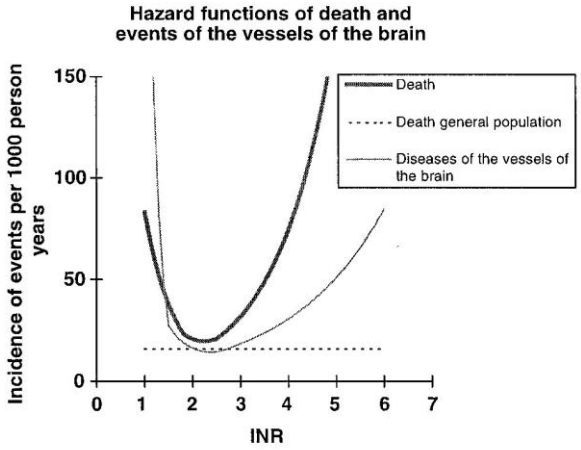
EPITOME
PHARMACEUTICALS

A new approach to warfarin dosing

The problem

A clinician administering anticoagulant treatment using warfarin or other coumarin drugs must steer the patient between the Scylla of thromboembolism and the Charybdis of haemorrhage. The risk of one or other of these events is a U-shaped function of the International Normalized Ratio (INR). Figure 1:



(from: Oden, A., Fahlen, M., and Hart, R. G. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. Thromb.Res. 117(5), 493-499. 2006; used by permission of the authors)

The principal objective of treatment is to keep the INR within the therapeutic range (TR), which is chosen to minimize the patient's risk. Consequently clinicians usually raise the patient's dose in response to an INR below the TR and lower it after an INR above the TR. An example of the resulting record over time for a sample patient #23 is shown in Fig. 2.

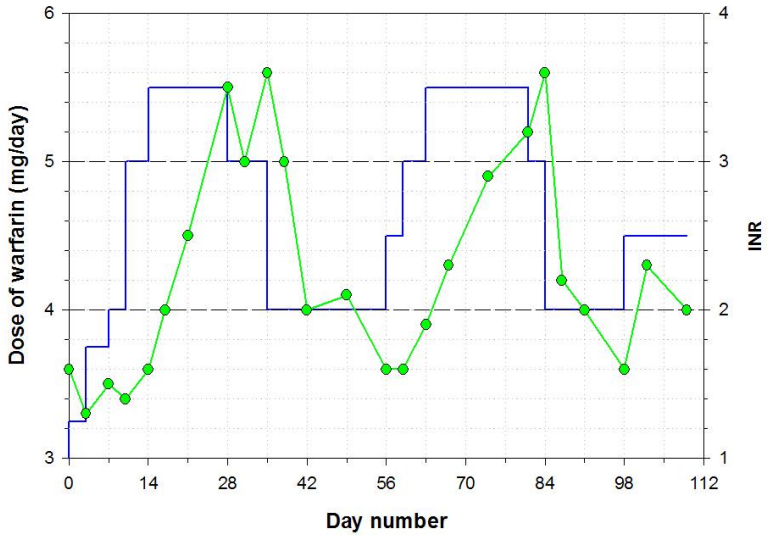


Figure 2. History of dosage (blue line) and INR (green line) over three and a half months for Patient #23. The dose was changed whenever the INR was outside the therapeutic range of 2.0 to 3.0; this occurred on 52% of the measurements. The INR is estimated to lag the dose by about 15 days.

WWW.EPITOMEPHARM.COM
4016 LARK ST., SAN DIEGO CA 92103 USA TEL (619) 255-5358 FAX (212) 354-6412 PWEGENER@EPITOMEPHARM.COM

The INR of the least stable quarter of patients is in the TR less than 50% of the time. As you would expect from Fig. 1, they account for a disproportionate number of deaths and therapy-related incidents. They also absorb a large proportion of the health resources devoted to anticoagulant therapy.

Can the treatment of these patients be improved?

How treatment can increase instability

Delayed response of INR. The INR typically lags the dose by about two weeks (see Fig. 2). Consequently there is a danger that the clinician will change the dose again before the INR has had a chance to respond to the previous change, with an effect like pushing a swing when it is already moving in the same direction. This seems to be what happened with the patient in Fig. 2.

Moreover, the INR has a "random" component due to such causes as diet, illness and other factors. By acting on extreme values of the INR, the clinician also runs the risk of changing the dose when the INR would have returned to the TR in a few days of its own accord. We propose that the dose should not be changed after an INR outside the TR unless it has been confirmed by a second measurement taken 3 or 4 days after the first.

Dose-responsiveness of INR. We show that a patient's INR depends on the current "effective dose", which takes account of the delayed response of the INR (see Fig. 3).

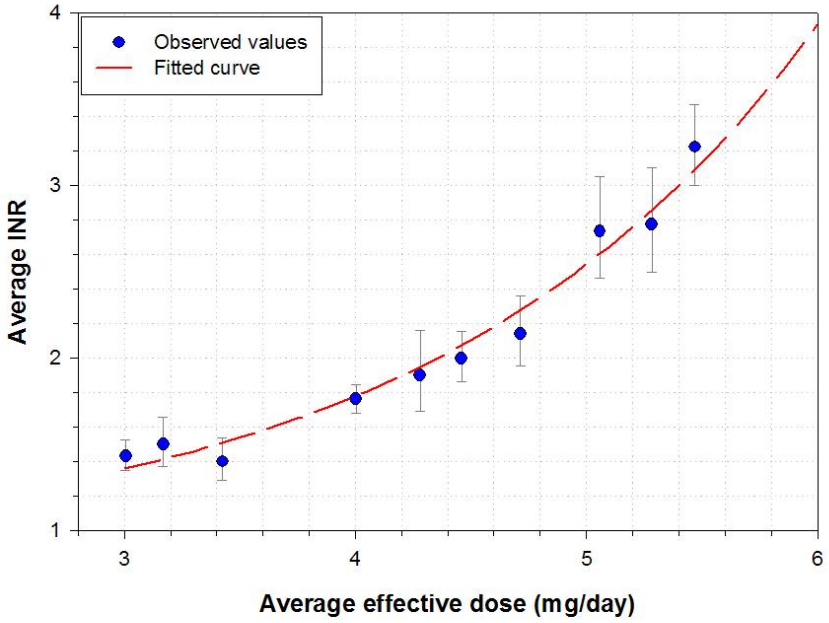


Figure 3. Dose-effect curve for Patient #23. The effective dose is a weighted average of previous doses. Effective doses were combined into groups according to the nearest multiple of 0.25 mg; the observed values are the means for each group.

Consequently it is possible to predict with some accuracy how the INR will respond on average to any given change of dose (see Fig. 4). The red line shows the INR expected from that dose in the future,

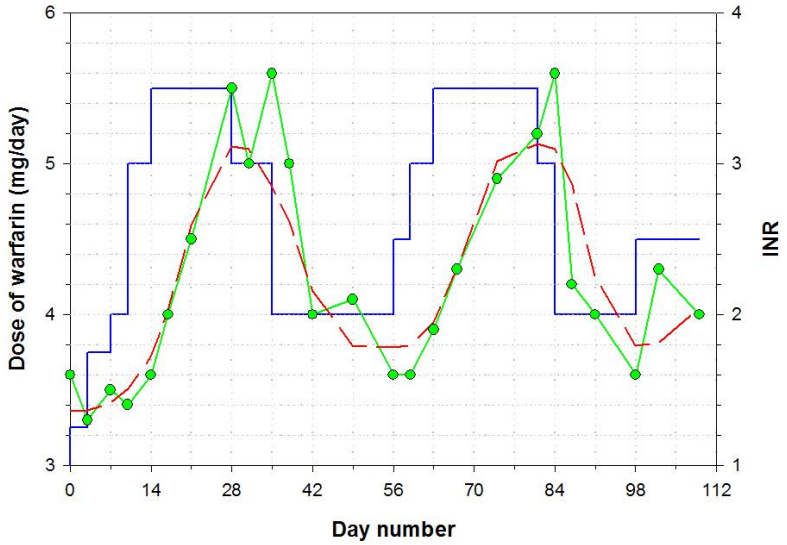


Figure 4. History of dosage (blue line) and INR (green line) over three and a half months for Patient #23, and the average INR predicted (red line) from the dose-effect curve shown in Figure 3.

once the INR is stabilized. It is evident that a very significant part of the variation of the INR in Fig. 2 is attributable to the clinician's variation of the dose.

There is a clear danger that the clinician's manipulation of the dose for a patient with an unstable INR will have the perverse effect of contributing further to that instability, rather like drilling a hole in the bottom of a boat to let the water out.

Individual differences. Dosing algorithms typically call for the same proportionate change in dose for every patient whose INR is in a given range. But the slope and lateral position of the dose-effect curve in Fig. 3 varies widely from one patient to another. As a result, the deviation of the INR from its target may be under- or over-corrected in patients whose dose-effect curve is atypical.

No set of proportionate changes of dose can be adequate for such patients. Many unstable patients have a dose-effect curve with a high slope, so their INR rises or falls more for a given change than the average. For some patients there is no dose achievable with a 5 mg tablet that will yield an INR in the Therapeutic Range. This mismatch between the patient and the tablet occurs quite often; we therefore specify which tablet should be used when the dose-effect curve has been fitted.

Shifted dose-effect curves. A patient's requirement for warfarin can be altered by factors such as interacting medications, hospitalization, change in life circumstances and non-compliance. Control may be lost under these conditions because, unaided, the clinician has a very limited ability to predict the course of the INR during the early stages of the interaction.

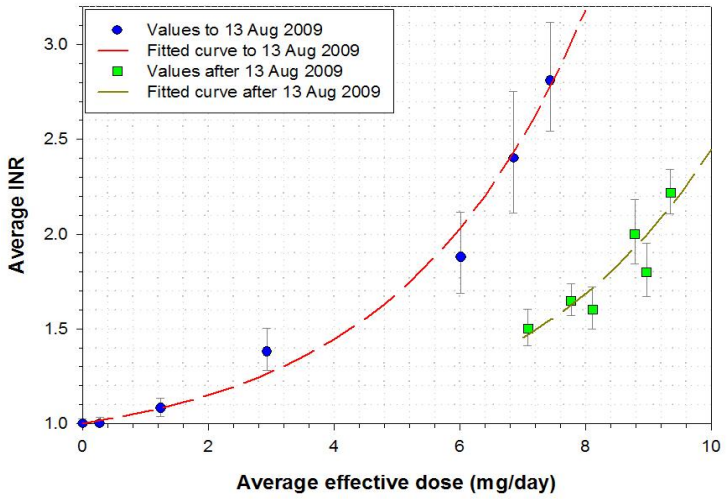


Figure 5. Dose-effect curves for Patient #1. The therapeutic range is 2.0 to 3.0. After 13 August 2009 the INR seems to have been affected by interaction with niacin and/or spironolactone.

We have found that the effect of these factors is usually an abrupt shift in the patient's dose-effect curve, with the INR thereafter following a persistent new curve (see Fig 5). In this case the optimum dose increased from 7 to 10 mg/day. Another example from the clinical trial of the Fearon algorithm conducted by Dan Witt and colleagues, see below, is shown in Figure 6.

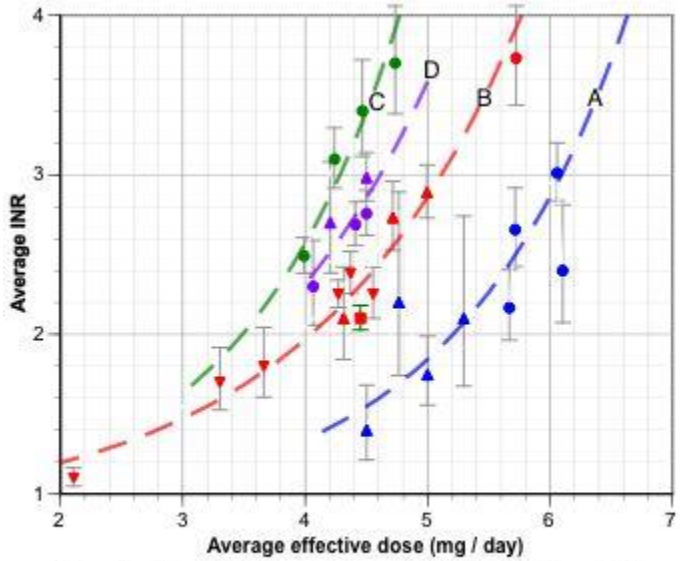


Figure 6. Patient #012 (therapeutic range 2.0 to 3.0): fitted dose-effect curves (lines). Effective doses are combined into groups according to the nearest multiple of 0.2 mg/day; the observed data (symbols) are the means for each group. See text for details.

We can confirm the shift and generate a new nomogram after 4 INRs have been measured on the new curve and the patient's new parameters can then be estimated.

The solution we propose:

Patient-specific nomogram. The nomogram below is tailored specifically for Patient #23 in Figs. 2-4. The indicated average daily dose is achieved by prescribing a weekly pattern of doses based on the 2 mg tablet. That tablet size was chosen because it would yield doses suited to the patient's dose-effect curve derived from their medical record of INR measurements, dates and warfarin doses. The sensitivity was derived from the slope of the dose-effect curve and determines the step size between doses in the bands.

The instability index was determined from the residual variance after the curve is fitted and indicates the dispersion of INR measurements when the predictable effect of the dose is discounted. It indicates the extent to which the INR varies randomly around the average value shown in the curve. When it is > 0.4, the random variation is so large that an investigation is required: the patient may be periodically taking interfering medications, varying vitamin K intake, or failing to comply with the prescribed dose.

Nomogram for Patient #23 (TR=2.0-3.0, tablet=2 mg, sensitivity=0.60, instability=0.22)

INR range		Retest	New dose (mg)		Expected average INR after 15 days	Probability of INR in this range at central dose
INR ≥	INR <		daily	weekly		
3.99		Retest the next day	Follow normal clinical procedure			0.07%
3.21	3.99	Retest in 3 to 5 days	4.43	31	2.05	2.8%
2.01	3.21	No retest needed	4.86	34	2.40	87.9%
1.61	2.01	Retest in 3 to 5 days	5.14	36	2.69	9.2%
	1.61	Retest the next day	Follow normal clinical procedure			0.05%

For INRs in the central range, 2.01 to 3.21, the dose of 4.86 mg/day is the closest one achievable with the pill size to the dose in Fig. 3 that would centre the INR in the TR. When the INR has had time to adjust to this dose, it should stay within the central range 88% of the time unless the patient's dose-effect curve has shifted. The probabilities that the INR will fall in other ranges when the patient's condition is the same, no change, are shown in the right hand column. This is why retesting before a dose change is important.

When the clinician receives early notice of a factor which may shift the dose-effect curve, such as a change of interacting drugs, the current nomogram should be abandoned and the INR should be measured frequently until the new curve can be estimated.

Otherwise, when the INR is outside the central range, the first step is to retest the INR in 3 or 4 days. Due to its inherent variability, INR values can come from the extremes of its distribution. The patient's next dose is determined by the range in which the second INR falls. If it is in the same direction as the first, the patient is probably on or moving toward a new dose-effect curve. The ranges in the nomogram above and below the central one allow for both possibilities.

When the INR is between 1.61 and 2.01 or between 3.21 and 3.99, as confirmed by a second measurement, this patient's dose is changed by 2 or 3 mg/week. If the patient continues on the old

curve, the average INR should still be inside the TR, and the probability is at least 56% that the next INR measurement will find this patient back to the central range. On the other hand, if the patient is now on a new curve, the dose will be following the track of the INR so that evidence of a shift can accumulate to the point where a revised nomogram can be produced.

When the INR falls outside these three ranges, the nomogram is suspended because there is a palpable danger that the patient's dose-effect curve has changed. Expert clinical judgment is then required to investigate the possible causes and to prescribe a new dose. If there is reason to suspect a shifted dose-effect curve, the current nomogram should be replaced. The patient should be tested frequently until the INR returns to the Therapeutic Range.

Dosage schedule. An important practical advantage of the nomogram is that there are only three possible doses while the INR of Patient #23 is between 1.61 and 3.99. The daily dosage schedules shown in the table below apply to this example patient.

Dosage schedule for Patient #23

INR range	*Weekly dose*	*Mon*	*Tue*	*Wed*	*Thu*	*Fri*	*Sat*	*Sun*
3.21 to 399	31 mg	4 mg	5mg	4 mg	5 mg	4 mg	5 mg	4 mg
2.01 to 3.21	34 mg	5 mg	5 mg	5 mg	4 mg	5 gm	5 mg	5 mg
1.61 to 2.01	36 mg	5 mg	5 mg	5 mg	6 mg	5 mg	5mg	5 mg

When the patient's unique characteristics are taken into account, the relation between the dose and the INR is so simplified that a self-testing patient could apply it without further clinical intervention until the INR goes outside the three central ranges of the nomogram.

Prospective clinical trial

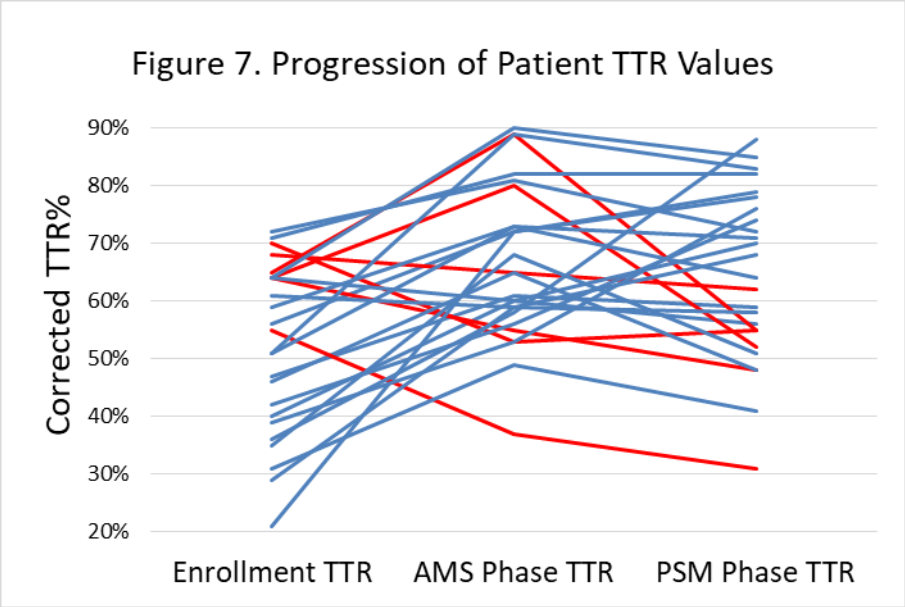
Dan Witt and colleagues at the University of Utah Thrombosis Center conducted a prospective clinical trial of the Fearon algorithm from 2018 to 2021, ClinicalTrials.gov Identifier: NCT03911661. 30 subjects with TTR < 60% in the previous year and willing to test their INR at home were enrolled; 17 of these were already testing at home. For the first six months (ASM phase), subjects continued to receive dosing instructions from their representative at the Thrombosis Center, who used the nomogram to provide the dosing based on the self-tested INR. 26 subjects then transitioned to managing their own dosing using the nomogram for six months (PSM phase) and completed the study. Roche provided support including home monitors and strips. The study began just 6 months before the COVID-19 pandemic. This required a heroic effort of managing the infrastructure, shipping home meters and training subjects on their use remotely.

Average TTR increased from 56% (Interquartile range 39% to 64%)[1] in the previous year to 65% (IQR, 57%-77%) during the ASM phase (P < 0.01) and remained consistent during the PSM phase 64% (IQR, 53%-77%) (P < 0.16). Figure 7 below shows the before and after for these 26 subjects; six subjects had a decline in TTR from the previous year at the end of PSM; two of these had improved considerably

[1] Some of the subjects qualified for screening with TTR < 60% for the previous year, but their TTR improved before their formal enrollment. Actual year up to enrollment date was used as the Previous Year comparator.

during the ASM phase. TTR for twenty subjects improved overall, or for two, stayed the same by the end, with an average increase of TTR by 21% (IQR 12 – 32%).

These are complicated patients; 70% of the original 30 required a second or third nomogram be calculated. Even so, two of the four subjects with a final TTR > 80% required a new nomogram; there is no correlation between requiring a new nomogram and final outcome. Many had intercurrent disease and were hospitalized during the study. The improvement in TTR seen by many of these patients demonstrates that the Fearon algorithm works.



Summary

- The INR lags behind a change of dose by about 2 weeks. It has a persistent dose-effect relation with warfarin.
- The patient may switch to a different dose-effect curve when factors like interacting medications come into play. The change can be confirmed and the new dose-effect curve derived after at least 4 INRs have been measured.
- Dose-effect curves vary significantly in shape and position between patients. A system of proportionate changes that does not take into account a patient's particular dose-effect curve will cause some patients to be unstable.
- We can produce dosing nomograms for individual patients which allow for these circumstances. We believe that they will help the control of unstable patients.
- The resulting nomogram enables many self-testing patients to administer it themselves until the INR becomes dangerously low or high.
- A prospective pilot trial of the Fearon Algorithm showed that 70% of these unstable patients had an increased TTR of at least 5%; a further prospective multi-center trial is required to validate this outcome and extend real-world experience with the method. We welcome participation.