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# A Method to Determine the Optimal Intensity of Oral Anticoagulant Therapy

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## Summary

Oral anticoagulant therapy has been shown to be effective for several indications. The optimal intensity of anticoagulation for each indication, however, is largely unknown. To determine this optimal intensity, randomised clinical trials are conducted in which two target levels of anticoagulation are compared. This approach is inefficient, since the choice of the target levels will be arbitrary. Moreover, the achieved intensity is not taken into account.

We propose a method to determine the optimal achieved intensity of anticoagulation. This method can be applied within a clinical trial as an "efficacy-analysis", but also on data gathered in day-to-day patient care.

In this method, INR-specific incidence rates of events, either thromboembolic or hemorrhagic, are calculated. The numerator of the incidence rate is based on data on the INR at the time of the event. The denominator consists of the person-time at each INR value, summed over all patients, and is calculated from all INR measurements of all patients during the follow-up interval. This INR-specific person-time is calculated with the assumption of a linear increase or decrease between two consecutive INR determinations. Since the incidence rates may be substratified on covariates, efficient assessment of the effects of other factors (e.g. age, sex, comedication) by multivariate regression analysis becomes possible.

This method allows the determination of the optimal pharmacological effects of anticoagulation, which can form a rational starting point for choosing the target levels in subsequent clinical trials.

## Introduction

Several randomised clinical trials have been conducted, or are in progress, in which two intensities of oral anticoagulant therapy are compared prospectively. This unfolding array of trial activity presents two problems to the field. First, it is unclear how the target levels of anticoagulation which are contrasted in these trials are predefined. Up to now, the choice of target levels is largely arbitrary and therefore a sheer infinite series of "trial and error" will inevitably follow. Second, the actually achieved intensity of anticoagulation is not taken into account. At best, the achieved intensity will fluctuate around the target level in a way that is dependent on particular patient characteristics and local organisation of anticoagulation monitoring. These randomised trials therefore offer only little information about the optimal intensity of anticoagulation, for the pharmacologic effect and the effects of extraneous factors influencing anticoagulation are inextricably intertwined.

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The efficacy of oral anticoagulant treatment has been unequivocally demonstrated for several indications. These include short term prophylaxis for venous thrombosis in high-risk situations, and short term treatment after an episode of deep venous thrombosis or pulmonary embolism. Long term treatment has been shown to be beneficial in patients with mechanical heart valves, in patients with atrial fibrillation, and in patients suffering from coronary artery disease (1). For all these indications anticoagulant treatment has proved to be effective compared to placebo. The next question is which intensity of anticoagulation offers the best benefit-risk-ratio, i.e., the optimal balance between thrombosis prevention and the occurrence of bleeding complications. This issue has gained relevance since the development and implementation of the ISI/INR system, which renders it possible to express the anticoagulation level, as measured routinely and locally with one of the many available thromboplastins, in one standardised measure (2).

Some of the trials in which two levels of anticoagulation were compared, for instance in patients with bioprostheses of the heart valves (3) and in patients with mechanical heart valves (4), have shown target levels lower (i.e. less anticoagulation) than those usually recommended to be as effective and as safe as the higher target levels. All these trials are obviously of the intention-to-treat type, since it is impossible to maintain a completely stable anticoagulant effect at the target level in all patients all of the time. Extraneous factors as patient's compliance, physician's experience and variations in cumarin sensitivity in the individual patient will cause differences between the achieved intensity and the target level. Therefore, little insight is obtained about the risk of untoward effects at different intensities of anticoagulation.

This can be illustrated by the study of Saour et al. (4), who compared target levels of INR 2.65 and INR 9.0 in patients with mechanical heart valves. In this study 33 thromboembolic events and 13 major bleedings were observed. The thromboembolic events were equally divided over both treatment groups, whereas most bleedings occurred in the group with the high target level. However, two-thirds of all thromboembolic events occurred at anticoagulation intensities (at the time of the event) below INR 2.65 and all occurred at intensities below INR 9.0. Similarly, in nine of the 13 patients with major bleeding, the anticoagulation intensity exceeded INR 14 at the time of the event. So, most complications occurred in patients in whom the achieved intensity of anticoagulation at the time of the event was far from the intended intensity. In addition, one may question the generalisability from the results of a study of this design to other centers, since patient compliance and quality of anticoagulation monitoring may be quite different.

We propose a method to determine the optimal achieved intensity of anticoagulation. In our view, this method should not replace, but precede trials in which target levels are compared, since knowledge of this optimal achieved intensity offers a rational starting point for setting the target levels in subsequent trials. In addition, our method will yield insight into the variability

at different target levels in a care system which is dedicated but still belongs to medical routine

## Method

The proposed method involves the calculation of incidence rates of both types of untoward events (thromboembolism and bleeding) for different achieved intensities of anticoagulation To perform these calculations, a study time frame has to be defined over which a cohort of patients is observed The required information include the dates of all prothrombin time assessments and the results of these measurements during the observation time, as well as the dates of all event occurrences and the prothrombin times at the time of the events Covariates, either general such as age and gender or specific such as hypertension, atrial fibrillation or co medication may be registered and incorporated by stratified analysis or multivariate modeling by Poisson regression Before describing the specific application of the calculation of incidence rates in anticoagulated patients, we will discuss the concepts of incidence rates and the categorisation of incidence rates

*Incidence Rates*

Mathematically, the incidence rate (incidence density or hazard rate) is the instantaneous probability of an event occurrence The average incidence rate is the number of events divided by the observation time, ususally expressed in patient-years It approximates the instantaneous incidence rate by the assumption that over short observation intervals the probability of disease is proportional to the observation time, i e , 10 patients followed for 2 years will yield the same incidence as 20 patients followed for 1 year Under this assumption, the incidence rate is easily calculated by determining the number of events and dividing this figure by the sum of the observation times of all patients in the cohort (5) For each individual patient, the observation time is counted from his entry in the study until either the end of the study time frame or the time of an event, whichever occurs first The probability of an event over a certain time interval (cumulative incidence) can be derived from the incidence rate by a simple exponential transformation (5, 6)

*Categorisation of the Observation Time*

In the simplest form, the incidence is calculated for one, unstratified cohort, by dividing the number of events by the sum of the observation times of all patients in the cohort A first extension is stratification over fixed covariates, such as sex In this case all men contribute person time only to the male stratum and all women only to the female stratum, with the result of two sex-specific incidence rates

Since, however the only constituents of the incidence rates are the stratum-specific number of events, and the stratum-specific total observation time, it is not required that patients only contribute patient-time to one stratum When stratification is performed on unfixed covariates, such as calendar-period or age as is usually done to allow standardised comparison of two incidence rates, one patient may contribute person-time to several strata For instance, if 5-year age categories are used and 10-year calendar time periods, a patient followed for 5 years, starting in 1988 at age 42 will contribute 2 years person time to the cell [40–44 years, 1980–1989], 1 year to the cell [40–44 years, 1990–2000] and 2 years to the cell [45–49 years, 1990–2000] Age- and calendar-period specific incidence rates are subsequently calculated as the number of events within each cell, divided by the total observation time in each cell, which is derived from several patients

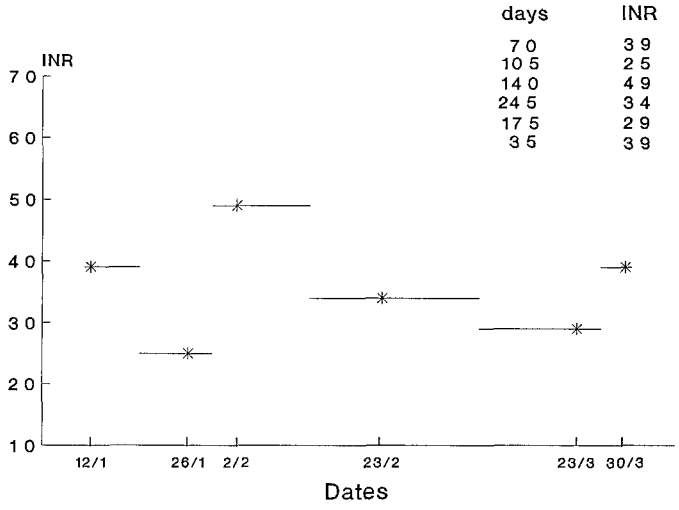


*Fig 1* Allocation of person-time at different INRs Six prothrombin time assessments and the dates of these assessments are shown for one patient The time elapsed between two measurements is divided over the INRs of these two assessments as indicated in the upper right The person-time will subsequently be divided over the predefined cells, i e , INR 2 5–2 9 28 0 days INR 3 0–3 4 24 5 days, INR 3 5–3 9 10 5 days and INR 4 5–4 9 14 0 days

*Application to the Level of Anticoagulation*

Fully analogous to the categorisation of the person time in cells determined by age sex and calendar periods, the observation time may be broken down in cells of the achieved level of anticoagulation The incidence rate of events at each level of anticoagulation is again calculated as the ratio of the number of events occurring at a particular intensity, over the summed person time at that intensity

*Events at Each Level (Incidence Numerator)*

Dependent on the events the study is aimed at, a system has to be set up in which all events are registered It seems most practical to limit the study to severe complications i e those that require hospitalisation or lead to death Ideally, one has to know the intensity of anticoagulation at the time of the event In case of hospitalisation, a prothrombin time will usually be performed When this has not been done the only approximation of the anticoagulation level a the time of the event is that of the last measurement before the event occurred

*Calculation of the Observation Time for Different Levels (Incidence Denominator)*

For each patient, prothrombin times have been measured at fixed or variable intervals, the length of which time intervals is known We assume that the INR value between two measurements will vary linearly from the value of the first, to the value of the second measurement With this assumption, two approaches may be employed to allocate the person-time between two measurements to particular INR values The most simple approximation is to divide the time between two measurement in halves, and allocate the first half to the INR value of the first, and the second half to the INR value of the second measurement So, if a 2-week interval is bounded by a prothrombin time of 3 6 INR as the first, and 4 3 INR as the second measurement, 1 week of person-time is allocated to 3 6 INR, and 1 week to 4 3 INR This is illustrated by Fig 1 Subsequently the person-time at each INR value is summed over all measurements of all patients, and then grouped into cells of 0 5 or 1 0 INR Although in this approximation the INR is treated as if it changes instantly halfway between two measurements, over large numbers it yields a fair approach to the assumption of a linear increase or decrease (Fig 2)

A second, more accurate approach is to divide the time between two measurements in days, and to use small steps of 0 1 INR over the range of the time interval In this approach, the INR is treated as gradually increasing or decreasing over the interval In the example above, 2 days are allocated to an INR of 3 6, 2 days to an INR of 3 7, and so on Subsequently, the person time of these small steps is collapsed into larger cells of 0 5 or 1 0 INR and then summed over all patients We have developed software to perform these calculations on a personal computer[1]

Fig 2 shows the results of the application of both approaches to the data of 392 patients with mechanical heart valves who visited the Leiden Thrombosis Service between 1985 and 1991 (total observation time

[1] Note The software can be made available on request

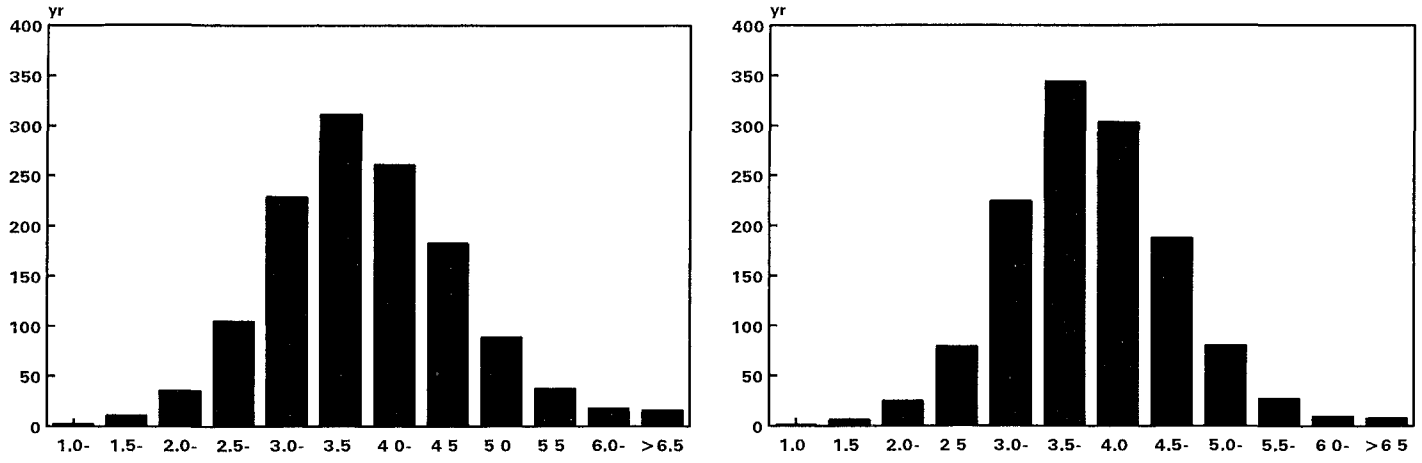


*Fig 2* Allocation of INR specific person-time of 392 patients with mechanical heart valves The achieved intensity, in person years at different INR values, is shown for 392 patients (1 297 patient years) with mechanical heart valves who were followed between 1985 and 1991 For the upper part of the figure, the approach depicted in Fig 1 has been employed, in which half of the time elapsed between two visits is allocated to the first, and half to the second measurement For the lower part the approach of a truly linear increase or decrease was used, in which the INR is calculated for each day of the interval For both parts of the figure, the results have been regrouped in 0 5 INR intervals, and the days have been converted to years

1,297 years) Both approaches yield very similar results, albeit that with the approach in which the time between two measurements is divided in halves, slightly more person-time is accumulated at the extreme values

*Analysis*

Since the number of events at each intensity and the summed person-time at each intensity are now known, incidence rates at each intensity can be calculated The cells may be further stratified by sex, age and other covariates, and by application of a multivariate Poisson regression model incidence rate ratios at the different intensities may be calculated, to control for confounding by this covariates and to examine the risk of complications associated with these covariates Standard errors for the incidence rates and the incidence rate ratios can be derived in the standard fashion based on the assumption of a Poisson distribution of the number of events These multivariate analyses can be performed by several of the commercially available software packages

*Application of the Method*

This method can be applied retrospectively, on data routinely registered by a thrombosis service, as well as prospectively as a secondary analysis within a randomized trial The method is presently employed in two studies In the first one, the Leiden Artificial Valves and Anticoagulation study (LAVA), we seek the optimal intensity of achieved anticoagulation in patients with mechanical heart valves as the level at which the incidence of stroke, combining infarction and bleeding, is lowest Since the risk of thrombosis on a mechanical valve and subsequent cerebral embolism is high in the absence of anticoagulation treatment (approximately 1–5% per year), patients with mechanical heart valves are intensely anticoagulated (target range in The Netherlands 3 6–4 8 INR) This implies that the risk of major bleedings, of which cerebral hemorrhage is the most severe, is relatively high, and the balance between thrombosis prophylaxis and risk of bleeding precious It is reasonable to assume that the risk of cerebral embolism and infarction increases with lower intensities of anticoagulation, whereas the risk of cerebral bleeding increases with higher intensities (Fig 3) So, we expect that the incidence of stroke will have a U-shaped distribution over the range of achieved intensities Preliminary results indicate that this U-shaped distribution does exist (7) For this analysis, it is not even necessary to distinguish between cerebral infarctions and cerebral bleeding and it avoids the difficult task of classifying a hemorrhagic infarction as either infarction or bleeding Since we are interested in the level of anticoagulation that has the lowest risk of stroke, whatever its origin, it is of more relevance to use a clinical classification system based on the severity of the sequelae of the stroke

In the second study, we use this method to investigate risk factors for bleeding in unselected patients who receive anticoagulant treatment for various indication (8) To this effect, we study minor and major bleeding complications during 1 year in the over 6,800 patients treated by the Leiden Thrombosis Service annually In this instance, the method serves two purposes First we examine the risk of bleeding for different intensities of anticoagulation Second we can by multivariate analysis, use the intensities as an adjustment factor and investigate the contribution of other factors to the risk of bleeding independent of the achieved intensity of anticoagulation

Yet another application of this method is as a measure for the quality of anticoagulation monitoring which is now usually given as the percentage of prothrombin times within the target zones By calculating the person-time spent at each intensity of anticoagulation we can express the quality of monitoring as the percentage of the total person time that lies within the target zones

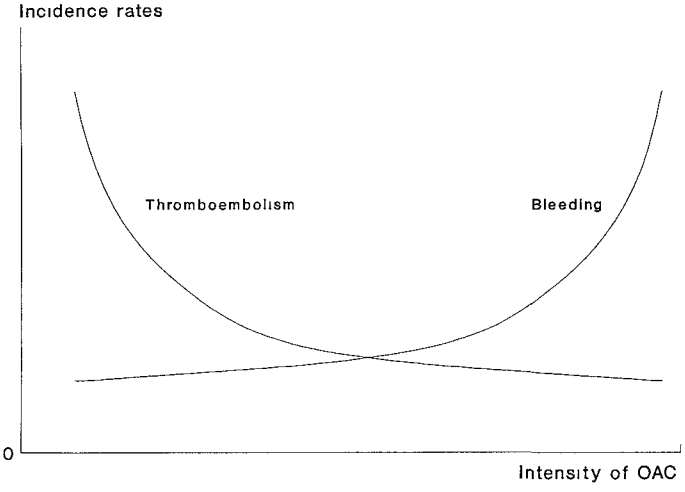


*Fig 3* Theoretical relation of the incidence of thromboembolism and bleeding with the achieved intensity of anticoagulation The risk of thromboembolism decreases exponentially with increased intensities of anticoagulation, whereas the risk of bleeding increases exponentially The lowest incidence of untoward effects i e the minimum of the superimposed graphs, denotes the optimal intensity of anticoagulation

## Discussion

We have proposed a method that allows assessment of the optimal achieved intensity of anticoagulation by the calculation of INR-specific incidence rates of untoward events The results of analysis by this method can be used to set the target ranges for clinical trials on oral anticoagulation for various indications In addition, the method can be employed to determine risk factors for complications, thrombosis or bleeding, adjusted for the achieved level of anticoagulation

A prerequisite for the use of this method is careful observation of all complication If, however, this is done routinely, as in the Dutch Thrombosis Services, and if dates and results of prothrombin time measurements are stored in computers over longer periods of time, this method can be applied retrospectively to large numbers of patients, and precise estimates may be expected

One of the assumptions of the allocation of person-time to different intensities of anticoagulation is a linear increase or decrease of the anticoagulation effect between subsequent measurements It may well be, however, that the change is greatest shortly after a measurement has been performed and a dose adjustment has been made, in particular when a prothrombin measurement shows excessive under- or overanticoagulation, in which case a booster-dose or vitamin K may be prescribed We feel that these effects will probably even out in the broad range around the target values, encompassing the majority of measurements This is especially so since the INR categories are broadly chosen, with intervals of 0 5 or 1 0 INR For extreme values, there may be a bias, with an overestimate of the person-time at very low, and at very high INR values This implies that the incidence rates at these extremes will be underestimated Since the optimal level will not be located at these extreme values, we consider this of minor importance It must be noted that this reasoning becomes less valid when anticoagulation control is of very poor quality, i e when all stability in anticoagulation is lacking

Assessment of the optimal achieved level of anticoagulation should precede studies comparing different target levels Since it is not possible to maintain an optimal level in all patients constantly, subsequent clinical trials remain necessary, to evaluate target levels set at or around the optimal achieved intensity on an intention-to-treat basis

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