CHALMERS
ENGINEERING MATHEMATICS
SE-412 96 GOTHENBURG, SWEDEN
PHONE: +46 (0)31-772 10 00 - WWW.CHALMERS.SE

Frequency of monitoring INR measurements and intensity of anticoagulation

Thesis By
Habib Ullah
(820210-7358)

CHALMERS

Adjunct professor Anders Odén.

Statiscal consultant , Romelanda, Sweden
Department of Mathematical Sciences

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Abstract

Patients have regular blood tests to monitor their INR, while taking Warfarin. Patients should also know their Warfarin (Coumadin) dosage and their INR, likewise they know their blood pressure numbers. The INR is about 1.0 in healthy subject while 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]
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 hospitalisation. The existence of point of care units for measuring INR at home makes more frequent measurements realizable.

1. Introduction

There are several drugs that are advised as "blood thinners" such as Coumadin (warfarin), Dicumarol (dicumarol), Miradon (anisinidione), Sintrom (acenocoumarol), Warfilone (warfarin) varies from country to country. Blood thinner are commonly recommended by the 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 thinner has 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 thinner.

Warfarin is the most widely used oral anticoagulant, which is effective for the prevention of stroke in aterial 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 involved in the blood clotting process. 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 and then later K1 is reduced to KH2 form, which is comparatively less sensitive to vitamin K antagonist. Warfarin exerts their anticoagulant effect by limiting the production of vitamin KH2, thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity[3]. Patient 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.

Warfarin is often referred to as a vitamin K antagonist (VKA), because they 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.

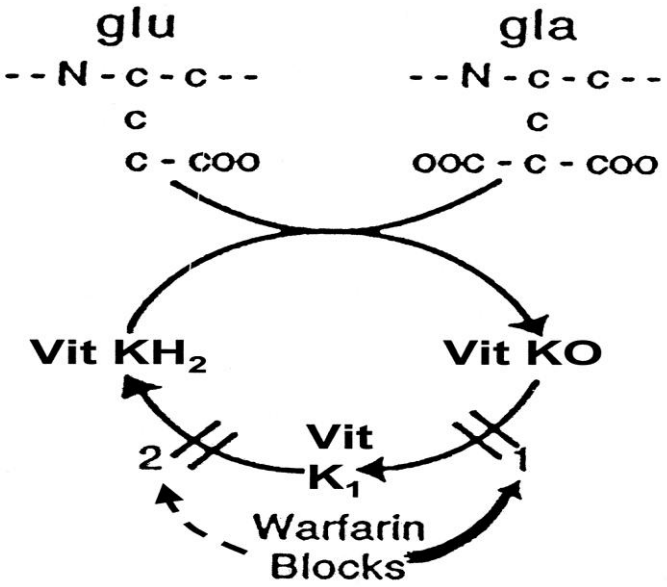


Fig 1. The diagram represents the mechanism of action warfarin and vitamin K cycle. Warfarin reduces the amount of KH2 which is necessary for the activation of coagulation factors by blocking two steps.

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 anticoagulant drug is very low so that 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 less or frequent 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 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 patient are treated with the warfarin it increases the PT, 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, affects the therapeutic effect that changes over time. Therefore frequent monitioring 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 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 physician 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 a 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 variety of preparation 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 a bit 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 have the correlation between INR and the effect of 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. Therefore, all this studies suggest that the monitoring of INR is very important to determine the level of warfarin remains in the effective range of a cardiac patient.

In a recent study[10] of more than 19000 patients with atrial fibrillation the relationship between variability of INR and the risk of death, stroke, bleeding and hospitalisations 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 the 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.

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 INR could be reduced by more frequent measurements of INR.

2. Materials and methods

2.1 Materials

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 patient was included during the period of 1986-1996 and among them thirty percent were women. The mean age of these patient staring were 66.2 years (SD=12.8 years).
According to the basis of the series of 56053 prescription of anticoagulation drugs, the estimation were completed. Prescription 2178 was increased where prescription 1825 was decreased . Those prescriptions of treatment were considered where the intervals were 0.5 – 1.5 years. The variable regression coefficient (y = INR, x = time period since start) was used to predict among others and 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 0.043 years (SD = 0.035) when the dose increased and the corresponding mean was 0.043 years (SD = 0.031) when the does 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 equipments it is probably unusual that the time intervals have other distributions than for the majority, whose INR is measured at hospital or at general practitioners.

2.2. Methods

Calculating the third central moments of the distribution divided by the third power of its standard deviation as well as the fourth central moments of the distribution divided by the fourth power of its standard deviation to verify whether the INR values had a normal distribution.
We have investigated this, since 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 H and Φ^{-1} are denoted as the estimated distribution

function and the inverse of the standardised normal distribution function. The value of $\Phi^{-1}(H(u))$ was obtained by the transformation of an INR value u and the consequence of that transformation had an almost perfect normal distribution. Some quantities of each prescription occasion were calculated by ordinary linear regression holding u-variable as time and the transformed INR value as v. Age, sex, dose change and In that case, quantities of regression were entered into s stepwise multivariate regression procedure. Let u is taken for the natural logarithm of the quotient between the doses closest both before and after the change. Then $u > 0, u = 0\ and\ u < 0$ correspond to increase, no change and decrease of the doses respectively. There by the regression function or the next transformed INR value was

$$\mathbf{V=a_0 + a_1 \cdot u + a_2 \cdot u \cdot z_2 + \dots + a_k \cdot u \cdot z_k + a_{k+1} \cdot z_{k+1} + \dots + a_n \cdot z_n} \qquad \mathbf{(1)}$$

Where a_i were coefficients and z_j different variables some of which were multiplied by u. In the final equation only the variables with a_i significantly different from zero were included. We denoted the visits as $1, \dots, j,$, where visit $j-1$ is the visit of dose change. In this way, $age_j - age_{j-1}$ 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 $does_{j-1}$ is the new dose applied between visit $j-1$ and j , so $does_{j-1}/does_{j-2}$ is the quotient between the new dose (after change) and the previous dose. As an independent variable, we use the natural logarithm of this quotient 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, 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 $SD_{regr,}$ was also calculated. The standard deviation reflected the INR variability of the patient 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. We denoted $beta_{3,}$ for the corresponding regression coefficient. In table 1, All the independent variables tested are summarised.

Table 1: Independent variables

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

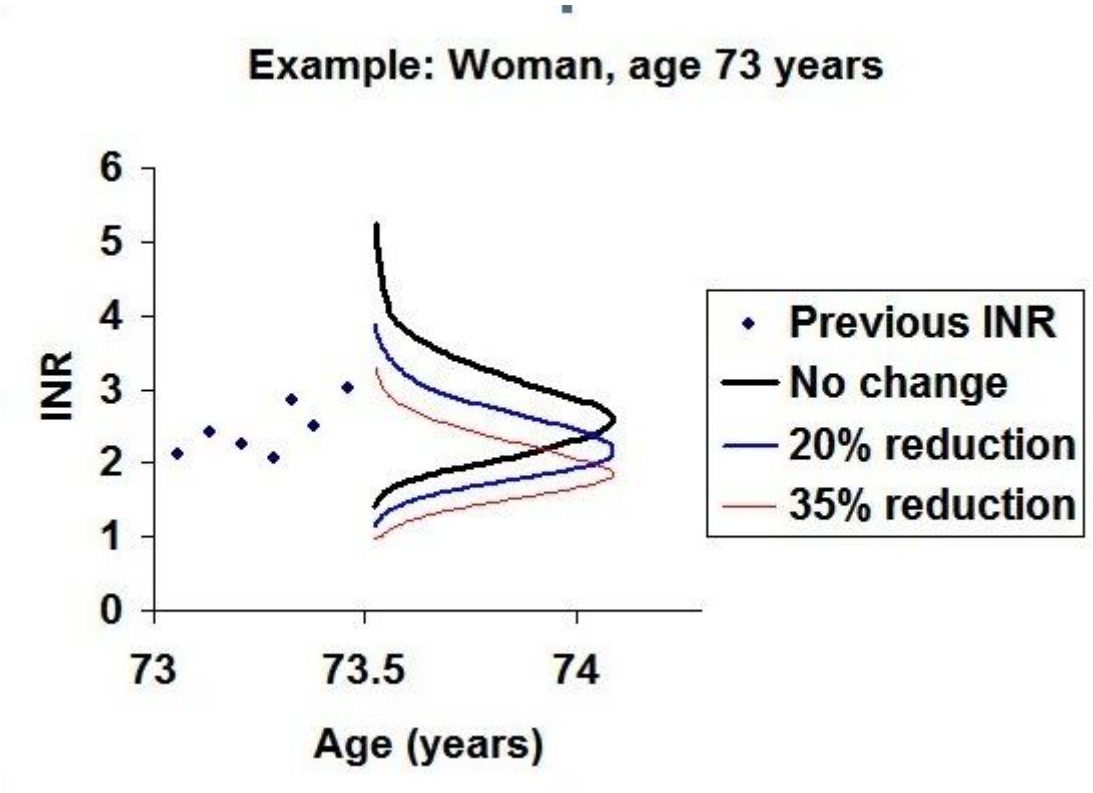
Homogeneous variance was adopted for the (forward) stepwise procedure ends with variables with a coefficient significantly different from zero. As a final step, it was assumed that the variance was not homogeneous, but equal to the square of $s.(1 + c.SD_{regr})$, where s and c were unknown constants. By an iterative procedure $b_o, b_1, \ldots\ldots, b_n$, 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 $\Phi^{-1}(\mathrm{H(u)})$ the conditional distribution of the future INR value in the original scale could be calculated.
The 3rd and 4th central moments of INR divided by the 3rd and 4th power of its standard deviation, respectively, were 1.38 and 8.78. The correspond quantities of a better normal distribution are 0 and 3. The non-normal distribution of INR in the exam material is also clear up by figure 1. the curve correspond to the bolded one would have been a straight line when INR had a normal distribution. Because of the non-normality a transformation of all INR values was performed which described in the method section. In order to alleviate applications establish on this article the estimated function $\Phi^{-1}(\mathrm{H(u)})$ was approximated by a piecewise linear and continuous function here denoted $T_r(x)$. Thus $T_r(INR)$ gives the transformed INR value having an almost perfect normal distribution. $Tr(x)=k \cdot x + l$ with different values of k and l in different intervals, see table 2.

Table 2 :
Piecewise linear transformation, $Tr(x)=k \cdot x + l$
carrying the INR value x normally distributed variable.

k	l	Interval
13.03	-15.701	$x \leq 1$
2.276	-4.947	$1< x \leq 2$
1.525	-3.445	$2< x \leq 3$
1.077	-2.101	$3< x \leq 4$
0.403	0.595	$4< x \leq 5$
0.422	0.500	$x > 5$

In figure 1 dotted lines are mapped different linear function. (8)

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. An example from that study is shown in figure 2.



In figure 2 . Between the age of 73 and 73.5 years 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 estimate the value of transformed 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 curve 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.

2.3 Assumptions of the simulations of INR :

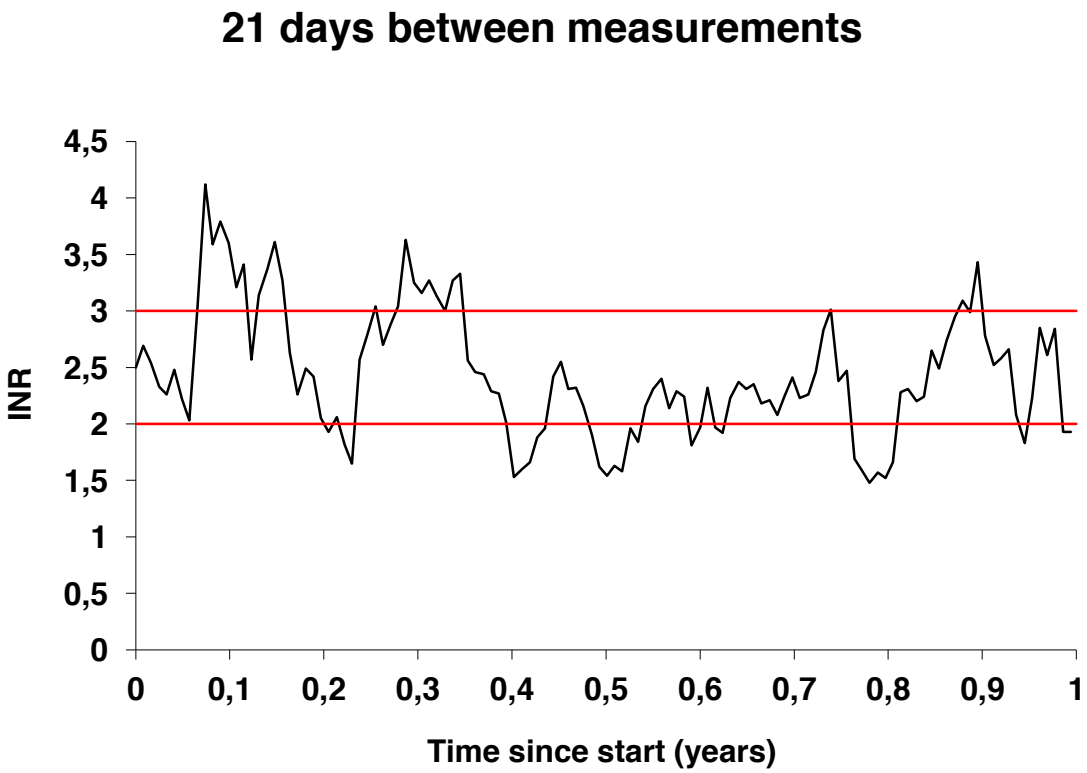
We performed 70 simulations, each one comprising a year of follow up. The INR value was simulated every third day. A simulation comprised 122 INR values. Measurement of INR was performed with different intervals for the different simulations. The intervals between measurements were 21, 18, 15, 12, 9, 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%.
We start with the dose 5 and the INR value 2.5. Here t denotes the time since start and INR(t) denotes the INR value at the time t. The dose of warfarin given before or at the time t is denoted D(t). Thus INR(0)=2.5 and D(0)=5. Immediately after the INR is measured the dose could be changed but not otherwise.

Let us denote the current transformed INR value by TRINR. Furthermore, the next INR value will be generated ST years after the current value. In the present case we have chosen ST to be 3/365.25 years (3 days). We use an exponentially decreasing function, FNR(x), which

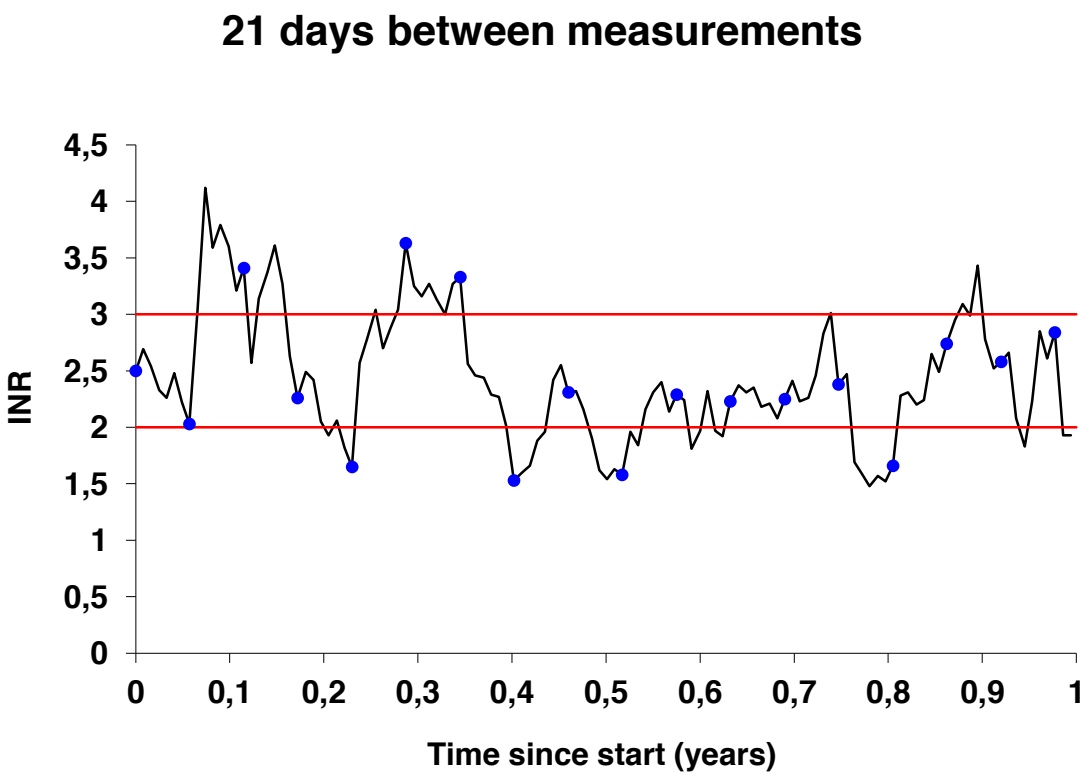
describes how the correlation coefficient between two transformed INR values decreases by the time x. FNR(x) = EXP(-.1-.7 ·x). DOSE1 is the dose just before the current INR and DOSE2 is the dose after. The mean of the next transformed INR value is assumed to be
MEAN = 0.3675 + FNR(ST) · (TRINR – 0.3675) + 4.5 · log(DOSE2 / DOSE1)
The standard deviation, SD, is assumed to be
$SD = 1.1 \cdot [2 \cdot (1-FNR(ST))]^{½}$
We assume that the first INR value is 2.5 and that every transformed INR value has a normal distribution. The transformed INR value corresponding to the INR 2.5 is 0.3675.
We have access to very large materials, but no material with very frequent measurements. The constants arising in the formulas for MEAN and SD above are determined from the large material, so they represent reasonable values. In the future we could have access to materials with more frequent measurements. Then simulations for special individuals could be performed.

Remark
The constants are not based on estimations.

3. Results :



In figure 3 : Here 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 we have (365/3 =122) 122 INR value. And the red lines denote the INR measurement of 2 and 3 respectively.



According to our assumption , we are not allowed to change the warfarin dose for 21 days though 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

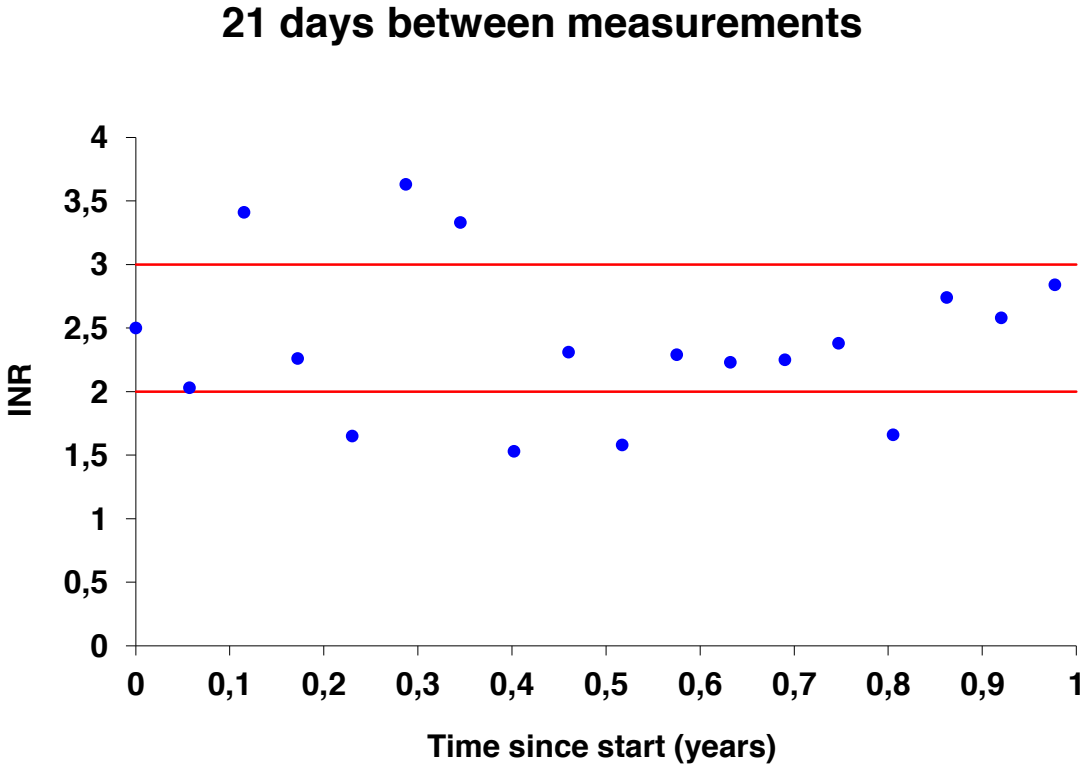


Figure 5 , : we have only identified the INR values for 21 days interval and they are denoted by blue dots, here we calculated only specific point. 18 dots plotted in a year.

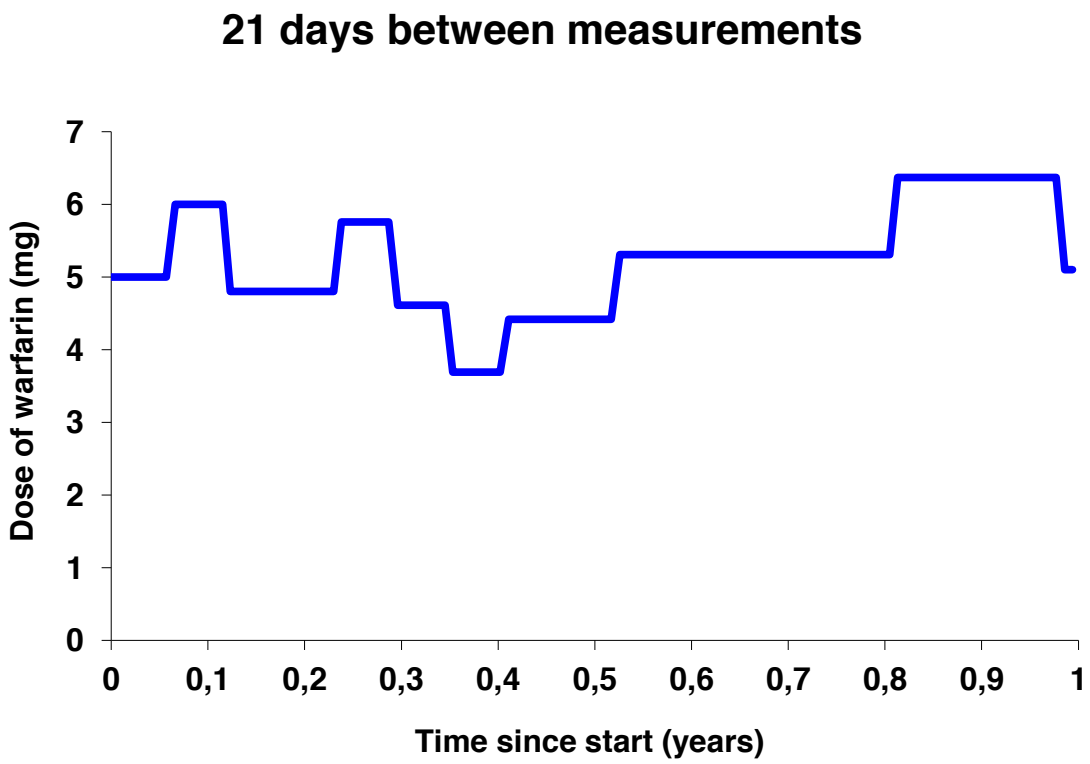


Fig 6 : In this figure we have plot the dose of warfarin for corresponding INR value for 21 days interval. We assume that there is no change of dose between 21 days interval . That's why this is a step wise graph

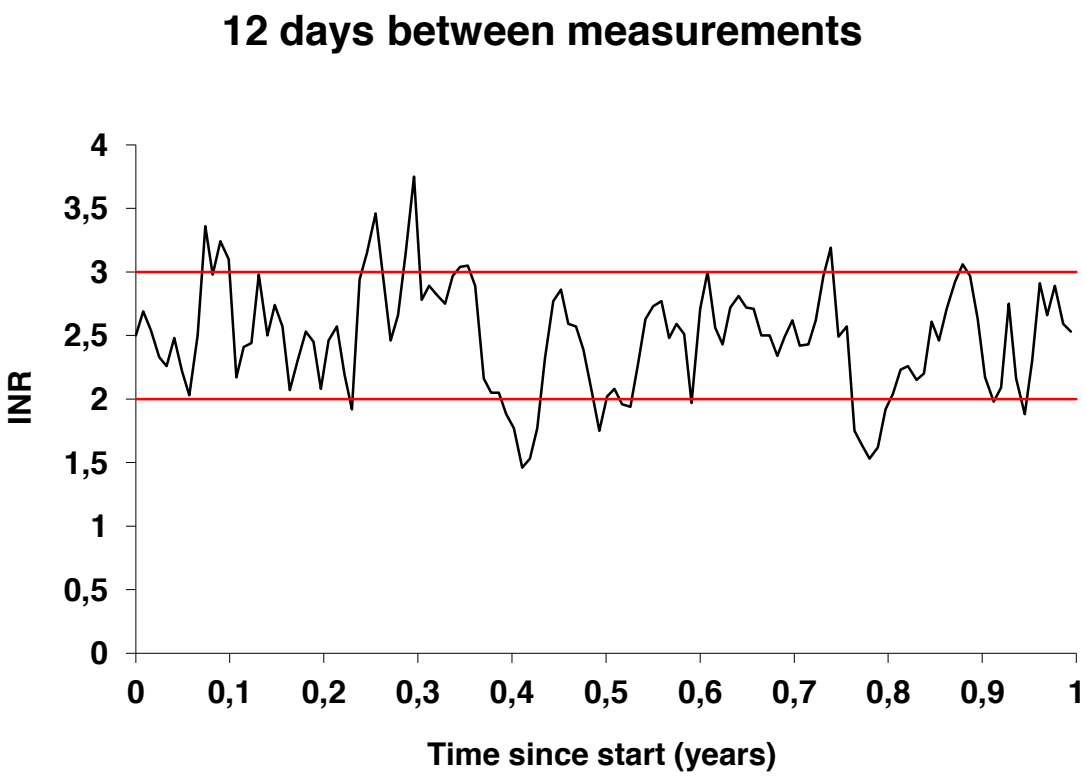


Fig 7 : Here in x axis we have plot the time interval of dose of warfarin and in y axis we have plot the corresponding INR values for every 3 days . And the red lines denote the INR measurement of 2 and 3 respectively.

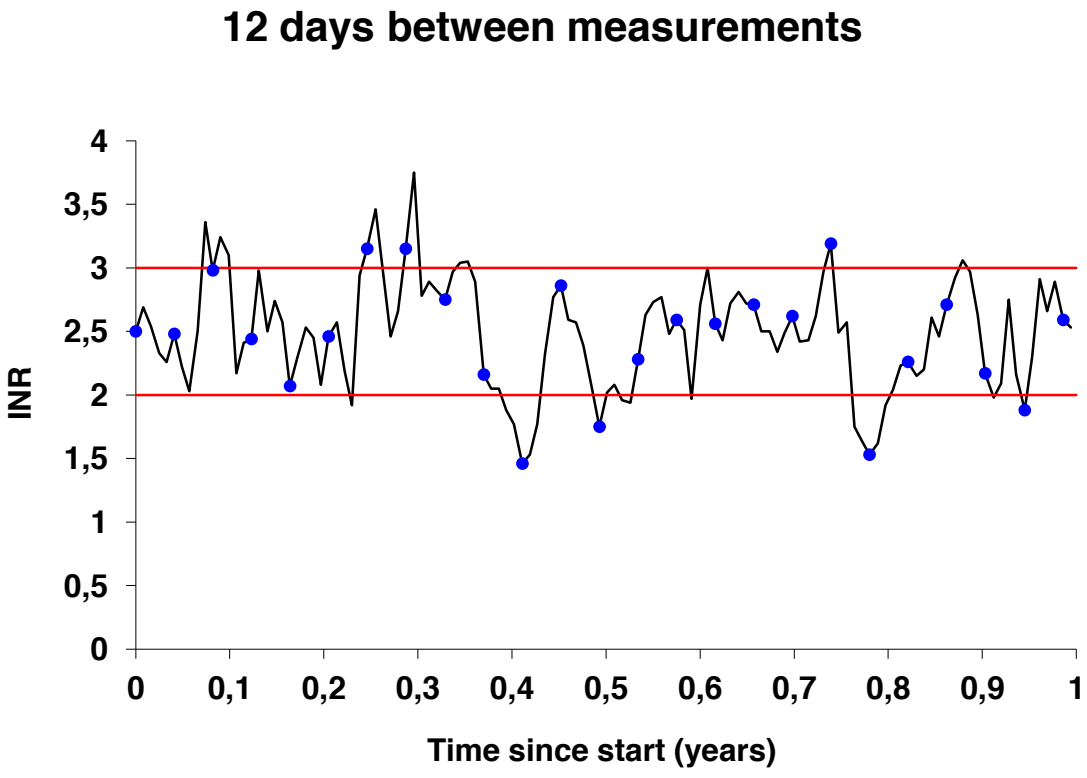


Fig 8 : In this figure we have only identified the INR values for dose change after 12 days interval and they are denoted by blue dots.

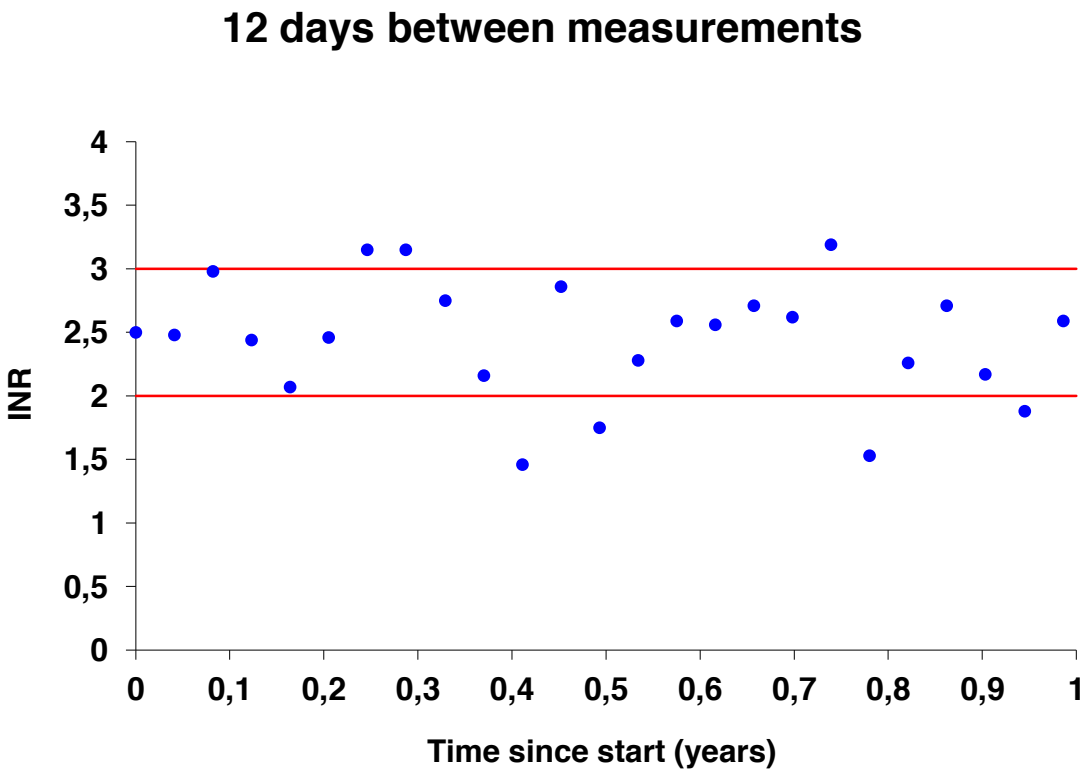


Fig 9: In this figure we have only identified the INR values only for 12 days interval and they are denoted by blue dots, here we calculated only specific point. 25 dots plotted in a year.

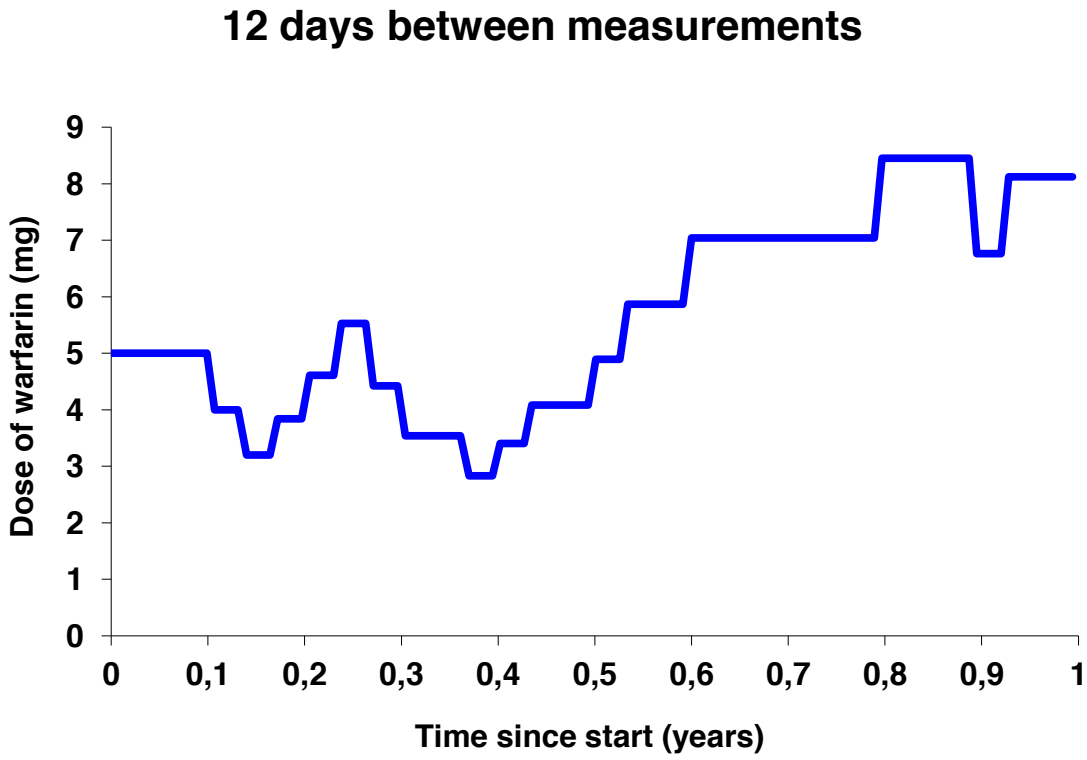


Fig 10 : In this figure we have plot the dose of warfarin for corresponding INR value for 12 days interval. We assume that there is no change of dose between 21 days interval . That's why this is a step wise graph.

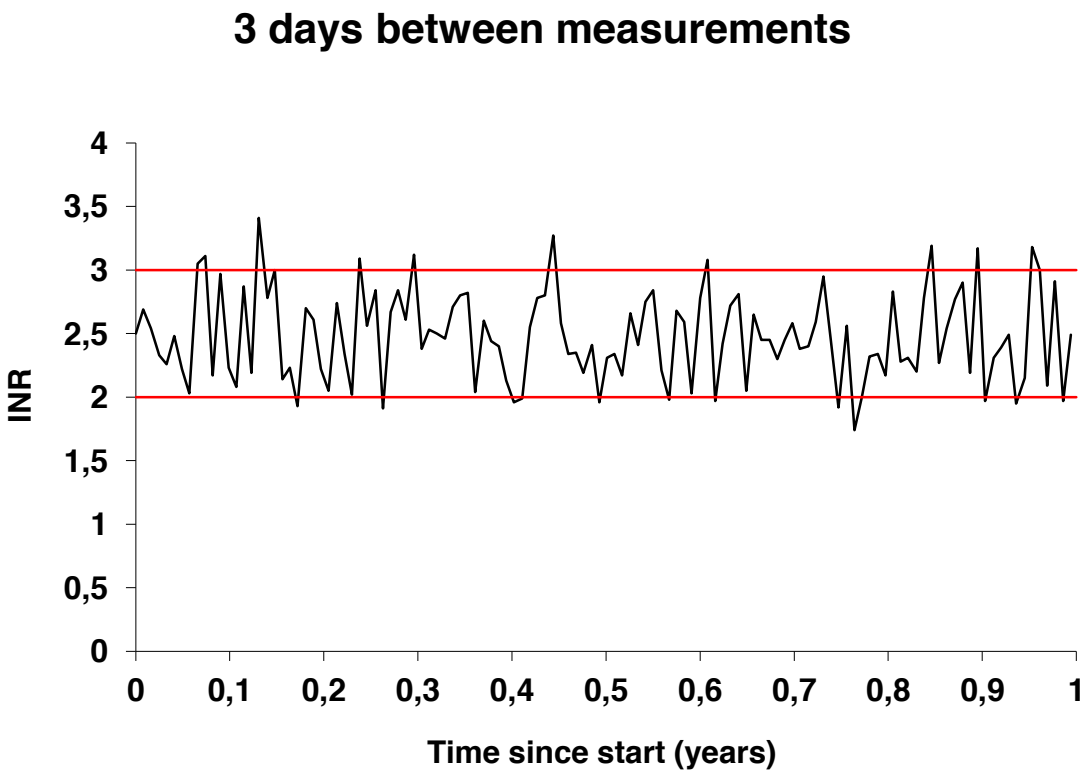


Fig 11 : Here in x axis we have plot the time interval of dose of warfarin and in y axis we have plot the corresponding INR values. And the red lines denote the INR measurement of 2 and 3 respectively.

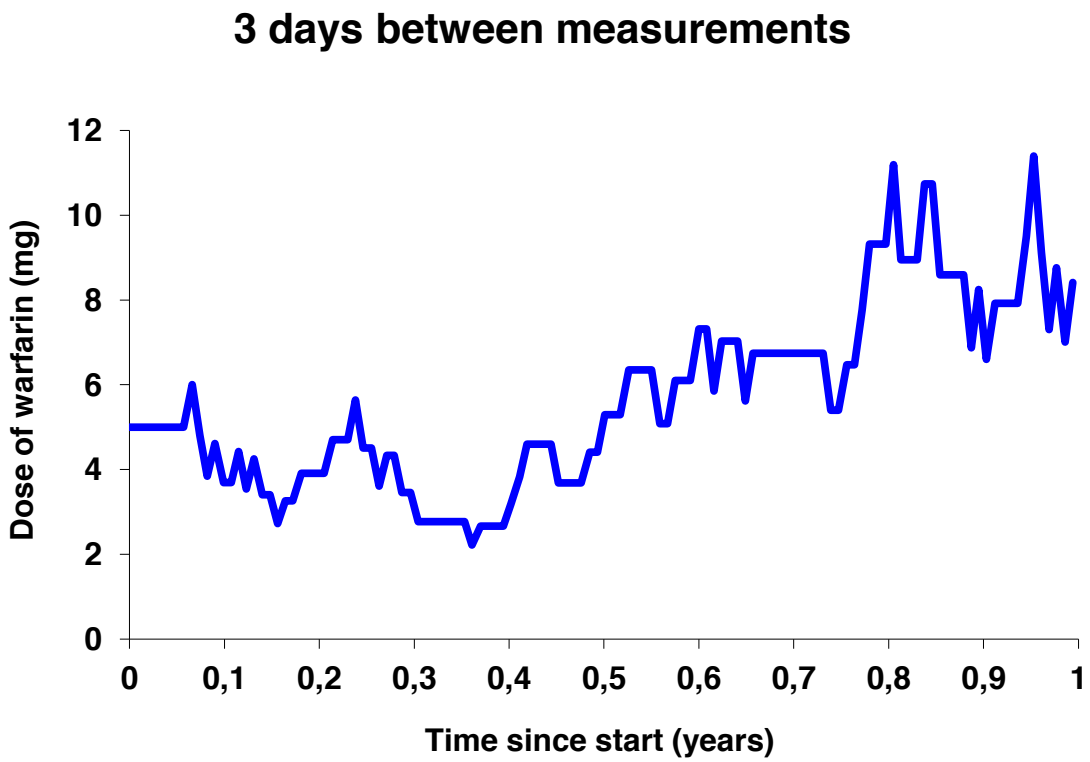


Fig 12: In this figure we have plot the dose of warfarin for corresponding INR value for 12 days interval. We assume that there is no change of dose between 21 days interval . That's why this is a step wise graph.

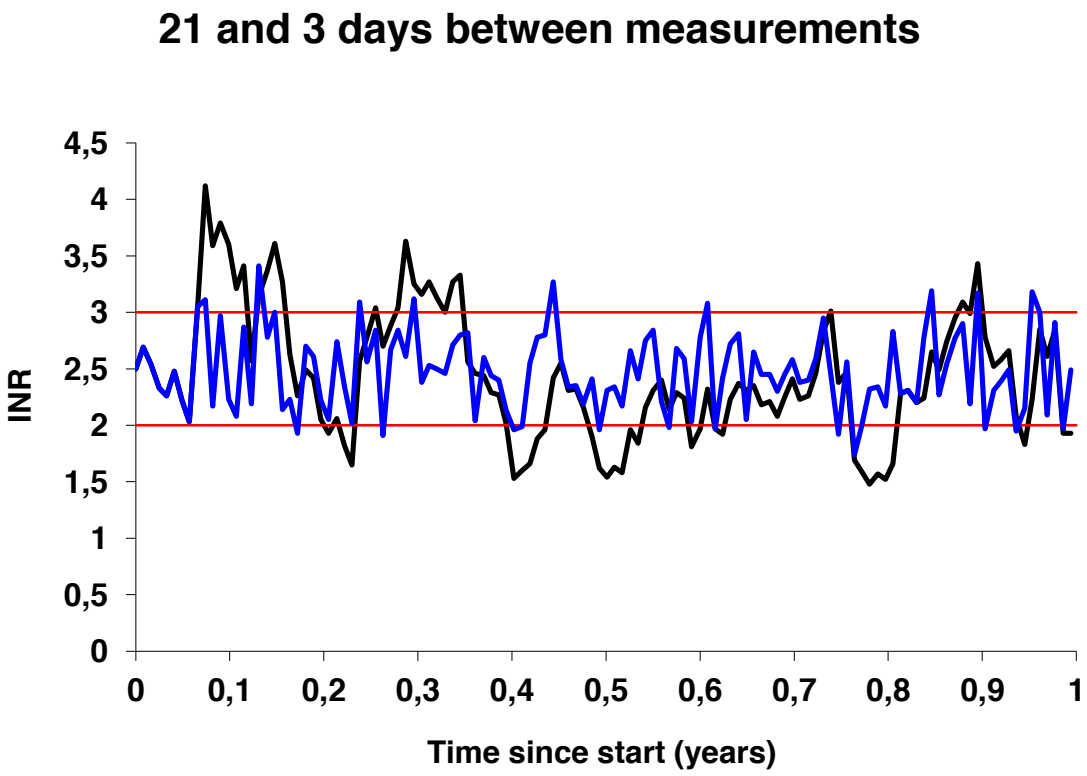


Fig 13 : Here in x axis we have plot the time interval of dose of warfarin and in y axis we have plot the corresponding INR values. For every different curve , INR value was simulate for every 3 days , but dose of warfarin only change after 21 and 3 days interval. And the red lines denote the INR measurement of 2 and 3 respectively. Block line denoted INR value after 21 days dose interval and blue line denotes 3 days dose interval

Table 3. The table gives 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.

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**

The percent inside the interval 2-3 was calculated as 100·(1-number outside/122).

Table 4. Standard deviation of transformed INR around the regression function, when time since start is independent variable.

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**

The study by (10) at the relationship between the standard deviation and the risk of events of different types 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 x (0.568 x 0.925))) x 100%)
Table 5. 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.

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%

4. 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 standardisation and a need for individualisation of therapy. In Sweden more than half of all hospitals have computerised units for anticoagulation. The computer will make the organisation more efficient with a proficient nurse educating the patient, monitoring and

reporting bleedings and rethrombosis. 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 diagnosis 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 range. 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 proved 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.

5.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 hospitalisation. 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 randomised study. Later the effect on the risk of different end-points could be studied.

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(9) A. K. Jacobson (&) Loma Linda VA Medical Center, 11201 Benton Street, Loma Linda, CA 92354, USA

(10) Marcus Lind M.D., Ph.D.[1]; Martin Fahlén[2]; Björn Eliasson[3]; Anders Odén[4]
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Appendix :

Basic program for simulation

```
10 DEF FNT(X)=1/(1+.3326*ABS(X))
20 DEF FNQ(X)=(SGN(X)+1)/2
30 DEF FNP(X)=(.436183*FNT(X)-.120167*FNT(X)^2+.937298*FNT(X)^3)*(1-
2*FNQ(X))
40 DEF FNFI(X)=FNP(X)*EXP(-X*X/2)/SQR(2*3.14159265#)+FNQ(X)
50 DEF FNNY(U,X)=(U-FNFI(X))*2.5066*EXP(X^2/2)+X
60 DEF FNR(X)=EXP(-.1-.7*X)
80 RANDOMIZE:REM ALLOWS THE PROGRAM TO PRODUCE DIFFERENT SEQUENCES OF
RANDOM NUMBERS FOR EACH RUN
82 REM THE LINES 90-120 ARE USED FOR THE TRANSFORMATION FROM INR TO
84 REM TRANSFORMED INR AND THE OTHER WAY
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
144 QN=0
146 REM ON LINE 148 A FILE IS OPENED WITH THE SIMULATION RESULTS
148 OPEN "O",2,"12B.003"
150 FOR T=0 TO 1 STEP ST
160 IF T=0 THEN DOSE2=5:DOSE1=5:TRINR=.3675:INR=2.5:GOTO 214
170 MEAN=.3675+FNR(ST)*(TRINR-.3675)+LOG(DOSE2/DOSE1)*4.5
180 SD=1.1*SQR(2*(1-FNR(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 240
220 PRINT#2,USING "##.###";T;:PRINT#2,",";:PRINT#2,USING
"##.##";INR;:PRINT#2,",";
230 PRINT#2,USING "##.##";DOSE2
240 DOSE1=DOSE2
250 IF ANT MOD 4 =0 THEN 270 ELSE 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*.8
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 PRINT :PRINT ANT,UTANF;
314 GOSUB 1000
316 PRINT USING "  ##.###";SD
320 CLOSE:STOP
330 REM A NORMALLY DISTRIBUTED RANDOM NUMBER X IS GENERATED BY THE NEXT
LINES (340-360)
```

```
340 FGX=0:X=0
350 X=FNNY(U,X):IF ABS(X-FGX)>.001 THEN FGX=X:GOTO 350
360 RETURN
370 INPUT "T TO INR IS 1 AND INR TO T IS 2";Q
380 IF Q=1 THEN 410
390 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 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
```