Control of anticoagulation with vitamin K antagonists: overestimation of median time in therapeutic range when assessed by linear interpolation

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Summary
Patients receiving vitamin K–antagonists are monitored by regular assessment of the International Normalized Ratio (INR). There are two popular methods for therapeutic control of anticoagulation in patient groups: 1) Time in Therapeutic Range (TTR) assessed by linear interpolation of successive INR measurements; 2) the cross-sectional proportion (CSP) of all patients’ last INRs within range. The purpose of the present study is to compare the two methods using data from 53 Dutch Thrombosis Centres and to develop a semi-quantitative model for TTR based on different types of INR change. Different groups of around 400,000 patients in four consecutive years were evaluated: patients in the induction phase, short-term, long-term, low-target range, high-target range, receiving either acenocoumarol or phenprocoumon, and performing self-management. Each Centre provided TTR and CSP results for each patient group. TTR and CSP were compared using the Wilcoxon signed-rank test. Separately, we analysed the relationship between consecutive INR results regarding in or out of range and their frequency of occurrence in patients of two different cohorts. Good correlation was observed between TTR and CSP (correlation coefficient 0.694–0.950 in low-target range). In long-term acenocoumarol patients (low-target range) the median TTR was significantly higher than CSP (80.0 % and 78.7 %, respectively; p<0.001). In long-term phenprocoumon patients (low-target range) there was no significant difference between median TTR (83.0 %) and median CSP (82.6 %). In conclusion, the correlation between TTR assessed by linear interpolation and CSP was good. TTR assessed by linear interpolation was higher than CSP in patients on acenocoumarol.

Keywords
Vitamin K antagonist, therapeutic control, time in therapeutic range

Introduction
Effectiveness and safety of treatment with vitamin K antagonists (VKA) depends on the intensity and quality of control of anticoagulation (1, 2). During VKA treatment, the prothrombin time expressed as international normalised ratio (INR) is monitored and VKA doses are adjusted if necessary in order to achieve INR values within a specified therapeutic or target range. Different methods have been used to assess the level of therapeutic control: a cross-sectional method based on the proportion of INR test results in range at one point in time (3), and a longitudinal method based on linear interpolation of successive INR measurements to obtain the proportion of person-time spent in range which is referred to as TTR (time in therapeutic range) (4–6). The cross-sectional method is useful only for assessment of average therapeutic control for a group of patients and not for an individual patient (3). The longitudinal TTR method is useful for assessment in an individual patient as well as a group of patients. Apart from the two above-mentioned methods for assessment of the quality of anticoagulation there are other methods. One of these is the percentage of INRs within the therapeutic range (PINRR). The PINRR method utilizes the number of INRs within the target range divided by the overall number of INRs during the selected time interval (7–10). The PINRR is simple to calculate but more frequent testing in unstable patients may bias overall results (7). Other methods have been described that are modifications of the original longitudinal TTR method using imputation of INR values between pairs of INR measurements (11, 12). Observational studies have reported strong associations between group means of individual patients’ TTR and reduced risks of ischaemic stroke and major bleeding in patients with atrial fibrillation (12–14). For effective stroke prevention therapy in
patients with atrial fibrillation it has been recommended to use either well-controlled VKA therapy with a high percentage of time in the therapeutic range (for example, at least 70%) or one of the novel direct-acting oral anticoagulant drugs (15, 16).

In the Netherlands the vast majority of patients receiving VKA are monitored by 56 Thrombosis Centres, which are members of the Dutch Federation of Thrombosis Centres. These centres achieved consensus on the intensity of anticoagulation for the various indications for treatment (17, 18). Low-intensity anticoagulation (target range INR 2.5–3.5; therapeutic range INR 2.0–3.5) has been used for patients with atrial fibrillation and venous thromboembolism (VTE). High-intensity anticoagulation (target range INR 3.0–4.0; therapeutic range INR 2.5–4.0) has been used for primary and secondary prevention of arterial thromboembolism, in patients with mechanical heart valve prostheses, and in patients with recurrent VTE despite VKA treatment. The target range was set higher than the internationally advised range to prevent inadequate anticoagulation (6). Approximately 80% of patients are treated with low-intensity and 20% with high-intensity anticoagulation. In the Netherlands, two different VKA drugs are used, i.e. acenocoumarol (short acting; half-life 12 hours [h]) and phenprocoumon (long acting; half-life 160 h). Acenocoumarol is used for approximately 77% of patients, and phenprocoumon for approximately 23% of patients. The majority of the Dutch Thrombosis Centres reported therapeutic quality control data both in terms of the cross-sectional method and in terms of the longitudinal method (19). It has not been established which of the two methods gives a better overall assessment of the control achieved by a Thrombosis Centre. The longitudinal method proposed by Rosendaal et al assumes that the INR between two measurements varies linearly from the first INR to the second INR (linear interpolation) (4). It is our hypothesis that the longitudinal method using linear interpolation of successive INR measurements is based on a simplification of the true time course and gives an overestimation of the TTR as will be explained in Methods. The purpose of the present study is to compare and evaluate the two methods using the data published by the Federation of the Dutch Thrombosis Centres for the years 2010, 2011, 2012 and 2013. A semi-quantitative model is presented to explain the overestimation of TTR.

Methods
Calculation of cross-sectional proportion of INRs in the therapeutic range and proportion of time in the therapeutic range

Each Thrombosis Centre reviewed INR results for all active patients and calculated the percentage of patients for whom the last INR was within the therapeutic range at two fixed dates (March 31 and October 31) each year (17, 18). The mean of the two assessments was used for the statistical analysis. This method is referred to as the cross-section-of-the-files method because only one INR result – of each patient is used. The percentage calculated with this method is referred to as the cross-sectional proportion (CSP).

In addition, each Thrombosis Centre used a method to estimate the percentage of time that each patient spent in the therapeutic range (TTR). In the latter method, the time between two INR measurements is divided in days and small steps of 0.1 INR over the range of the time interval (4). In this approach, the INR is treated as gradually increasing or decreasing over the time interval. This method is referred to as TTR by linear interpolation (LI). TTR(LI) is expressed as the proportion of the total person-time that lies within the range. Advantages and disadvantages of the cross-section-of-the-files method and the TTR are shown in Table 1. The cross-section-of-the-files method is not useful for a single patient but can be used for a group of patients, e.g. all long-term patients monitored by one Thrombosis Centre.

CSP and TTR(LI) were assessed for various groups of patients. Patients receiving vitamin K antagonists are classified as induction phase (first 6 weeks of treatment), as short-term (longer than 6 weeks up to 6 months), or as long-term (longer than 6 months). Patients’ data were provided anonymously for statistical analysis. Hence the data could not be traced back to the patients’ identification and informed consent was not required. Thrombosis Centres used various (commercial) computer algorithms for anticoagulant dosing (20). At least five different computer systems were used by multiple Dutch Thrombosis Centres, e.g. Portavita, TDAS, Trodis, Glims, and Tromis (19). To study the influence of the computer algorithm used we compared TTR(LI) and CSP for Portavita centres only and for the non-Portavita centres using the combined data of four years.

Statistical methods

The Wilcoxon signed-ranks test was used to compare CSP with the TTR(LI) results obtained in each year. Spearman’s coefficient (rho) for bivariate correlation between CSP and TTR(LI) was calculated. In addition, the pooled results from 2010, 2011, 2012 and 2013 were analysed with the above-mentioned statistical tests. P-values of less than 0.05 were considered statistically significant. Statistical analyses were performed with SPSS 20 (IBM Corporation, Armonk, NY, USA) for Windows.
Model for INR change

Here we develop a model which may assist us to explain the difference between TTR(LI) and the true TTR. Four hypothetical examples of the time course of INR between successive measurements are shown in Figure 1. In Figure 1A, two successive measurements are both within the therapeutic range. Evidently TTR(LI) is 100% for this case. In reality, this patient's INR may have been out of range for some time and the true TTR is less than 100%. In Figure 1C, two successive measurements are both out of range at the same side of the range. Evidently TTR(LI) is 0%. In reality, this patient's INR may have been within the range for some time between measurements and the true TTR may be greater than 0%. Figure 1B represents a situation where one measurement is within the range and the other out of range. In this case both TTR(LI) and the true TTR are between 0 and 100%. The depicted true course in Figure 1B would give a lower TTR than TTR(LI). It should be realised that many other true courses are possible in Figure 1B but the mean true TTR of all possible courses cannot be predicted. Figure 1D represents a situation in which two successive measurements are both out of range on opposite sides of the range. The true course depicted in Figure 1D would give a lower TTR than TTR(LI). Again, there are many other possible true courses for two consecutive INR measurements on opposite sides of the range, but the mean true TTR cannot be predicted with certainty. The hypothetical examples shown in Figure 1 refer to individual patients. To assess the total effect of linear interpolation for a group of real patients, we would like to know the frequency of the different types of INR change. This information is not available from the annual medical reports of the Netherlands Federation of Thrombosis Services (19) and was obtained from a previous study (see below).

Assessment of frequency of INR change

Recently, a retrospective cohort study was performed using the data from the anticoagulation clinic of the Star-Medical Diagnostic Center at Rotterdam (21). We used the data from this study to assess the relative frequency of the different types of INR change in each patient. The study population consisted of two independent cohorts that were followed up for one year. One cohort was monitored using a laboratory method for venous plasma (STA Hepato Quick) and the other cohort was monitored using a point-of-care method for capillary blood (CoaguChek XS Pro). 1555 Patients in the first cohort and 1589 patients in the second cohort were treated with acenocoumarol (therapeutic range: INR 2.0–3.5). The number of INR measurements in the aforementioned patients was 30,003 and 33,060, respectively. We assessed the relationships between consecutive INR results with respect to each recorded patient and calculated their frequency of occurrence. Finally, we added the numbers of the different categories of INR change for all patients in each cohort to calculate the frequency of each category of change.

Results

The total number of patients monitored by the members of the Dutch Federation of Thrombosis Centres was 398,312 in 2010,
408,869 in 2011, 417,594 in 2012 and 438,411 in 2013 (19). The number of treated patients per year by each Thrombosis Centre varied from approximately 600 to approximately 27,000 (19).

Table 2 shows some characteristics of the patients monitored by the members of the Dutch Federation of Thrombosis Centres. The majority of patients were treated for arterial indications (e.g. atrial fibrillation). In the period 2010–2013 there was a steady increase not only of the absolute number of patients treated for atrial fibrillation, but also as a percentage of all arterial indications.

Comparison of CSP and TTR(LI)

The majority of Thrombosis Centres provided results for CSP and TTR(LI) calculated with their own computer algorithms. The median CSP and TTR(LI) results stratified by treatment duration are shown in Table 3. In almost all cases, the median TTR(LI) was higher than the median CSP. The results shown in Table 3 were obtained irrespective of the type of VKA used. The median CSP and TTR(LI) for long-term patients on either acenocoumarol or phenprocoumon are given in Table 4. For acenocoumarol, the median TTR(LI) was always significantly higher than the median CSP. As an example of the correlation between TTR(LI) and CSP, a scatterplot for long-term patients receiving acenocoumarol is shown in Figure 2. Practically all Thrombosis Centres had TTR(LI) and CSP values higher than 70%. For phenprocoumon, in seven out of eight comparisons during the years 2010–2013, differences between TTR(LI) and CSP were not significant (Table 4). Several Thrombosis Centres had only few long-term patients on phenprocoumon.

To avoid conclusions based on inclusion of centres with few patients, a separate analysis was performed of centres with more than 1000 long-term patients per year in the 2.0–3.5 INR therapeutic range. This analysis showed that TTR(LI) was significantly greater than CSP for the acenocoumarol patients (Table 4). Separately, we selected 9–12 centres with more than 1000 long-term phenprocoumon patients. TTR(LI) and CSP were not significantly different for the selected centres (Table 4).

In the vast majority of the Thrombosis Centres, a proportion of the patients performed self-management using a point-of-care whole blood monitor for INR determination. This proportion varied from 2% to 15% of the patients. Patient self-management means that the patients are enabled to measure their own INR, to interpret the result, and to make adjustments to their VKA dosage by themselves (22). Patients who measure their own INR but do not make dosage adjustments are considered as regular patients and their results are included in Table 3 and Table 4. CSP and TTR(LI) for self-management patients are given in Table 5. TTR(LI) was significantly higher than CSP. The results shown in Table 5 were obtained irrespective of the type of VKA used.

In most cases, the correlation coefficients between TTR(LI) and CSP were higher for the low target patients (Therapeutic range: INR 2.0–3.5) than for the high target (Therapeutic range: INR 2.5–4.0). There was a trend of increasing correlation coefficients between TTR(LI) and CSP with increasing treatment duration (Table 3).

Table 3: Therapeutic control in patients by duration of treatment. The median values of CSP and TTR(LI) are given. N is the number of Thrombosis Centres in each year for each therapeutic range or the total number of comparisons between CSP and TTR over all years. CSP, cross-sectional proportion; TTR(LI), time in therapeutic range by linear interpolation.
Different dosing algorithms were used by the Thrombosis Centres. Of all computer algorithms, the “Portavita” system was used by approximately 26% (in 2010) to 44% (in 2013) of centres. We compared TTR(LI) and CSP for Portavita centres only and for the non-Portavita centres and observed similar differences (not shown), suggesting that findings were independent of the computer dosing algorithm used.

Assessment of frequency of INR change

▶ Table 6 shows the nine different categories of INR change between two consecutive measurements in patients on acenocoumarol (therapeutic range: INR 2.0–3.5) in a cohort study (21). For each patient and for each pair of consecutive INR measurements, the category of change was determined. Then the total number

<table>
<thead>
<tr>
<th>Vitamin K antagonist</th>
<th>Year</th>
<th>Therapeutic range: INR 2.0–3.5</th>
<th>Therapeutic range: INR 2.5–4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>CSP (%)</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>2010</td>
<td>48</td>
<td>76.6</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>52</td>
<td>79.1</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>53</td>
<td>78.8</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>52</td>
<td>79.9</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>205</td>
<td>78.7</td>
</tr>
<tr>
<td></td>
<td>All*</td>
<td>177</td>
<td>78.3</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>2010</td>
<td>48</td>
<td>81.6</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>52</td>
<td>82.3</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>53</td>
<td>83.9</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>52</td>
<td>83.2</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>205</td>
<td>82.6</td>
</tr>
<tr>
<td></td>
<td>All*</td>
<td>42</td>
<td>83.8</td>
</tr>
</tbody>
</table>

Table 4: Therapeutic control in long-term patients by type of vitamin K antagonist. The median values of CSP and TTR(LI) are given. N is the number of Thrombosis Centres in each year or the total number of comparisons between CSP and TTR over all years. A separate analysis was performed for Thrombosis Centres with more than 1000 patients (All*). CSP, cross-sectional proportion; TTR(LI), time in therapeutic range by linear interpolation.
and proportion of cases in each category was determined. The proportion of paired measurements within the therapeutic range was 52.4% in the first cohort and 47.6% in the second. The proportion of paired measurements for which both INRs were out of the therapeutic range on the same side of the range was small (7.7% and 8.5%, respectively). As expected, the number of cases in which INRs crossed a border of the therapeutic range in one direction was similar to the number of cases in which INRs crossed the same border in the opposite direction.

Discussion

The present study was an analysis of data published by the Dutch Federation of Thrombosis Centres. The purpose of our study was to compare TTR(LI) with CSP using data from the majority of VKA users in the Netherlands. In general, there was good correlation between the two methods to evaluate control of anticoagulation in groups of patients, which is in agreement with a previous single-centre study (6). TTR(LI) was slightly higher than CSP in most comparisons. The greatest difference between the two methods was observed for patients in the induction phase of treatment (Table 3) and the smallest difference for long-term patients receiving phenprocoumon (Table 4).

Our working hypothesis is that the probability to find an individual patient’s INR at any time in the therapeutic range is equal to the true proportion of time spent in the therapeutic range. Therefore, CSP is expected to be equal to TTR. Why then is TTR(LI) slightly greater than CSP? It should be realised that the true TTR cannot be determined and that TTR(LI) is an approximation of the true TTR, because the assumed linear INR change is an approximation of the true time-course. In contrast, CSP is calculated independently from any model of the INR time-course in individual patients. CSP is always calculated for one point in time. TTR(LI) is calculated for a certain time interval, e.g. one year. The patients used for calculation of CSP were not completely the same as the patients used for calculation of TTR(LI) because some patients included in TTR(LI) may have stopped anticoagulation treatment before CSP was calculated. It is unlikely that the difference in individual patients could completely explain the consistently observed pattern of differences between CSP and TTR(LI).

In this paper we present a model for the change of INR with regard to the calculation of TTR(LI). The relative frequency of the different types of INR change shown in Figure 1 may help us to

Table 5: Therapeutic control in long-term patients performing self-management. The median values of CSP and TTR(LI) are given. N is the number of Thrombosis Centres in each year for each therapeutic range or the total number of comparisons between CSP and TTR over all years. CSP, cross-sectional proportion; TTR(LI), time in therapeutic range by linear interpolation.

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Therapeutic range: INR 2.0–3.5</th>
<th>Therapeutic range: INR 2.5–4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSP (%)</td>
<td>TTRLI (%)</td>
<td>Wilcoxon</td>
</tr>
<tr>
<td>2010</td>
<td>32</td>
<td>80.3</td>
<td>82.8</td>
</tr>
<tr>
<td>2011</td>
<td>40</td>
<td>81.6</td>
<td>83.3</td>
</tr>
<tr>
<td>2012</td>
<td>45</td>
<td>82.7</td>
<td>84.7</td>
</tr>
<tr>
<td>2013</td>
<td>46</td>
<td>82.2</td>
<td>84.1</td>
</tr>
<tr>
<td>All</td>
<td>163</td>
<td>81.9</td>
<td>83.8</td>
</tr>
</tbody>
</table>

Table 6: Number of INR changes between two consecutive measurements in acenocoumarol patients with therapeutic range INR 2.0–3.5. The frequency of INR changes is given in percent (between brackets). Two independent cohorts were analysed, each cohort being monitored with a different prothrombin time reagent (STA Hepato Quick and CoaguChek XS Pro, respectively).
explain the difference between TTR(LI) and CSP. Since the major-
ity of INR measurements is within the therapeutic range, situation
1A occurs more often than situation 1C, which is confirmed by
observed frequencies in the cohort study (Table 6). INR changes
within the therapeutic range (situation 1A) that may overestimate
TTR(LI) occur approximately 5–7 times more frequently than
INR changes that may underestimate TTR(LI) (Table 6). As a
result, the true TTR summed over all patients will be less than the
TTR(LI) and therefore calculation of TTR(LI) will result in an
overestimation of the true TTR. A limitation of our semi-quantita-
tive model is that we cannot predict the exact magnitude of the
difference between TTR(LI) and the true TTR. The difference be-
tween TTR(LI) and the true TTR will depend on the magnitude of
INR variation over time. If the within-subject INR variation is in-
creased, there will be an increased probability that the INR devi-
ates from a straight-line path between successive measurements.
INR variation will be greater in the induction phase of treatment
than in patients who are treated for more than six months (i.e.
long-term treatment). Therefore, the difference between TTR(LI)
and the true TTR will be greater in the induction phase than in the
long-term steady state of treatment. Other investigators concluded
that the validity of the linear interpolation method could be im-
proved by using a hybrid method that takes into account potential
effects of dosage modifications when INRs are far out of the target
range (11).

INR variation is also greater in patients receiving the short-act-
ing acenocoumarol than in patients receiving the long-acting
phenprocoumon (23). This can explain why the difference be-
tween TTR(LI) and CSP is smaller for phenprocoumon than for
acenocoumarol. When there is more variation of INR, there is
greater probability that the INR is out of therapeutic range be-
tween two successive measurements which are both within the
range. In long-term patients receiving phenprocoumon, the vari-
ation of INR is smaller compared to acenocoumarol and the linear
interpolation may be a good approximation of the true time
course of INR.

Our study is limited to patients treated with acenocoumarol
and phenprocoumon. Warfarin (half-life 40 h) is not used in the
Netherlands. Other investigators compared therapeutic control in
warfarin treated patients to that in acenocoumarol treated patients
using the cross-sectional method (24). They reported that the
cross-sectional method did not show any difference between the
two drugs (24). Furthermore, daily fluctuations of factor VII levels
were similar with both drugs (24). It seems that warfarin is more
similar to acenocoumarol than to phenprocoumon with regard to
the pharmacodynamics and INR variability. Further studies
should be performed to investigate whether the difference between
CSP and TTR(LI) is also observed in warfarin patients.

The strength of our study is the large number of Thrombosis
Centres, patients and INR measurements used for the analysis.
Because of the large numbers, the pattern of differences between
TTR and CSP could consistently be evaluated with adequate
power thereby reducing the risk of observations by chance. A limi-
tation of our study is that the number of patients varied between
the individual Thrombosis Centres but nevertheless the data from
each centre were treated with equal weight. It has been stated that
CSP determined for few patients may be unrealistic (5). However,
when our analysis was limited to centres with a large number of
patients, i.e. those with at least 1000 long-term patients per year,
similar differences between CSP and TTR(LI) were obtained and
the statistical significance of the differences did not change. A sec-
ond limitation of our study is that we cannot perform an analysis
of the same data with other methods such as the PINRR (8–10) or
a hybrid method that takes into account potential effects of dosage
modifications when INRs are far out of the target range (11, 12).
We would like to emphasise that our data apply to the evaluation
of the quality of anticoagulation of a Thrombosis Centre and can-
not be applied to the single patient. Despite these limitations it is
reassuring that in nearly all Dutch Thrombosis Centres the medi-
an of percentage long-term patients within the low-intensity thera-
peutic range was at least 70 %. The high overall median TTR(LI)
for long-term patients (Table 3) with respect to other reports
(12, 25–27) may be explained in part by the use of long-acting
phenprocoumon, and in part by the slightly wider therapeutic
range (e.g. INR 2.0–3.5, rather than 2.0–3.0). By comparing
Table 3 and Table 5, it can be concluded that therapeutic
groups of long-term patients performing self-management is at
least as good as or even better than the quality of long-term patients
managed by the regular system, in agreement with a previous
study (28).

In conclusion, we have shown that there is good correlation be-
tween TTR assessed by linear interpolation and CSP obtained by
Dutch Thrombosis Centres. Our model which is based on ob-
served frequencies of the relationship between consecutive INR
measurements, predicts that the linear interpolation method over-
estimates the true TTR. The difference between TTR and CSP is
greater in the induction phase than in the long-term steady state
phase of anticoagulation and is greater in acenocoumarol patients
than in phenprocoumon patients.

What is known about this topic?
- Average quality of anticoagulation for a group of patients can be
calculated as the average time in therapeutic range by linear in-
terpolation of successive INR determinations (TTR(LI)).
- Alternatively, average quality for a group of patients can be cal-
culated as the percentage of INRs within the therapeutic range on
a certain date (cross-sectional proportion, CSP).
- Average time in therapeutic range and percentage of INRs within
the therapeutic range are higher for phenprocoumon than for
acenocoumarol patients.

What does this paper add?
- The correlation between TTR(LI) and CSP in long-term patients is
good.
- TTR(LI) is significantly higher than CSP in acenocoumarol, but not
in phenprocoumon patients.
- A model is presented predicting overestimation of TTR(LI).
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Conflicts of interest
None declared.

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