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Master of Science Thesis [Engineering Mathematics and Computational Science]

Frequency of monitoring INR measurements and intensity of anticoagulation

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Abstract

Patients have regular blood tests to monitor their International Normalized Ratio (INR), while taking Warfarin. Patients should also know their Warfarin (Coumadin) dosage and their INR, like the way they know their blood pressure numbers. The INR is about 1.0 in healthy subject while for anticoagulant dependent patients, the INR typically should be between 2.0 and 3.0 for patients with atrial fibrillation, or between 3.0 and 4.0 for patients with mechanical heart valves in accordance with old suggestions. According to the new findings about the relationship between INR and different complications (including death), there has been a trend towards lower target intervals [7] [8]. However, different results have been obtained by simulations when the time interval of INR measurements varies between 21, 18, 15, 12, 9, 6 and 3 days in order to optimize the INR range of 2 to 3 in patients who take blood thinners steadily. In our analysis we have not been able to take different variables into account, but we are convinced that it is important for the doctor or any dose monitoring person to be aware of different changes. The results of simulations in this study indicate that more frequent measurements and adjustment of dose could decrease the variation of INR substantially. Recent analyses of risk say that smaller variation is related to lower risk of death, stroke, bleedings and hospitalization. The existence of point of care units for measuring INR at home makes more frequent measurements realizable.

Keywords: INR; Warfarin; Blood clotting; Blood thinner; INR measurement;

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Habib Ullah
Göteborg, Sweden

Dedication

To My Parents

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Abbreviations

INR = International Normalized Ratio (Appendix 1)

PT = The prothrombin time (Appendix 1)

1.1. Background of the study

There are several drugs that are advised as "blood thinners" such as Coumadin (Warfarin), Dicumarol (Dicumarol), Miradon (Anisimidione), Sintrom (Acenocoumarol), Warfilone (Warfarin) varies from country to country. Blood thinner are commonly recommended by physicians for the prevention of thrombosis, heart attack and stroke. Anticoagulants and antiplatelets are the two main types of blood thinners. Although each of these blood thinners has a different mode of action, they ultimately reduces the formation of blood clotting in the arteries and deep veins. Blood clotting is the most important mechanism to prevent or stop bleeding, but harmful blood clots can cause a stroke, heart attack, deep vein thrombosis, or pulmonary embolism. Each year, nearly two million people start taking blood thinners.

Warfarin is the most widely used oral anticoagulant, which is effective for the prevention of stroke in atrial fibrillation (1, 2). It decreases the body's ability to form blood clots by blocking the formation of vitamin K–dependent clotting factors. There are several proteins called clotting factors involved in the blood clotting process. These proteins (called factors II, VII, IX, and X) are converted to biologically active substances in the presence of Vitamin K. The reduced form of vitamin K (KH_2) helps to add a γ -carboxylic group to the N terminal residue of the coagulation protein and make it biologically active (fig. 1). Simultaneously, KH_2 yields Vitamin K epoxide. Vitamin K epoxide is then recycled to KH_2 through two reductase steps. In the first step Vitamin K is reduced to K1 form, which is sensitive to vitamin K antagonists and then later K1 is reduced to KH_2 form, which is comparatively less sensitive to vitamin K antagonists. Warfarin exerts its anticoagulant effect by limiting the production of vitamin KH_2 , thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity. Patient treatment with large doses of K1 can overcome the effect of Warfarin because K1 accumulates in the liver and is available to the Warfarin-insensitive reductase.

Warfarin is often referred to as a vitamin K antagonist (VKA), because the two tend to work against each other. If we increase the intake of vitamin K, to keep our blood from clotting we

will need more warfarin. Similarly if we reduce the intake of vitamin K, our dose of Warfarin will also have to be reduced in order to keep away from bleeding.

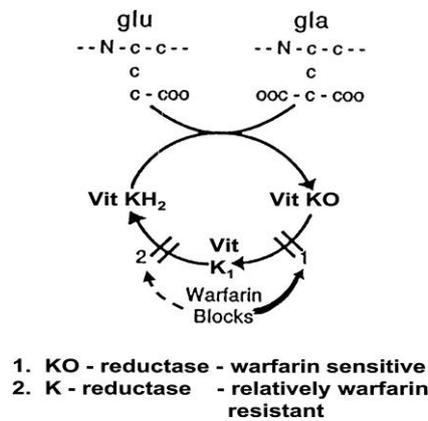


Figure 1: Mechanism of action of Warfarin

Figure 1, represents the mechanism of action Warfarin and vitamin K. Warfarin reduces the amount of KH₂ which is necessary for the activation of coagulation factors by blocking two steps.

Warfarin therapy is used in order to decrease the clotting tendency of blood, not to prevent clotting completely. Therefore, it is very important to monitor the effect of warfarin in blood with carefully conducted blood testing. On the basis of the blood test results, the dose of Warfarin needs to be adjusted in order to keep the clotting time within a targeted range. Since the therapeutic range of the anticoagulant drug is very low the high and low doses can be life threatening for the patient [4]. The actual doses of anticoagulant can overcome this problem and the intensity of this therapy are determined by testing of Blood Prothrombin Time (PT test). PT is the most common test to screen the intensity of the anticoagulant therapy in the cardiac patient. It is a measure of how quickly blood clots and also how it let out the qualitative and quantitative abnormalities of vitamin K dependent coagulation factors (II, VII, and X). The traditional method for performing a PT test is to have our blood drawn and sent to a lab. At the lab, calcium and thromboplastin is added to the citrated plasma. This reagent causes the blood to begin clotting. When patients are treated with Warfarin the PT increases, which reflects the reduction of vitamin K dependent coagulation factors. During the first few days PT results indicate the reduction of factor VII and afterwards it also reflects a reduction of factors X and II. The PT result is the time in seconds that is required for the blood to clot.

The unpredictability of the warfarin dose due to different factors e.g- changes in diet or concomitant medications, consequences from the therapeutic effect that changes over time. Therefore frequent monitoring of warfarin is needed for safe and effective utilisation. For this reason, to develop novel methods of monitoring warfarin that could lower the burden of patients as well as care providers, Point-of-care INR (Appendix 1.1) monitoring has been suggested as a way of providing more flexible monitoring options. Point-of-care INR monitoring could be provided either in home environment or physicans office. In the professional context that provides immediate feedback and interaction yet requiring the patient to travel to a centralized system. However patient self-testing provides the opportunity for advanced frequency of testing by providing improved access to testing [9]. Thromboplastin is one kind of principal reagent, which is used for PT test. It refers to a phospholipid-protein, which is extracted from varieties of tissues. This is commercially available in a variety of preparations of human or animal origin or human or animal recombinant materials. Thromboplastins differ in their responsiveness to the anticoagulant effects of Warfarin, depending on their phospholipids content, source, and preparation [5]. Since each of these reagents containing thromboplastin works differently, a PT result obtained with one reagent cannot be compared to a PT result obtained with another reagent. To account for the different reagents, the result of a PT test must be converted into standard units that can be compared regardless of the reagent used. These standard units are known as INR units. The PT is reported as the International Normalized Ratio (INR). The INR is a standardized way of expressing the PT value. The INR ensures that PT results obtained by different laboratories can be compared. It has been reported that there exist a correlation between INR and the effect of the anticoagulation therapy. Warfarin therapy is effective for thrombosis and embolism but this effect will depend on the value of INR during this therapy [6]. Hence, INR is useful in monitoring the impact of anticoagulant (“blood thinning”) medicines, such as Warfarin.

Patients have regular blood tests to monitor their INR, while taking Warfarin. Patients should also know their Warfarin (Coumadin) dosage and their INR, just as they know their blood pressure numbers. The INR is about 1.0 in healthy people. For anticoagulants dependent patients, the INR typically should be between 2.0 and 3.0 for patients with atrial fibrillation, or between 3.0 and 4.0 for patients with mechanical heart valves in accordance with old suggestions. According to the new findings about the relationship between INR and different complications (including death), there has been a trend towards lower target intervals [7] [8].

An INR can be too high; a number greater than 4.0 may indicate that blood is clotting too slowly, creating a risk of uncontrolled bleedings. An INR less than 2.0 may not provide adequate protection from clotting. All studies suggest that the monitoring of INR is very important to determine the level of Warfarin remaining in the effective range of a cardiac patient.

In a recent study of more than 19000 patients with atrial fibrillation the relationship between variability of INR and the risk of death, stroke, bleeding and hospitalizations was investigated. The variability was reflected by two variables, the calculated proportion of time when INR was within the limits 2-3 and the standard deviation of transformed INR. Especially the last mentioned variable was strongly related to all types of events. The results indicate the possibility that the risk could be lower if we can reduce the standard deviation of the transformed INR.

1.2. Aim of the study

Intuitively it seems reasonable that the variation of INR could be reduced by more frequent measurements and thereby more occasions to adjust the dose. The reader could think about the following simile. Children are playing a game, where they go by bikes on a road with closed eyes except for non-frequent occasions when they are allowed to have a quick glance on the road and correct the direction of their ride. The risk of being off the road will be large, especially when the frequency of glances is low. In the same way, if the dose of warfarin is seldom adjusted the risk of being outside the INR interval 2-3 will be large.

The aim of the present study is to investigate by simulation how the variability of Blood clotting could be reduced by more frequent measurements of INR.

1.3. Overview of thesis organization

Chapter 1 contains a brief literature review, background and aim of the study. In chapter 2, materials, methods and assumption of the study and simulation is discussed. Chapter 3 contains the results of the study and Chapter 4 presents the conclusion of the present study.

Materials, methods and assumptions of study

2.1. Materials of the study

To monitor anticoagulant therapy, a computerised system (Journalia Inc., Sweden) has been used at the hospital of Kungaelv in Sweden since 1986. In the system, 1560 patients were included during the period of 1986-1996 and among them thirty percent were women. The mean age of these patients was 66.2 years (SD=12.8 years).

The estimation was done according to the basis of the series of 56053 prescriptions of anticoagulation drugs. 2178 prescriptions show the number of prescriptions for increased dosage, while 1825 prescriptions are the amount of decreased dosage.

Those prescriptions of treatment were considered where the intervals were 0.5 – 1.5 years. The variable regression coefficient ($y = \text{INR}$, $x = \text{time period since start}$) was used to predict INR values after 0.25 years since start was also accepted to calculate that coefficient. After start with coagulation measurement before the occasion of increase or decrease of the dose, it was required that there were at least two occasions in the interval 0.25-1.5 years for contributing to the system.

The mean of the time period to the next INR measurement was 15 days ($15/365 = 0.043$ years) (SD = 0.035) when the dose increased and the corresponding mean was 15 days ($15/365 = 0.043$ years) (SD = 0.031) when the dose decreased.

The material was used to determine a transformation from INR to a normally distributed variable. Ideally we would like to have a material with very frequent measurements for the purpose of studying the variation of INR. Unfortunately, though many patients measure their INR values at home by use of point of care equipment it is probably unusual that the time intervals have other distributions than for the majority whose INR is measured at hospital or by general practitioners.

2.2. Methods of the study

In order to investigate whether the INR values had a normal distribution, the third and fourth central moments of the distribution divided by the third and fourth power of its standard deviation, respectively, were calculated.

Because of the non-normal distribution of the INR values, a special transformation was applied. All registered INR values were used to estimate the distribution of a randomly selected INR value. Let F denote the estimated distribution function and let Φ^{-1} be the inverse of the standardized normal distribution function. An INR value x was transformed to the value $\Phi^{-1}(F(x))$ and by that transformation the new values had an almost perfect normal distribution (Bloms transformation, Appendix 2)

For each prescription occasion some quantities (Estimated transformed INR) were calculated by ordinary linear regression with time as x variable and the transformed INR value as Y (Appendix 1.2). Age, sex, dose change are the regression quantities were entered into a stepwise multivariate regression procedure. The regression model is defined as follows.

$$Y = \beta_0 + \beta_1 z_1 + \beta_2 z_2 + \dots + \beta_k z_k + \beta_{k+1} z_{k+1} + \dots + \beta_n z_n \quad (1)$$

$Y =$ *Dependent variable (Estimated transformed INR)*

$\beta_i =$ *Regression coefficient*

$z_i =$ *Different variable (Age, sex, dose change etc.)*

In the final equation only the variables (z) with β_i significantly different from zero were included. The visits are here denoted by $1 \dots j$, where visit $(j - 1)$ is the visit of dose change. Thus $age_j - age_{j-1}$ is the length of the time interval after the dose change to the next measurement of INR, and the value of INR at the visit of dose change is INR_{j-1} . The index used for dose is special because at visit $(j - 1)$ for example the dose denoted $DOSE_{j-1}$ is the new dose applied between visit $(j - 1)$ and j , so $\frac{DOSE_{j-1}}{DOSE_{j-2}}$ is the quotient between the new

dose (after change) and the previous dose. We use the natural logarithm of this quotient as an independent variable as well as products with that variable and other ones, i. e. sex.

Two simple linear regression analyses were performed for each occasion of dose change, one using all visits before and including visit $(j - 1)$ provided that they are later than 0.25 years after start and that the visit is no longer than a year before visit $(j - 1)$. We required that there had to be at least two visits before the visit $(j - 1)$ in order to include the current dose change into the analysis. The regression coefficient, here denoted *beta* (β), of the linear regression function was calculated with transformed INR as dependent variable and time (years with 3 decimals) as independent variable. The standard deviation around the regression line, here denoted SD_{reg} , was also calculated. The standard deviation reflected the INR variability of the patients before the dose change. Another regression analysis was also performed including only the visits $j-3, j-2$ and $j-1$, i. e. the three last visits before change. The corresponding regression coefficient is here denoted by β_3 (β_3). Those regression coefficients reflect whether there is a tendency that the INR values are going up or down for the current patients

$$\beta = \text{Regression coefficient}$$

$$\beta_3 = \text{Regression coefficient based on 3 measurement}$$

Homogeneous variance was assumed for the (forward) stepwise procedure ending up with the variables with b coefficients (β or β_3) significantly different from zero. As a final step it was assumed that the variance was not homogeneous but equal to the square of $S \cdot (1 + C \cdot SD_{reg})$, where S and C were unknown constants. By an iterative procedure $\beta_0, \beta_1, \dots, \beta_n, s$ and c were estimated by the maximum likelihood method with the variables remaining at the last step of the stepwise method with homogeneous variance. When applying the result for an occasion of prescription the distribution of the future transformed INR value will first be determined as a normal distribution with the mean and standard deviation calculated as described above. Then by applying the inverse transformation to $\Phi^{-1}(F(x))$ the conditional distribution of the future INR value in the original scale could be calculated.

For our simulations, β coefficients (neither Increase nor Decrease) were not used for the simulations and we don't consider real patients, only simulated patients.

The regression models with the β coefficients were calculated by use of a material where the interval between measurements was much more than 3 days. The aim of the simulations was to see whether the variation of INR would be much less if the measurements were performed for example every third day (for diabetes it is known very well the measurements are more frequent, every day). The simulations said us that a short interval will probably give a lower variation. A next step would be to test on real patients how the variation could be reduced. A further step would be to perform new regression analyses, when we have more material with short intervals between measurements.

By use of multivariable regression analyses the relationship between a set of variables and the conditional distribution of the new INR variable was determined in a previous study [13]. An example from that study is shown in the figure.

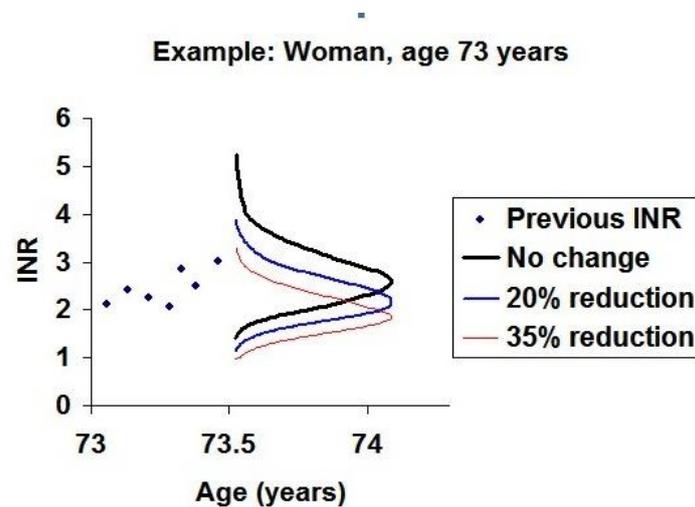


Figure 2: Effect of reduction of warfarin dose on INR

In the figure 2, between the age interval 73.5-74 we have estimate should 7 measurements of INR with warfarin dose 5 unit for a single patient were performed. At the end of the period the INR was 3.0, which was higher than before. Then for the age interval 73.5-74 we have predicted the next INR by equation (1). The uppermost curve is the conditional frequency function of the next INR if the dose is not changed, median 2.59 and mean 2.62. The next curve corresponds to 20% reduction of the dose, median 2.17 and mean 2.21. The lowest curves corresponds to 35% reduction, median 1.85 and mean 1.88. We can see that a reduction of approximately 20% of the dose would be an appropriate change in the example shown in figure.

2.3. Assumptions of the simulations of INR

We performed 70 simulations, each one comprising a year of follow up. The INR value was simulated every third day. A simulation comprised 122 ($365 / 3 = 122$) INR values. Measurement of INR was performed with different intervals for the different simulations. The intervals between measurements were 21, 18, 15, 12, 9, 6 and 3 days. A change of the dose was applied if the measured INR value was below 2.2 or above 2.8. In the first mentioned case the dose was increased by 20% and in the last mentioned case decreased by 20%.

For simulation, we start with the dose 5 and the INR value 2.5. Here t denotes the time since start and $INR(t)$ is the value of INR at the time t . The dose of warfarin given before or at the time t is denoted by $D(t)$. Thus $INR(0) = 2.5$ and $D(0) = 5.0$. Immediately after the INR is measured the dose could be changed but not otherwise.

When considering two consecutive INR values, $INR(t_1)$ and $INR(t_2)$, we make the assumptions given below.

$INR(t_2)$, has a normally distribution with mean (conditional) m and standard deviation v . (Appendix 1.3)

$$INR(t_2) \sim \text{Normal Distribution}(m, v^2) \quad (2)$$

$$\begin{aligned} \text{mean of } INR(t_2) &= m \\ &= 2.5 + \rho(t_2 - t_1)(INR(t_1) - 2.5) \\ &\quad + \log\left(\frac{D(t_1)}{D(t_2)}\right) f(t_2 - t_1) \end{aligned} \quad (3)$$

Where

$$\rho(x) = \exp(-0.1 - 0.7x) \text{ and } f(x) = 1 - \exp(-40x) \quad (4)$$

The argument x is a time difference and the unit is years. For example, if the time difference is 3 days, then x is $(3/365) 0.0082$. In a more realistic settings the $f(x)$ may depend on more than the length of the last interval.

$$\begin{aligned} \text{Standard deviation of INR } (t_2) &= v \\ &= 1.3 \sqrt{2(1 - \rho(t_2 - t_1))} \end{aligned} \tag{5}$$

For simplicity we apply a simple rule for dose changing. If INR is below 2.2 then we increase the last dose with 20%. If INR is above 2.8 then we decrease the dose by 20%. This is noted that the constants are not based on estimations.

Results and discussion of the study

3.1. Results of the simulation

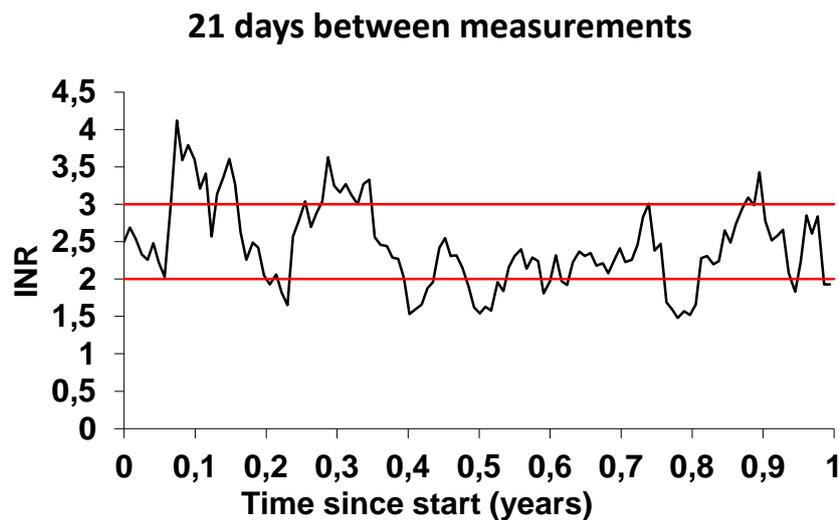


Figure 3: Change of dose of warfarin in every 21 days

In figure 3, in x axis we have plot the time interval of dose of warfarin for 1 year and in y axis we have plot the corresponding INR values. In this figure we have simulate the value of warfarin in every 3 days. So in 1 year time interval we have $(365/21 = 122)$ 122 simulated INR value. According to assumption, if the value of INR is more than 2.8 then we reduce the next dose by 20 % and if the INR value is less than 2.2, then we increase the dose of warfarin by 20 %. While simulation we don't change the dose in every 3 days. We have possibility to change the dose in every 21 days. That means the dose has changed based on assumption of INR value after every 21 days. If the INR value in every 21 days is more than 2.8, we decrease the next warfarin dose by 20 % and if it less than 2.2, then we increase the next warfarin by 20 %. The two red lines in the figure 3 denote the INR measurement of 2 and 3 respectively.

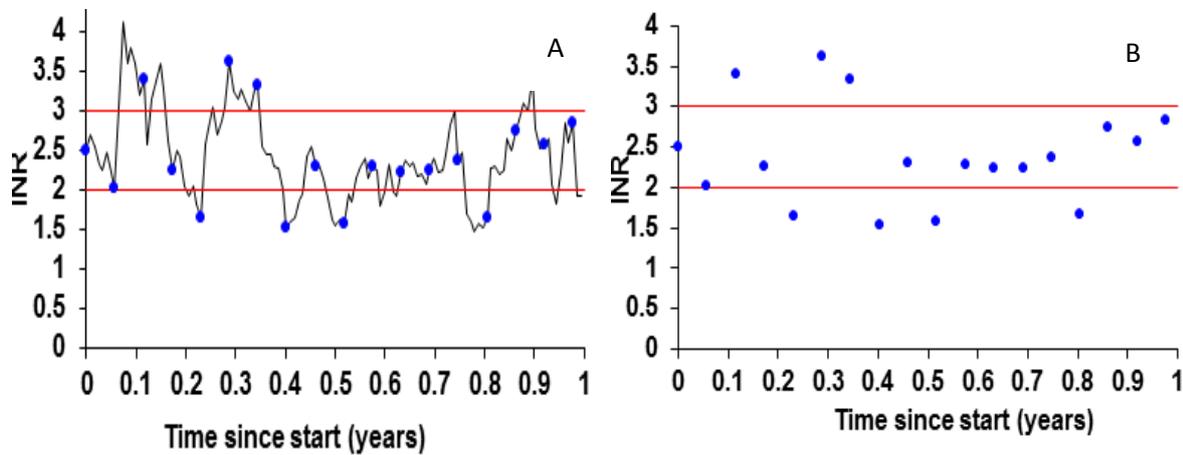


Figure 4 : Identify the dose changing point in change of dose of warfarin in every 21 days

In figure 4 only the dose changing points are identified in blue dot point. In figure 4A, the trend of change of INR values is shown but in figure 4B only the dose changing points are shown. According to our assumption, we are not allowed to change the warfarin dose for 21 days although the value of INR is out of red line. In figure 4 we have only identified the INR values for 21 days interval after each dose change and they are denoted by blue dots. So in a year for 21 days dose interval, we have only $(356/21=18)$ 18 points of INR after dose change.

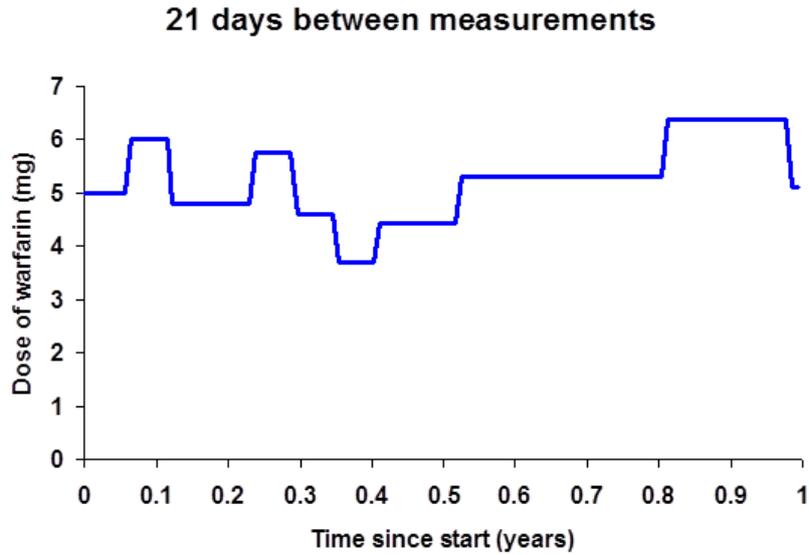


Figure 5: Change of dose of Warfarin in 21 days interval

In figure 5, we have plotted the dose of warfarin for corresponding INR value for 21 days interval. We assume that there is no change of dose between 21 days interval. That's why this is a step wise graph.

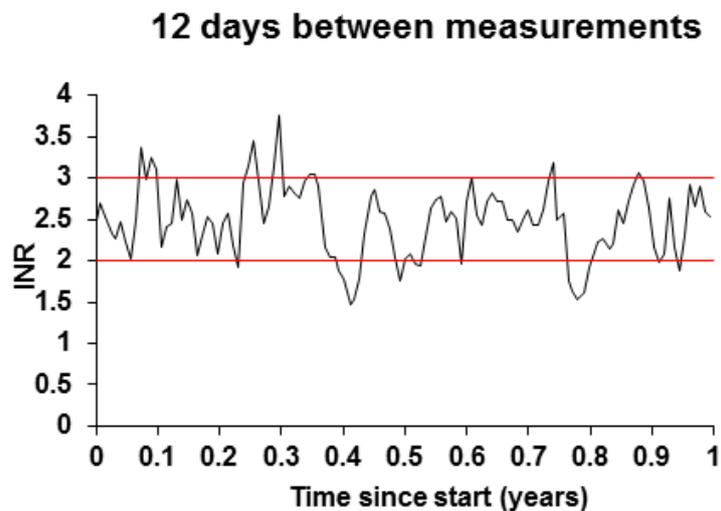


Figure 6 : Change of dose of Warfarin in every 12 days

In figure 6, , in x axis we have plot the time interval of dose of warfarin for 1 year and in y axis we have plot the corresponding INR values. In this figure we have simulate the value of warfarin in every 3 days. So in 1 year time interval we have $(365/3 = 122)$ 122 simulated INR value. According to assumption, if the value of INR is more than 2.8 then we reduce the next

dose by 20 % and if the INR value is less than 2.2, then we increase the dose of warfarin by 20 %. While simulation we don't change the dose in every 3 days. We have change the dose in every 12 days. That means the dose has changed based on assumption of INR value after every 12 days. If the INR value in every 12 days is more than 2.8, we decrease the next warfarin dose by 20 % and if it less than 2.2, then we increase the next warfarin by 20 %. The two red lines in the figure 3 denote the INR measurement of 2 and 3 respectively.

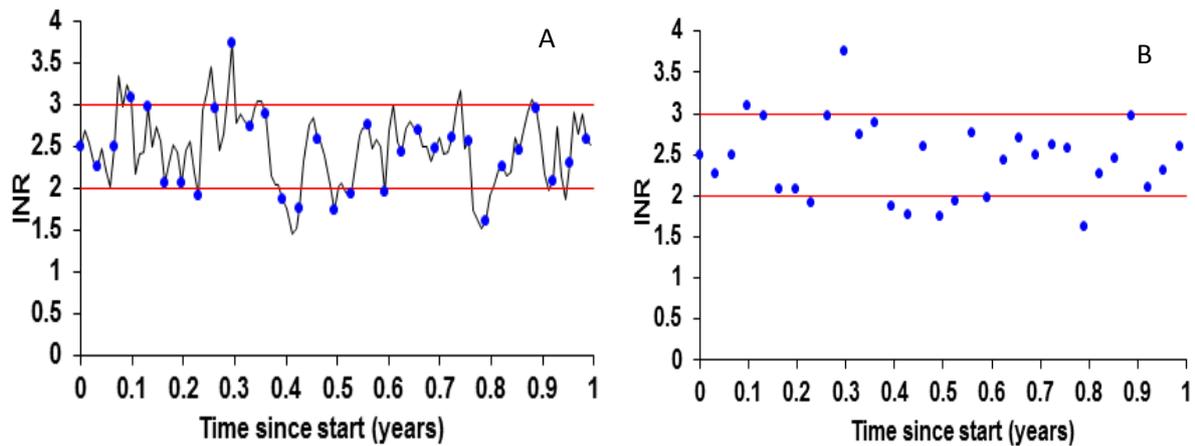


Figure 7 : Identify the dose changing point in change of dose of Warfarin in every 12 days

In figure 7, only the dose changing points are identified in blue dot point. In figure 7A, the trend of change of INR values is shown but in figure 7B only the dose changing points are shown. According to our assumption, we are not allowed to change the warfarin dose for 12 days although the value of INR is out of red line. In figure 7 we have only identified the INR values for 12 days interval after each dose change and they are denoted by blue dots. So in a year for 12 days dose interval, we have only $(365/12=31)$ 31 points of INR after dose change.

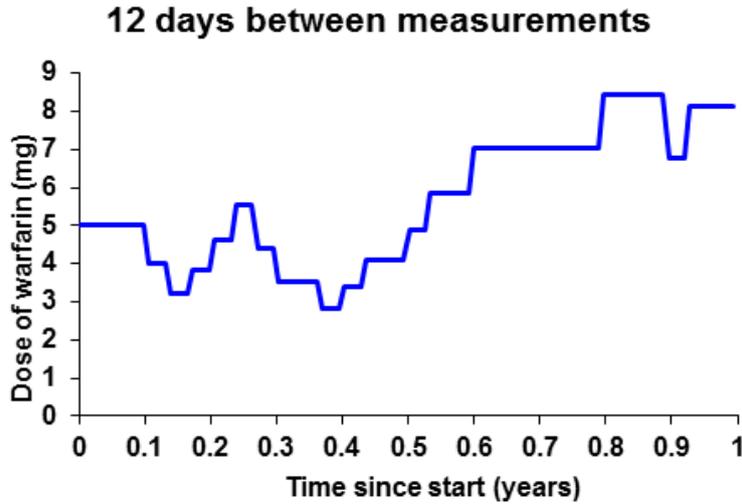


Figure 8 : Change of dose of Warfarin in 12 days interval

In figure 8, we have plot the dose of warfarin for corresponding INR value for 12 days interval. We assume that there is no change of dose between 12 days interval. That's why this is a step wise graph.

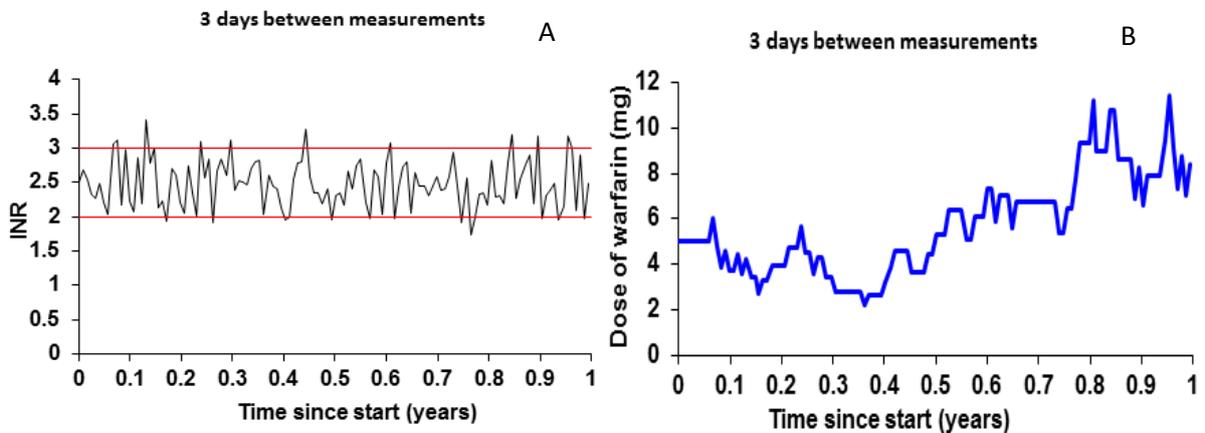


Figure 9 : Change of dose of Warfarin and corresponding INR in every 3 days

In figure 9A, in x axis we have plot the time interval of dose of warfarin and in y axis we have plot the corresponding INR values. And the red lines denote the INR measurement of 2 and 3 respectively. In figure 9B, we have plot the dose of warfarin for corresponding INR value for 3 days interval. We assume that there is no change of dose between 3 days interval. That's why this is a step wise graph.

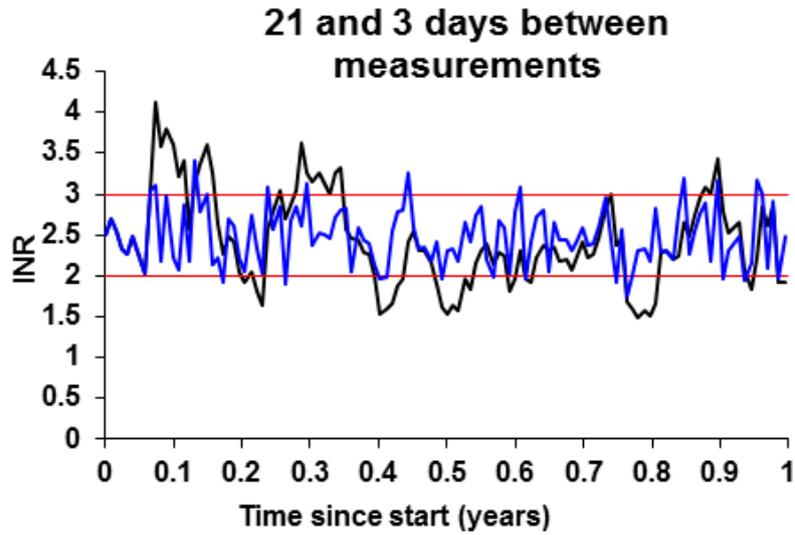


Figure 10 : Compare the INR value between 21 and 3 days measurements

In figure 10, we have plot the INR value in y axis for 21 days and 3 days interval before changing the dose. Here the black line indicate the reading from 21 days interval before changing the dose and blue line indicate the reading from 3 days interval before changing the dose. In x axis we have plot the time interval of dose of warfarin and in y axis we have plot the corresponding INR values. For every different curve , INR value was simulate for every 3 days , but dose of warfarin only change after 21 and 3 days interval. And the red lines denote the INR measurement of 2 and 3 respectively.

Table 1, shows the number of occasions when INR is outside the interval 2-3. In order to make it possible to repeat each simulation the random seed numbers are given. In table 1, the percent inside the interval 2-3 was calculated as $100 \cdot (1 - \text{number outside} / 122)$.

Table 1: Number of occasions when value of INR is outside the interval 2-3

Simulation number	Number of days between INR measurements						
	21	18	15	12	9	6	3
1	53	43	48	52	40	28	24
2	53	54	46	44	39	32	28
3	56	48	47	31	35	33	16
4	38	41	31	34	31	24	22

5	51	50	41	28	25	24	23
6	58	47	43	45	35	37	20
7	34	31	30	42	30	30	19
8	59	58	51	42	44	29	32
9	59	60	63	48	46	35	25
10	51	55	56	45	37	40	27
Sum outside 2-3 of 1220	512	487	456	411	362	312	236
% inside 2-3	58.0	60.1	62.6	66.3	70.3	74.4	80.7

Table 2 shows the standard deviation of transformed INR around the regression function, when time since start is independent variable.

Table 2: Standard deviation of transformed INR around the regression function

Simulation Number	Number of days between INR measurements						
	21	18	15	12	9	6	3
1	0.906	0.809	0.907	0.816	0.720	0.668	0.589
2	0.931	0.970	0.877	0.832	0.730	0.647	0.569
3	0.968	0.906	0.850	0.673	0.699	0.710	0.522
4	0.755	0.789	0.712	0.767	0.689	0.576	0.577
5	0.843	0.841	0.793	0.687	0.671	0.574	0.542
6	1.023	0.897	0.907	0.916	0.777	0.827	0.560
7	0.715	0.669	0.647	0.723	0.602	0.635	0.532
8	1.080	0.993	0.913	0.895	0.793	0.651	0.592
9	0.969	0.881	1.005	0.855	0.838	0.748	0.612
10	0.990	0.920	0.971	0.875	0.771	0.723	0.578
Pooled SD	0.925	0.872	0.865	0.808	0.732	0.680	0.568

One study (10) shows a relationship between the standard deviation and the risk of events of different types of event have been investigated. Death is one of the events studied. The difference between the SD 0.925 (21 days between measurements) and 0.568 (3 days between measurements) corresponds to a reduction of the risk of 39%.

$$39 \% = (1 - \exp(\log(1.59) / 0.332 \times (0.568 - 0.925))) \times 100\%$$

In Table 3, it shows the calculated reduction of risk when the standard deviation of transformed INR is reduced with the amount corresponding to the change from 21 days between measurements to 3 days for different events.

Table 3: Calculated reduction of risk [Dose change from 21 days between measurements to 3 days]

Type of end-point	Gradient of risk per 1 SD	Calculated reduction of risk
Death	1.59	39%
Stroke	1.30	25%
Bleed	1.27	23%
Admit to Hospital	1.47	34%

3.2. Discussion

Information technology is needed within risky and costly areas of health care. The need is becoming mandatory for those who manage anticoagulant therapy as the use of anticoagulants have expanded to clinical situations where embolism is not present but the treated patients often have only clusters of risk factors for embolism such as atrial fibrillation, heart failure and high age. Severe bleedings (11,12) or death (13) may occur in cases where there is very little risk for embolism. The ethical dilemma is that we cannot identify these individuals and to justify the use of anticoagulants we have to do what we can to carefully monitor our patients by the most accurate techniques. Besides this there are geographical variations (14) to be corrected by standardization and a need for individualization of therapy. In Sweden more than half of all hospitals have computerized units for anticoagulation. The computer will make the organization more efficient with a proficient nurse educating the patients, monitoring and reporting bleedings and re-thrombosis. Computer assisted control will facilitate at transfer of patients to primary care (15) and support self-management of oral anticoagulation (16).

Different results have been observed when the time interval of INR measurements varies between 21, 12 and 3 days in order to optimize the INR range of 2 to 3 in patients who take

blood thinners steadily. The reason why the results differ lies in early detection of hence more frequently taking of blood thinners with quantities depending on INR measurements.

In the case of 21 days sequence of INR measurement the percentage of INR values outside of the 2-3 range have been found to be 42% whereas this percentage is 33.7% for 12 days sequence of measurement. The table 2 depicts all the percentage values of different measurement sequences. According to simulation studies the most optimum and satisfactory results have been found in measurement of 3 days sequence in which more than 80% of the INR values are detected within the secure range that is 2 to 3.

Apart from aforementioned, the INR graphs depict 3 different intervals as 21, 12 and 3 days. The secure range is drawn by red lines and values vary depending on the quantity of the warfarin taking which is decided upon the INR measurements. As it is seen on the 21 and 3 days sequence comparison graph, blue line belonging to 3 days sequence is much more favorable than the black line of 21 days in terms of having INR to be more likely squeezed between the secure ranges. Patients who measure their INR values can change the dose of warfarin uptake much more rapidly as it is seen on the warfarin graphs. This causes them to control their blood thickness favorably hence preventing unforeseen complications including uncontrolled bleeding, stroke and other thrombotic events.

As it is shown in table 3, the 3 days sequence interval of measurement results in 39% less risk than the 21 days interval. Therefore it is indicated with this study that more rapid INR measurement creates best results for the anticoagulant dependent patients in terms of determining the dose of warfarin uptake. Since there is correlation between INR values and complications including dangerous strokes, the study suggests the measurement interval of 3 days sequence to the patients.

In our analysis we have not been able to take such variables into account, but we are convinced that it is important for the doctor or any dose monitoring person to be aware of such changes. If very high doses are needed (warfarin resistance) special conditions may be present, some of which are listed in (17). Neither was any account taken to temporary changing of doses suggested for a few days after a visit, e.g. an extra tablet or a complete stop of medication for a day or two in the present study. The effect on INR of a discontinuation was studied by (18). They found that after the last dose of warfarin there was a period of the mean length 29 hours before an exponentially decreasing of the INR started with the mean

INR half-life of 0.9 days. Thus the expected time period to a decrease of INR from 4 to 2.5, e.g., is $29 + 31.2 \ln(4/2.5) = 44$ hours. That type of results could be used for calculation of the duration of a temporary stop when the INR is high. However, the material of that study was relatively small a new studies are needed to get estimations of great accuracy. The influence of a temporary change on the INR values after 14 days or more may be limited.

Efforts have been made to find optimal INR for special groups of patients when considering ischemic stroke as endpoint (19). However, it has turned out (13) that not only ischemic stroke and bleedings are related to INR but death in general. By use of the estimated hazard function of death the change of INR can be performed so the lowest risk will be achieved in accordance with the function, see figure 2. By simulations it was possible to study the effect of changing the intervals between measurements.

Conclusion

The results of simulations in this study indicate that more frequent measurements and adjustment of dose could decrease the variation of INR substantially. Recent analyses of risk say that smaller variation is related to lower risk of death, stroke, bleedings and hospitalization. The existence of point of care units for measuring INR at home makes more frequent measurements realizable. The findings could be used for further studies. First the reduction of variation of INR by using smaller intervals between measurements could be assessed in a randomized study. Later the effect on the risk of different end-points could be studied.

Appendix

Appendix 1

1.1. International normalized ration (INR)

The calculated international normalized ratio is obtained using the first primary WHO reference thromboplastin (67/40 human combined) to test the blood sample with manual technique. It is calculated as follows:

$$\text{INR} = [\text{PT patient} \div \text{MN PT}]^{\text{ISI}}$$

$$\text{Observed ratio} = \text{PT patient} \div \text{MN PT}$$

$$\text{INR} = (\text{Observed ratio})^{\text{ISI}}$$

Where the ISI (International Sensitivity index) is derived from calibration of the reagent against the International Reference Preparation (IRP).

For example, a working thromboplastin with an ISI of 2.0 gives with a prothrombin ration of 1.5 an INR of 2.25. i.e.: $\text{INR} = 1.5^{2.0} = 2.25$

ISI Calculation:

The prothrombin time of all plasma specimens (20 healthy subjects and 60 patients) are converted to the corresponding logarithms. Let y be the logarithm of a prothrombin time/s determined with the IRP and x be the logarithm of prothrombin time/s determined with the local reagent to be calibrated. The relationship $y = a_1 + b_1x$ is calculated by the formula following in a_1 and b_1 are the orthogonal regression line parameters representing the intercept and the slope respectively.

$$b_1 = m + \sqrt{n^2 + 1}$$

$$\text{Where, } m = \frac{\sum(x-\bar{x})^2 - \sum(y-\bar{y})^2}{2\sum(x-\bar{x})(y-\bar{y})} = \frac{1}{2r} \left[\frac{s_y}{s_x} - \frac{s_x}{s_y} \right]$$

$$\text{and } a_1 = \bar{y} - b_1\bar{x};$$

\bar{x} is the arithmetic mean of x and \bar{y} the mean of y , s_x and s_y are the standard deviation of the x and y values and r the correlation coefficient.

This orthogonal regression slope estimates the relationship between log prothrombin time/s of IRP and local thromboplastin. The ISI of the newly calibrated reagent is determined as follows:

ISI= ($b_1 \times \text{ISI}$) of the reference reagent, where b_1 is the newly determined calibration slope. To the transform the logarithmic value into the value that would have been obtained with the first WHO IRP human combined (67/40) the following equation has used:

$$PT_{67/40} = \text{antilog}(a_1 + b_1 x)$$

Where, a_1 and b_1 are the certified parameters and x is the log PT (20)

1.2. Distribution of INR:

$INR(t_2) \sim \text{Normal Distribution}(m, v^2)$

$$\text{Mean of } INR(t_2) = m = 2.5 + \rho(t_2 - t_1)(INR(t_1) - 2.5) + \log\left(\frac{D(t_1)}{D(t_2)}\right)f(t_2 - t_1)$$

$$\text{where, } \rho(x) = \exp(-0.1 - 0.7x) \text{ and } f(x) = 1 - \exp(-40x)$$

$$\text{Standard deviation of } INR(t_2) = v = 1.3 \sqrt{2(1 - \rho(t_2 - t_1))}$$

Explanation:

It is noted that, actually we assume not that the INR is normal but that the logarithm of the INR at t_2 is normal given the INR at t_1 .

We have not yet any data on the change of INR (or transformed INR) when there are very frequent measurements. From data on less frequent measurements we have guessed (extrapolated) how the change of transformed INR could be for a patient. The distribution of the change varies from patient to patient (different individuals are not equally sensitive to Warfarin). If there is no change of the dose the expected value of the new transformed INR value is equal to the mean of transformed INR (=0.3675) plus the product of the correlation coefficient (ρ) between the new and the earlier transformed INR values times the difference (Earlier transformed INR – 0.3675). The described relationship is a general one for linear regression. Notice that INR 2.5 corresponds to transformed INR 0.3675. In the program (Appendix 4) the correlation coefficient is denoted RA(ST). ST is the step of three days =3/365.25 years. The correlation coefficient decreases exponentially with the length of the period between the INR values. That is exactly true for a certain type of stochastic processes (Gaussian Markov processes). In our case we assume that it is approximately true. By use of

our data we have estimated the function to be $\exp(-0.1 - 0.7 \times \text{time})$. The (-0.1) corresponds to an assumed measurement error of the transformed INR. When the dose changes from $DOSE_1$ to $DOSE_2$, we add $\log\left(\frac{DOSE_2}{DOSE_1}\right)$ times a factor, which here was guessed to be 4.5. Indeed we used the manuscript effects of dose changes of oral anticoagulants to find reasonable values of the constant 4.5.

The variance of the difference between two transformed INR values, which are assumed to have the same variance V^2 , is equal to $(2V^2 - 2V^2\rho)$, where ρ is the correlation coefficient. Thus the standard deviation is $\sqrt{2V^2(1 - \rho)}$. Here the square root of V was put to 1.3.

1.3. Regression Model

In the method section of the report, I have used a simplified version of the results of the regression analysis. In the simulation program a coefficient equal to 4.5 has used. From the regression model we can see that, the next transformed INR depends on the present transformed INR, and of course dose changes also are of importance.

Let X be the present INR and Y the next INR. Furthermore, assume that σ_1 and σ_2 are the standard deviations of Y and X , respectively, and that r is the correlation coefficient. A general relationship for regression functions tells that

$$E[Y | x] = E[Y] + \rho\sigma_1/\sigma_2 (x - E[X])$$

Provided that there is no dose change. In the presence of dose change we assume that the relationship is

$$E[Y | x] = E[Y] + \rho\sigma_1/\sigma_2 (x - E[X]) + b \cdot \ln(\text{Dose}_2/\text{Dose}_1)$$

The term $b \cdot \ln(\text{Dose}_2/\text{Dose}_1)$ equals zero if there is no change of the dose because the ratio $\text{Dose}_2/\text{Dose}_1=1$, and the logarithm of 1 equals 0.

From the result of the regression analyses we have found that $b=4.5$ could be a reasonable value. We should keep in mind that the sensitivity to dose changes are different to different individuals.

I performed two regression analysis, one for increase and one for decrease. The coefficients for $\ln(\text{Dose}_2/\text{Dose}_1)$ when considering decrease is $70.02 \cdot (\text{age}_j - \text{age}_{j-1}) + 0.9526 \cdot \text{sex}$. If we consider a woman and the number of days between the measurements are 20 days then the

coefficient is 4.78. There are individuals who are more or less sensitive to dose changes. We chose 4.5 as a reasonable value for the simulations.

All the independent variables tested are summarised.

Table 6: Independent variables

Variable
$u = \ln\left(\frac{dose_{j-1}}{dose_{j-2}}\right)$
$u.age_{j-1}$
$u.(age_j - age_{j-1})$
$u.sex(0 = man, 1 = women)$
$u.Tr(INR_{j-1})$
$u.beta(\text{regression coefficient})$
$u.SD_{regr}$
$u.beta_3(\text{regression coefficient based on 3 measurements})$
$Tr(INR_{j-1})$
$Beta$
$beta.(age_j - age_{j-1})$

After transformation INR has a normal distribution. The dependent variable in the regression analysis is the transformed INR. There are several independent variables, some of which are quantities calculated by use of simpler regression analysis. There is one variable called β and another one called β_3 . Furthermore, the standard deviation of the dependent variable (transformed INR) is not assumed to be homogenous, i.e. equal to a constant, but depending of the variation of previous INR values. The non-homogenous variance (or standard deviation) means difficulties to determine parameters of the model. In later time I have developed more efficient methods to determine the parameters. There is another peculiarity with the regression model. The products between each variable and $X = \ln(dose_{j-1} / dose_{j-2})$ are considered. For technical reason the interaction with X was performed more simplified than

usual. If the interaction between a variable Z and X is studied, one considers a model of the following type $b_0 + b_1 \cdot X + b_2 \cdot Z + b_3 \cdot X \cdot Z$. Thus the dependence of the dependent variable on X is $X \cdot (b_1 + b_3 \cdot Z)$. The coefficient before X is $(b_1 + b_3 \cdot Z)$, which depends on Z . Compared to this general approach the coefficient b_1 was put to zero. That procedure made the number of coefficients to estimate less.

The next step is to determine the likelihood function and then the derivatives of the likelihood function with respect to the coefficients, put the derivatives equal to zero and finally solve the System of equations (maximum likelihood estimates).

Why do we allow the standard deviation to be non-homogenous, i.e. to varies depending on the variation of previous INR? If the INR values of a patient have varied before we think it is likely that they will vary also in the future.

In order to perform the simulation of the next INR value we simulate the transformed INR value, which has a normal distribution. In fact we simulate a variable, which has a normal distribution with mean zero and standard deviation 1. Then we multiply that variable with the standard deviation, which we have determined, and add the mean of the transformed INR value. Thereby the simulated variable will have the correct standard deviation and mean. The procedure is repeated the number we want to. By comparing different simulations at the end we can see the effect of having shorter periods between measurements (at least for some individuals). If we can demonstrate that the variation of INR can be reduced for some individuals (who are note extreme) by more frequent measurements and simple changing of the dose then it is likely that almost every patient have something to gain when it comes to variation of INR. Therefore they also have something to gain when it comes to risk of different events including death due to the relationship between variation of INR and risk.

We have to calculate the conditional mean and standard deviation of the next transformed INR successively because they change all the time since they depend of the previous INR, which are successively simulated.

1.4. Mechanism of action of Warfarin

Warfarin is the most widely used oral anticoagulant, which is effective for the prevention of stroke in atrial fibrillation (1, 2). It decreases the body's ability to form blood clots by blocking the formation of vitamin K-dependent clotting factors. There are multiples numbers of proteins called clotting factors involve in the process of blood clotting. These proteins (factors II, VII, IX, and X) are converted to biologically active substances in the presence of Vitamin K. The reduced form of vitamin K (KH₂) helps to add g-carboxylic group to the N terminal residue of the coagulation protein and make them biologically active (fig. 1). Simultaneously, KH₂ yields Vitamin K epoxide. Vitamin K epoxide then recycled to KH₂ through two reductase steps. In the first step, Vitamin K is reduced to K₁ form, which is sensitive to vitamin K antagonist (Warfarin) and then later K₁ is reduced to KH₂ form, which is comparatively less sensitive to vitamin K antagonist. Warfarin exerts it's anticoagulant effect by limiting the production of vitamin KH₂, thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity. Patients treatment with large doses of K₁ can be overcome the effect of warfarin because K₁ accumulates in the liver and is available to the warfarin-insensitive reductase.

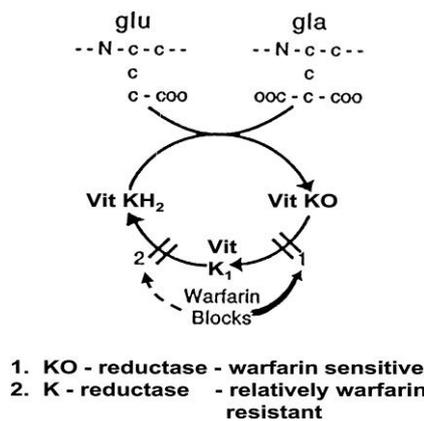


Figure: Mechanism of action of Warfarin

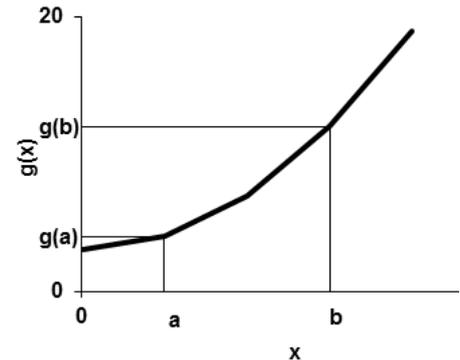
The above figure represents the mechanism of action warfarin and vitamin K cycle. Warfarin block the above two indicated steps (step-1 and step-2) and thereby reduces the amount of KH₂ which is necessary for the activation of coagulation factors.

Appendix 2

Theorem: Bloms transformation

If X is a continuous random variable with a non-zero frequency function and the distribution function F then $\Phi^{-1}(F(x))$, where Φ^{-1} the inverse of the standardized normal distribution is, has a normal distribution.

Proof: Before going to prove the theorem, we focused on some basic mathematical facts: If g is a non-decreasing function and $a \leq b$ then $g(a) \leq g(b)$. If g is increasing, then the inverse of g is also increasing. If $a < b$ then $g(a) < g(b)$



Now let us first prove the following theorem:

Theorem 1: If X is a continuous random variable then $F(x)$ has a uniform distribution on the interval $0 - 1$.

Proof of theorem 1:

F is as before the distribution function of X . That means that we shall prove that

$$P(F(x) \leq u) = u$$

where u is a number in the interval $0-1$.

$$P(F(x) \leq u) = P(F^{-1}(F(x)) \leq F^{-1}(u))$$

By definition of a distribution function we have

$$P(X \leq x) = F(x).$$

F is a non-decreasing function. That means that

$$F(X) \leq u \text{ is equivalent to } F^{-1}(F(X)) \leq F^{-1}(u),$$

Where, F^{-1} is the inverse function of F . By the definition of inverse function we have $F^{-1}(F(X)) = X$. Thus

$$P(F(X) \leq u) = P(X < F^{-1}(u)).$$

By the definition of distribution function, $P(X \leq x) = F(x)$, we find that

$$P(X < F^{-1}(u)) = F(F^{-1}(u)) = u$$

The last mentioned equality we find by again applying the definition of inverse function. Thus we have

$$P(F(X) \leq u) = P(F^{-1}(F(X)) \leq F^{-1}(u)) = P(X < F^{-1}(u)) = F(F^{-1}(u)) = u$$

where u is a number in the interval 0-1.

Now we are ready to prove the original statement that $\Phi^{-1}(F(x))$ has a normal distribution, i.e. $P(\Phi^{-1}(F(X)) \leq z) = \Phi(z)$

$$P(\Phi^{-1}(F(X)) \leq z) = P(\Phi(\Phi^{-1}(F(X))) \leq \Phi(z)) = P(F(X) \leq \Phi(z))$$

Now we apply that $P(F(X) \leq u) = u$ which we proved above. Then we find

$$P(F(X) \leq \Phi(z)) = \Phi(z)$$

Thus

$$P(\Phi^{-1}(F(X)) \leq z) = P(\Phi(\Phi^{-1}(F(X))) \leq \Phi(z)) = P(F(X) \leq \Phi(z)) = \Phi(z)$$

Appendix 3

In figure 10 and figure 12 the dose after a year was higher than 5 mg. Did that happen by chance? In order to investigate that in detail we analyzed the assumptions of the simulations and performed several series of simulations each comprising 1000 simulations of a year of follow-up.

The rule of dose change was that there was a decrease of the dose by 20% if INR was above 2.8 and an increase by 20% if the INR was below 2.2. At a first glance that may look as a symmetric rule of changing the dose. However, the reduction of the dose has to be $100 \times (1 - 1/1.20)\% = 16.7\%$ to avoid a successive reduction of the dose. If there are equal numbers of reductions and increases and the changes are 16.7% and 20%, respectively, the final dose is equal to the starting dose 5 mg. Thus, we could guess that the tendency to doses above 5 mg at the end was by chance. Indeed the tendency was in the opposite direction, which was confirmed by the simulations, see table below. When we changed the rule to decrease by 16.7% no tendency to end doses below (or above) 5 mg could be assessed. 20% reduction column of table 1 has obtained by using the program in appendix 4. 16.7% reduction column of table 1 has obtained by changing the line 270 of the program in appendix 4 which is

270 IF TRINR > .825 THEN DOSE2 = DOSE1 * .8

Table 4 : Number of cases when the final dose is less than 5 unit in both 20% and 16.7% dose reduction

Random seed number	MF	
	20% reduction	16.7% reduction
45	572	504
46	564	498,5
47	579	515
50	571	516,5
51	559	496
57	583	518,5
60	581	514,5
61	579	509,5
62	568	513
58	579	522

This noted that MF is the number of cases of 1000 simulations when the final dose is less than 5 plus half of the number when it is equal to 5. The program counts the number (MF) of times when the last dose is below 5 mg plus half the times when it is equal to 5. The last dose is after a year. When the program is run 1 time it performs 1000 simulations of the length 1 year. Then sometimes MF will be above 500 and sometimes below 500. By symmetry reasons we expect that the dose at the end will be above 5 mg equally often as it is below, which means that MF should vary around 500. In order to simplify the reading of the program a transformation table of INR is given in table 2. The program has included in appendix 4.

Table 5 : The transformation table of INR

INR	Transformed INR
2.5	0.3675
2.8	0.825
2.2	-0.090
2.0	-0.39499
3.0	1.13

Appendix 4

Program for simulation (QB64):

```
80 RANDOMIZE: REM ALLOWS THE PROGRAM TO PRODUCE DIFFERENT SEQUENCES
OF RANDOM NUMBERS FOR EACH RUN
90 FOR I = 1 TO 6: READ BE(I), L(I): L(I) = -L(I) / BE(I): BE(I) = 1 / BE(I): NEXT I
100 DATA 13.03,-15.701,2.276,-4.947,1.525,-3.445,1.077,-2.101,0.403,0.595,0.422,0.500
110 FOR I = 1 TO 5: READ G(I): NEXT I
120 DATA -2.671001,-0.3950,1.1300,2.2070,2.6100
130 ST = 3 / 365.25: REM THE LENGTH OF A STEP BETWEEN MEASUREMENTS. IN THIS
CASE 3 DAYS.
132 DIM TRINR(122), X(122)
140 REM TRINR DENOTES THE TRANSFORMED INR-VALUE
142 FOR R = 1 TO 1000
  144 QN = 0
  150 FOR T = 0 TO 1 STEP ST
    160 REM IF T = 0 THEN DOSE2 = 5: DOSE1 = 5: TRINR = .3675: INR = 2.5: GOTO 214
    162 IF T = 0 THEN DOSE2 = 5: DOSE1 = 5: TRINR = .3675: GOTO 214
    170 MEAN = .3675 + RA(ST) * (TRINR - .3675) + LOG(DOSE2 / DOSE1) * 4.5
    180 SD = 1.1 * SQR(2 * (1 - RA(ST)))
    190 U = RND(5): IF Y > .9999 THEN U = .9999
    200 GOSUB 340
    210 TRINR = X * SD + MEAN: GOSUB 420
    212 QN = QN + 1: X(QN) = T: TRINR(QN) = TRINR
    214 IF ANT MOD 4 = 0 THEN 220 ELSE GOTO 240
    220 REM PRINT USING "###.###"; T; : PRINT ", "; : PRINT USING "###.###"; INR; : PRINT ", ";
    230 REM PRINT USING "###.###"; DOSE2
    240 DOSE1 = DOSE2
    250 IF ANT MOD 4 = 0 THEN 270 ELSE GOTO 290
    260 REM THE LIMITS 2.2 AND 2.8 FOR INR CORRESPOND TO -0.090 AND 0.825,
RESPECTIVELY FOR THE TRANSFORMED INR
    270 IF TRINR > .825 THEN DOSE2 = DOSE1 * 1 / 1.2
    280 IF TRINR < -9.000001E-02 THEN DOSE2 = DOSE1 * 1.2
    290 ANT = ANT + 1: IF TRINR < -.3949998 OR TRINR > 1.13 THEN UTANF = UTANF + 1
    300 REM A$=INKEY$:IF A$="" THEN 300
  310 NEXT T
  312 REM PRINT : PRINT ANT, UTANF;
  314 GOSUB 1000
  316 REM PRINT USING " ###.###"; SD
  318 MF = MF - (DOSE2 = 5) * .5 - (DOSE2 < 5)
319 NEXT R
320 PRINT MF: CLOSE: END
330 REM A NORMALLY DISTRIBUTED RANDOM NUMBER X IS GENERATED BY THE
NEXT LINES
340 FGX = 0: X = 0
350 X = NY(U, X): IF ABS(X - FGX) > .001 THEN FGX = X: GOTO 350
360 RETURN
370 REM INPUT "T TO INR IS 1 AND INR TO T IS 2"; Q
380 REM IF Q = 1 THEN 410
390 REM IF Q = 2 THEN 470
400 GOTO 370
410 INPUT "T"; T
```

```

420 I = 1: IF TRINR > G(1) THEN I = 2: IF TRINR > G(2) THEN I = 3: IF TRINR > G(3) THEN I =
4: IF TRINR > G(4) THEN I = 5: IF TRINR > G(5) THEN I = 6
430 INR = TRINR * BE(I) + L(I): REM GER INR-VZRDET
440 REM PRINT "INR = ";INR
450 RETURN
460 GOTO 370
470 INPUT "INR"; INR
480 I = INT(INR) + 1: I = (I + 6) / 2 - ABS(I - 6) / 2: T = (INR - L(I)) / BE(I)
490 REM PRINT "T = "; T
500 GOTO 370
1000 MEAN = 0
1010 FOR I = 1 TO QN: MEAN = MEAN + X(I): NEXT I
1020 MEAN = MEAN / QN
1030 SY(1) = 0: NOM = 0: DENOM = 0
1040 FOR I = 1 TO QN
    1050 SY(1) = SY(1) + TRINR(I): NOM = NOM + (X(I) - MEAN) * TRINR(I): DEN = DEN +
(X(I) - MEAN) ^ 2
1060 NEXT I
1070 ALFA = SY(1) / QN: BETA = NOM / DEN
1080 VA = 0
1090 FOR I = 1 TO QN
    1100 VA = VA + (TRINR(I) - ALFA - BETA * (X(I) - MEAN)) ^ 2
1110 NEXT I
1120 SD = SQR(VA / (QN - 2)): REM PRINT SD;
1130 RETURN
FUNCTION P (X)
P = (.436183 * TF(X) - .120167 * TF(X) ^ 2 + .937298 * TF(X) ^ 3) * (1 - 2 * Q(X))
END FUNCTION
FUNCTION FI (X)
FI = P(X) * EXP(-X * X / 2) / SQR(2 * 3.14159265#) + Q(X)
END FUNCTION
FUNCTION NY (U, X)
NY = (U - FI(X)) * 2.5066 * EXP(X ^ 2 / 2) + X
END FUNCTION
FUNCTION RA (X)
RA = EXP(-.1 - .7 * X)
END FUNCTION
FUNCTION TF (X)
TF = 1 / (1 + .3326 * ABS(X))
END FUNCTION
FUNCTION Q (X)
Q = (SGN(X) + 1) / 2
END FUNCTION

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Reference

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