (4.8-7.5)	5.5 (4.3-7.0)
	40-49%	520	334	4.0 (3.3-4.9)	3.5 (2.8-4.4)
	50-59%	612	428	3.7 (3.0-4.4)	3.4 (2.7-4.1)
	60-69%	564	564	2.6 (2.1-3.1)	2.4 (2.0-3.0)
	70-79%	431	560	2.0 (1.6-2.4)	1.8 (1.5-2.3)
	80-89%	330	479	1.7 (1.4-2.1)	1.7 (1.4-2.1)
	90-99%	182	339	1.4 (1.1-1.8)	1.4 (1.1-1.8)

† Compared to 100% TTR

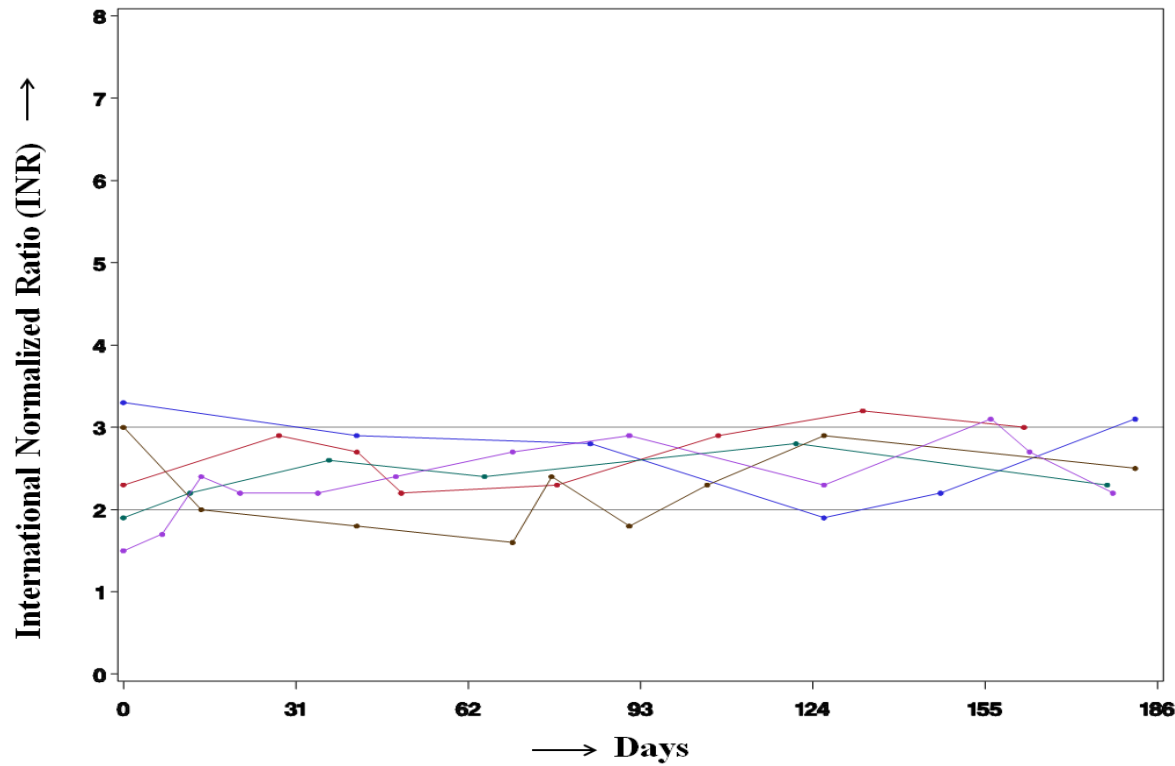
Results

Outcome (CPRD)	INR % Time in range	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Stroke†	<30%	60	233	2.7 (1.7-4.0)	2.6 (1.7-4.0)
	30-39%	40	155	2.5 (1.6-4.0)	2.4 (1.5-3.9)
	40-49%	40	237	1.6 (1.0-2.5)	1.6 (1.0-2.5)
	50-59%	60	324	1.8 (1.2-2.6)	1.8 (1.2-2.7)
	60-69%	59	378	1.5 (1.0-2.3)	1.3 (0.9-2.0)
	70-79%	67	340	1.9 (1.3-2.8)	1.9 (1.3-2.8)
	80-89%	53	384	1.3 (0.9-2.0)	1.3 (0.9-2.0)
	90-99%	38	264	1.4 (0.9-2.1)	1.4 (0.9-2.1)
Minor bleed‡	<40%	147	345	1.6 (1.2-1.9)	1.6 (1.2-2.0)
	40-59%	202	567	1.3 (1.0-1.6)	1.8 (1.3-2.4)
	60-80%	287	811	1.3 (1.1-1.5)	1.3 (1.1-1.5)
Major bleed‡	<40%	226	582	1.3 (1.0-1.5)	1.4 (1.0-1.5)
	40-59%	308	915	1.1 (0.9-1.3)	1.1 (0.9-1.3)
	60-80%	447	1340	1.1 (0.9-1.2)	1.1 (0.9-1.2)

† Compared to 100% TTR

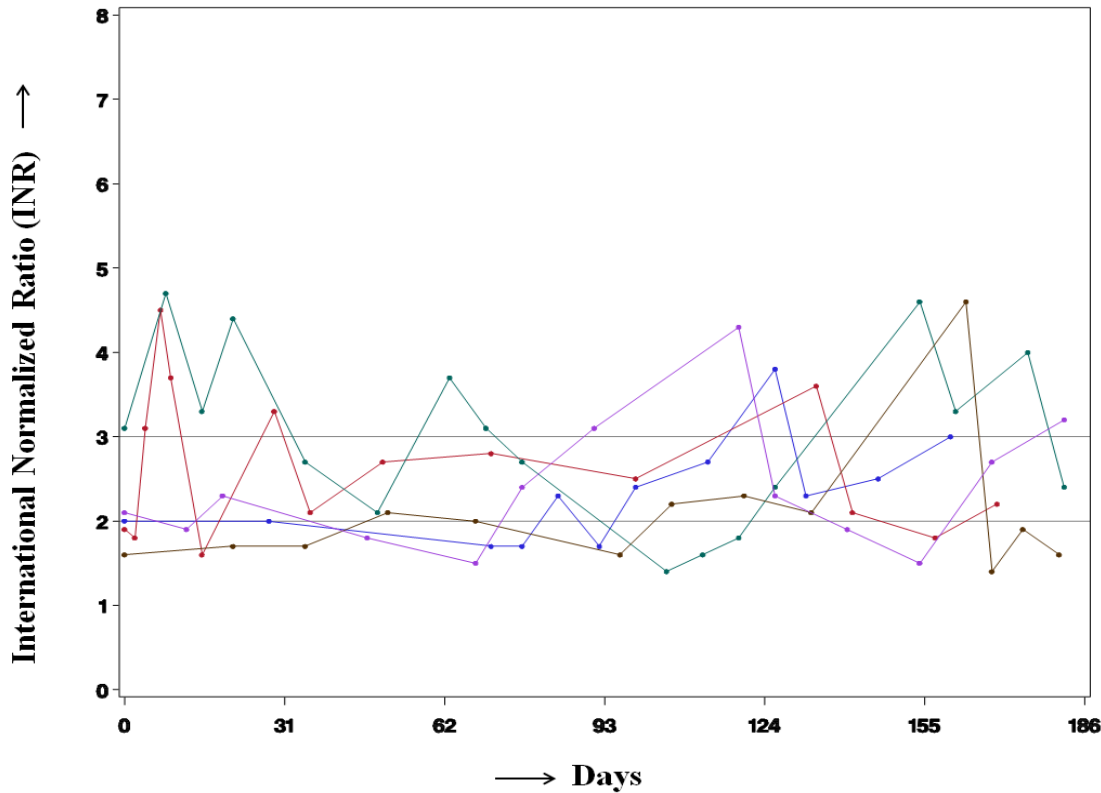
‡ Compared to > 80% TTR

Cluster 1 'Stable'



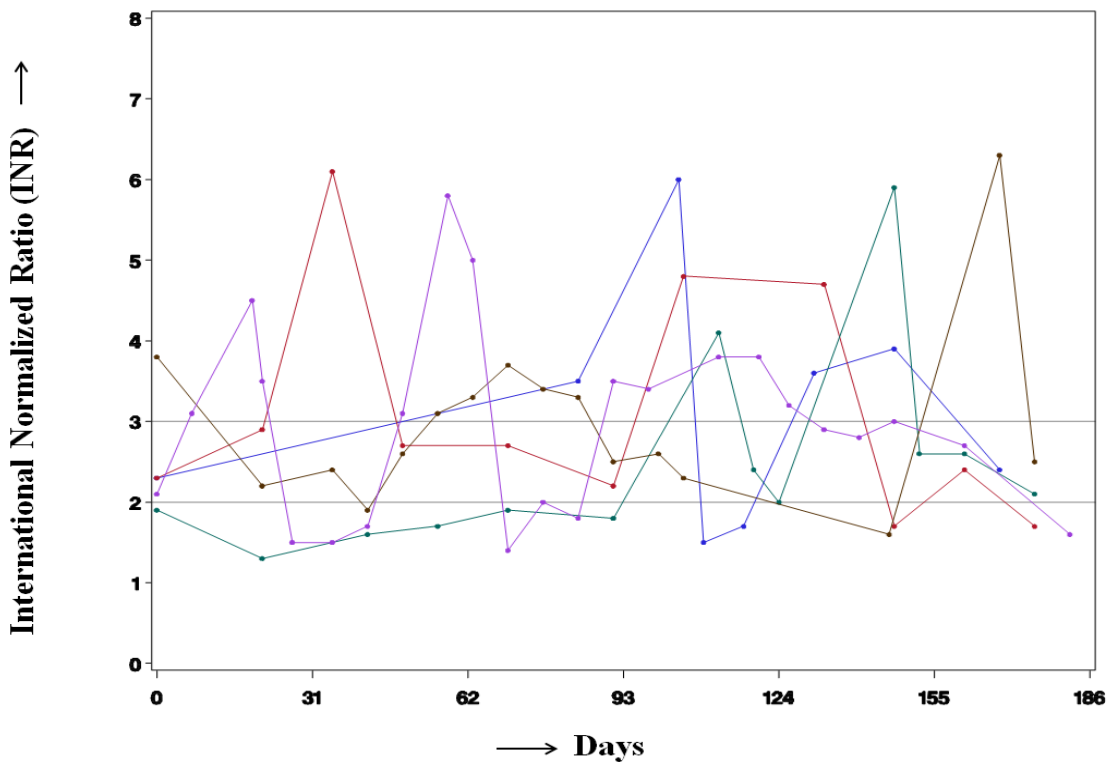
Outcome	OR (95% CI)
CPRD Death	1.76 (1.44 -2.14)
CPRD Stroke	1.73 (1.2 -2.51)
CPRD Major bleed	1.16 (0.95 -1.41)
CPRD Minor bleed	1.16 (0.9 -1.5)

Cluster 5 'Unstable'



Outcome	OR (95% CI)
CPRD Death	3.37(2.71-4.20)
CPRD Stroke	2.14(1.40-3.25)
CPRD Major bleed	1.45(1.13-1.81)
CPRD Minor bleed	1.81(1.35-2.41)

Cluster 6 'Most Unstable'



Outcome	OR (95% CI)
CPRD Death	10.7(8.27-13.85)
CPRD Stroke	3.42(2.08-5.63)
CPRD Major bleed	1.60(1.13-2.26)
CPRD Minor bleed	2.13(1.39-3.27)

Results

Outcome	Parameter	Odds ratio (95%CI)	p-value*
Death	Maximum of the absolute difference between two subsequent INR measurements	1.60 (1.46-1.76)	<0.0001
	Mean of INR values above therapeutic range	1.18 (1.07-1.31)	0.001327
	Change relative to the mean over time	1.14 (1.08-1.20)	<0.0001
	Number of INR measurements	1.12 (1.05-1.19)	0.000272
	Percentage above therapeutic range	1.08 (1.01-1.16)	0.035452
Stroke	Maximum of the absolute difference between two subsequent INR measurements	1.20 (1.09-1.32)	0.000195
Major bleed	Mean of INR values above therapeutic range	1.12 (1.04-1.20)	0.00129
	Change/ mean over time	1.09 (1.03-1.15)	0.003613
Minor bleed	Mean of INR values above therapeutic range	1.17 (1.07-1.28)	0.000699
	Change/ mean over time	1.16 (1.07-1.25)	0.000137

Discussion

- INR patterns can be classified into distinct clusters and are correlated to risk of stroke, minor/major bleed and mortality
- Rosendaal method can be improved by also measuring the magnitude and timing of deviations of INR values from the reference range
- Not all associations may be causal: intercurrent illness may lead to unstable INR and to death
- Benefit-risk balance of warfarin is extremely dependent on anticoagulation control

Questions

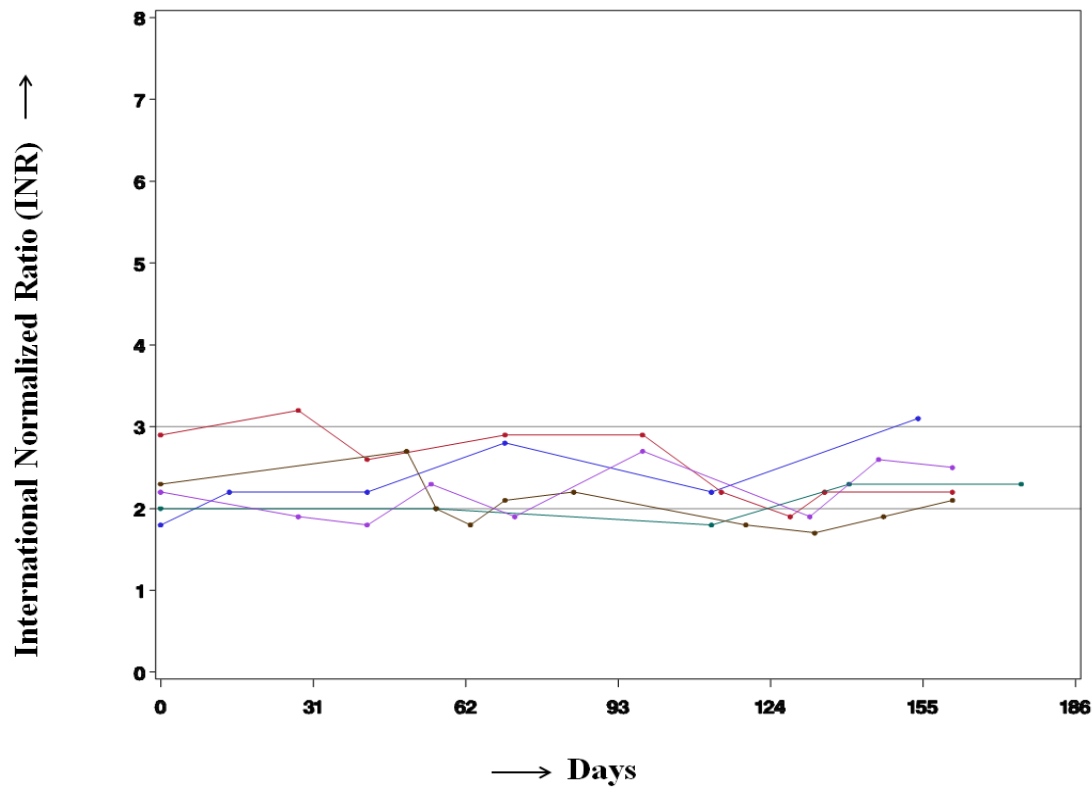




PROTECT

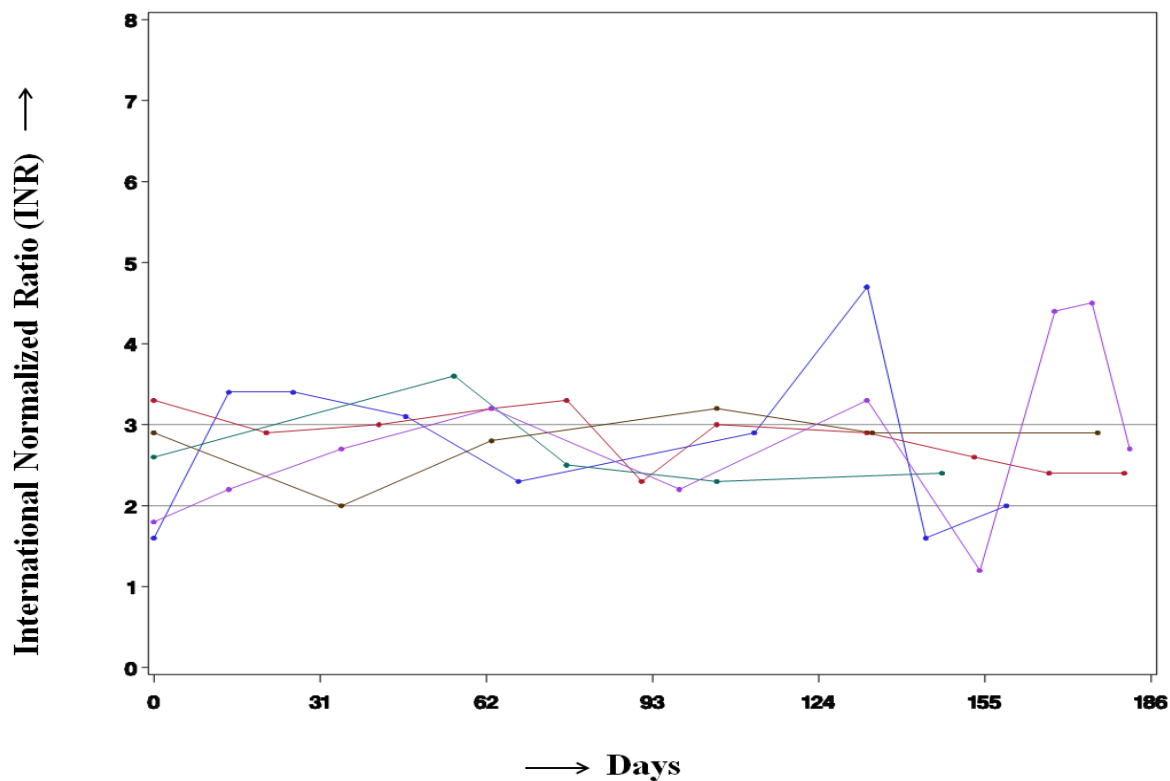
Back up

Cluster 2



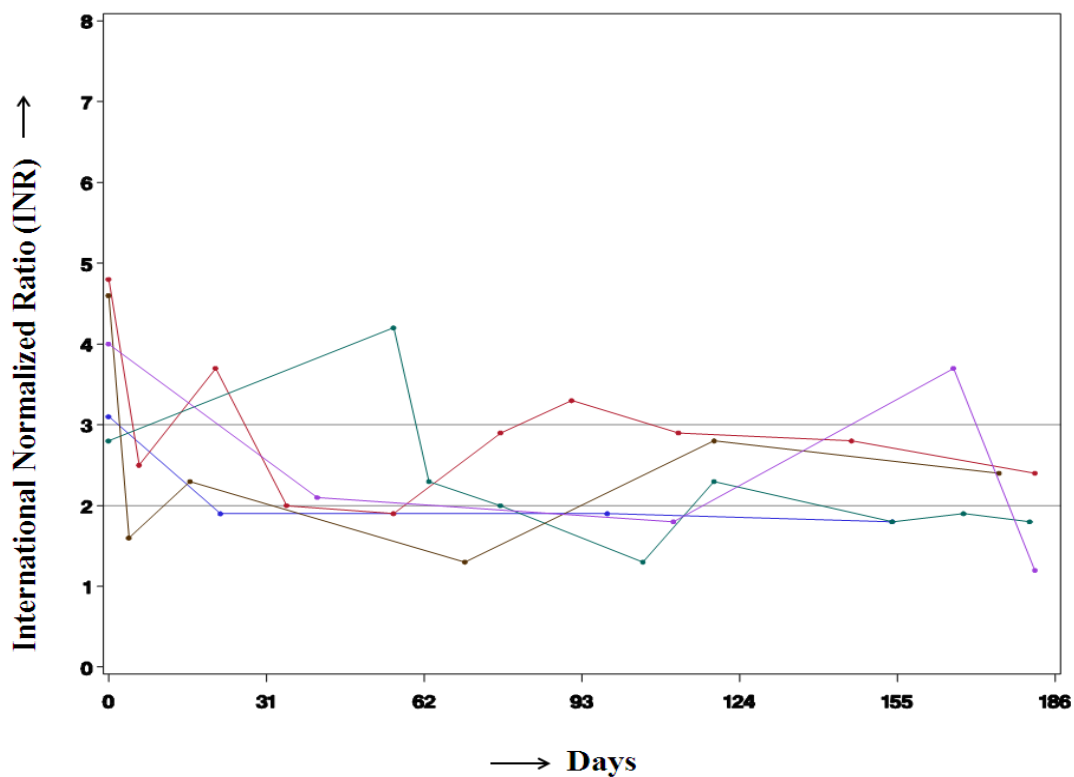
Outcome	OR (95% CI)
CPRD Death	1.81(1.50-2.19)
CPRD Stroke	1.44(1.02-2.05)
CPRD Major bleed	1.34(1.12-1.61)
CPRD Minor bleed	1.19(0.93-1.51)

Cluster 3



Outcome	OR (95% CI)
CPRD Death	3.06(2.52-3.72)
CPRD Stroke	1.59(1.09-2.32)
CPRD Major bleed	1.31(1.07-1.59)
CPRD Minor bleed	1.46(1.13-1.89)

Cluster 4



Outcome	OR (95% CI)
CPRD Death	3.31 (2.61-4.18)
CPRD Stroke	1.74 (1.07-2.83)
CPRD Major bleed	1.21 (0.91-1.60)
CPRD Minor bleed	1.41 (1.00-2.00)