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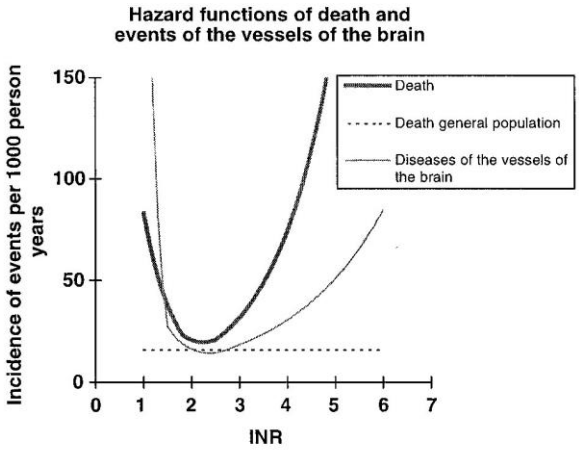
A new approach to warfarin dosing

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 (see Fig .1) of the International Normalized Ratio (INR).



(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 is shown in Fig. 2.

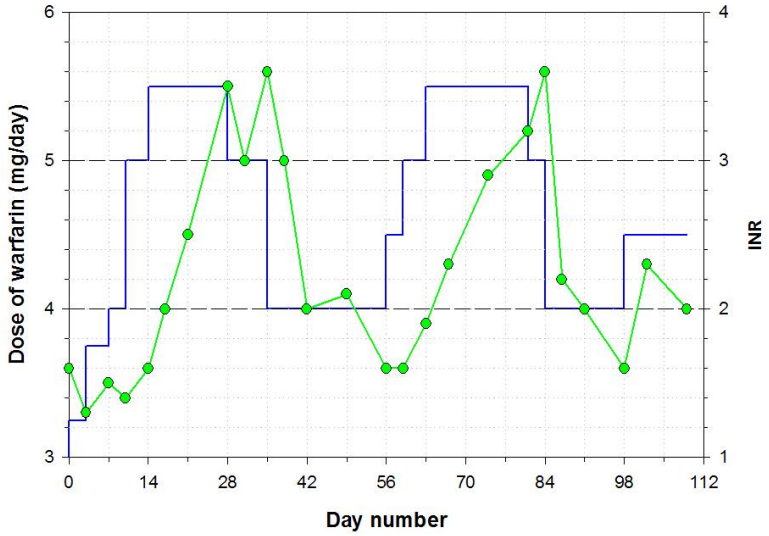


Figure 2. History of dosage (blue line) and INR (green line) over three and a half months for Patient #23. The dose was changed whenever the INR was outside the therapeutic range of 2.0 to 3.0; this occurred on 52% of the measurements. The INR is estimated to lag the dose by about 15 days.

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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. We can show that 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 the patient's varying intake of vitamin K. 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, if possible (and if prudent), 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).

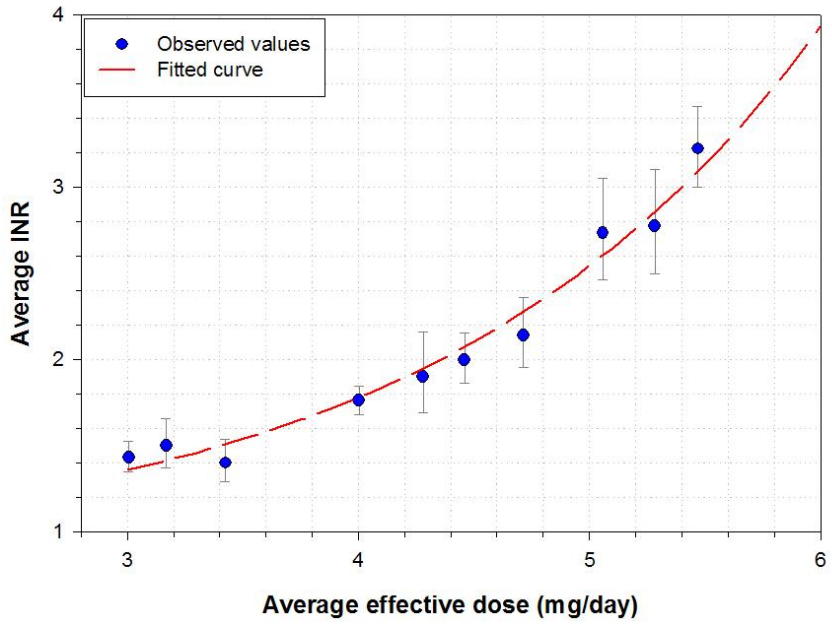

Figure 3. Dose-effect curve for Patient #23. The effective dose is a weighted average of previous doses. Effective doses were combined into groups according to the nearest multiple of 0.25 mg; the observed values are the means for each group.

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, 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.

Effect of the same dose changes on the INR of two patients

Dose (mg)		*Expected average INR*		*Percent change from preceding dose*		
Weekly	***Daily***	***Pt #21***	***Pt #11***	***Dose***	***INR, Pt #21***	***INR, Pt #11***
22.5	3.21	2.01	1.60	---	---	---
25.0	3.57	2.19	2.13	11.1%	8.8%	33.2%
27.5	3.93	2.39	3.04	10.0%	9.4%	42.6%
30.0	4.29	2.63	4.59	9.1%	9.9%	51.0%
32.5	4.64	2.90	7.24	8.3%	10.4%	57.7%

The table above compares the average INR expected from the dose-effect curves of two patients with almost identical INR at a dose of 25 mg/week and a common TR of 2.0 - 3.0. When that dose is increased by 10% to 27.5 mg/week, the INR of Pt #21 increases by 9.4%, but the INR of Pt #11 increases by 42.6%. While the INR of Pt #21 generally increases roughly in the same proportion as the dose, the increase in the INR of Pt #11 is about four times larger. Over half of a sample of 20 unstable patients at a major anticoagulation clinic had exceptional dose-effect curves like that of Pt #11.

No set of proportionate changes of dose can be adequate for both of these patients. The doses shown kept the INR of Pt #21 within the TR 84% of the time but caused the INR of Pt #11 to swing wildly, with only 43% in the TR. The doses for Pt #11 shown in the table were the only ones available at the time, because they were based on the 5 mg tablet. Better control could not have been achieved without the finer graduation provided by the 2 mg tablet. 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.

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.

We can confirm the shift after about 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 the patient 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		New dose (mg)		Expected average INR after 15 days	Probability of INR in this range at central dose
INR ≥	INR <	daily	weekly		
3.99		Follow normal clinical procedure			0.07%
3.21	3.99	4.43	31	2.05	2.8%
2.01	3.21	4.86	34	2.40	87.9%
1.61	2.01	5.14	36	2.69	9.2%
	1.61	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.

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. It takes at least four new INR measurements to deduce the position of the new curve and the new nomogram; note that following a retest, two measurements have already been recorded. 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 is between 1.61 and 3.99. The daily dosage schedules shown in the table below apply to this example patient. Dosage schedules are delivered with every nomogram proposed and should be given to the patient for reference.

Dosage schedule for Patient #23

INR range	*Weekly dose*	*Daily 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.

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 a self-testing patient to administer it themselves until the INR becomes dangerously low or high.

We welcome inquiries to help make this algorithm available as an aid to clinicians and patients to improve warfarin dosing.