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ORIGINAL ARTICLE

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Is the time in therapeutic range on coumarins predicted by previous time in therapeutic range?

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Abstract

Background: The benefit of vitamin K antagonists depends on the time within the therapeutic range (TTR). A patient's previous TTR could be a factor in the decision to change the anticoagulation regimen. However, the predictive value of a previous TTR for a future TTR is not well established, nor is it clear which TTR should prompt action.

Objectives: To investigate the predictive performance of a TTR and identify a threshold below which no recovery of TTR should be expected.

Patients/Methods: From 18 031 patients who used acenocoumarol in a first-line anticoagulation clinic, a TTR was calculated over multiple periods of 90, 180, and 365 days each. We assessed the correlation between baseline and later TTR and the separation between groups by quintile of baseline TTR. We describe the proportion of patients who obtain a TTR≥ 70% conditional on baseline TTR.

Results: The correlation between baseline and later TTR was 0.25 (95% confidence interval [CI], 0.24-0.26), 0.27 (95% CI, 0.26-0.28) and 0.34 (95% CI, 0.32-0.35) for analyses over 90, 180, and 365 days. Corresponding c statistics for discrimination by baseline group were 0.60, 0.61, and 0.63. The probability to obtain a TTR ≥70% increased with baseline TTR: from 42% with a baseline TTR of 50%-65% when TTR was 100% (TTR calculated over 180 days).

Conclusions: We conclude that a current TTR hardly predicts a future TTR. Physicians and patients should deliberate together which probabilities to accept, take measures to improve TTR, and consider potential alternatives.

KEYWORDS

acenocoumarol, anticoagulants, coumarins, decision support techniques, quality control

Essentials

- The benefit of vitamin K antagonist treatment depends on the time in the therapeutic range (TTR).
- In 18 031 patients we analyzed whether future TTR can be predicted by previous TTR.
- Pearson correlation with future TTR was 0.27; groups had poor discrimination (c statistic, 0.61)
- Individuals with higher baseline TTR are more likely, yet far from certain, to obtain a TTR ≥70%.

1 | INTRODUCTION

Vitamin K antagonists (VKAs) are widely used to treat and prevent thrombosis. Their unpredictable effect and narrow therapeutic window necessitate monitoring and dose adjustments to maintain the anticoagulation intensity (expressed as the International Normalized Ratio [INR]) within a specified range, where the combined risk of bleeding and thrombosis is lowest. The higher the proportion of time a patient's INR is within this therapeutic range (TTR), the fewer adverse events.[1-3] Therefore, the TTR is used as a quality indicator for anticoagulation clinics.

The role of TTR in individual patient care is less clear. The current guideline by the American College of Chest Physicians (ACCP) recommends to switch to a direct oral anticoagulant (DOAC) or consider intervening to improve TTR when TTR is consistently low,[4] to prevent complications in the future. Intuitively, this is reasonable advice. However, it is partly founded on the assumption that a patient's past TTR predicts future TTR or clinical events. Data for this are scant. Furthermore, it is not clear which TTR can still be accepted or when action is required. The mentioned ACCP guidelines give the example of a TTR <65%[4] to intervene, while the HAS-BLED score identified a TTR <60% as a risk factor for bleeding.[5] The European Society of Cardiology, in contrast, defines "high-quality treatment" as a TTR ≥70%.[6] However, the TTR threshold below which the risk of adverse events increases starkly could very well be much lower: 45%[2] or even less.

We performed this study to investigate the predictive performance of a TTR, and identify a threshold below which no recovery of TTR should be expected.

2 | METHODS

2.1 | Participants and period

Certe Trombosedienst is a large first-line anticoagulation clinic in the north of the Netherlands. We extracted all data from patients using acenocoumarol (the most commonly used VKA in our clinic) for any indication with an INR target range of 2.0-3.0 and 2.5-3.5. These target ranges have been in effect since January 2016; before 2016, wider target ranges were used. Hence, data collection ranged from January 1, 2016, to June 30, 2018 (date of extraction). We excluded data from the first 90 days of treatment with VKA, as the initial treatment phase is known to be unstable.

Patients were included when they had enough INRs to provide a baseline period and an outcome period. We performed the analyses at periods of 90 days, 180 days, or 1 year. This led to small differences in the number and characteristics of patients included in analyses with different durations. For brevity, characteristics will be given for the 180-day sample only.

2.2 | Outcomes

The TTR was derived using linear interpolation according to the Rosendaal method.[7] No interpolations were performed when the number of days between INR measurements exceeded 56 (the average time between measurements was around 3 weeks, with a maximum of 6 weeks for stable patients). We defined a "good TTR" as a TTR ≥70%, based on the cutoff by the European Society of Cardiology.[6]

We performed separate analyses for the prognostic value of a TTR calculated over 90, 180 days, and 1 year. For the 90-day analysis, the first INR after 90 days of follow-up was defined as time point 0. Hence, the baseline TTR is calculated over the period between −90 days and day 0. Therefore, the TTRs dated >90 days do not share any INRs with the baseline TTR. The same is true, mutatis mutandis, for analyses over 180 days or 1 year. This is illustrated in Figure 1.

2.3 | Analyses

To investigate the predictive performance of the TTR, we first assessed the stability of an individual's TTR over time. We calculated the correlation between a patient's TTR in the baseline period and their TTR in the consecutive period.

Furthermore, we assessed the stability of the TTR on the group level. Patients were divided into 5 groups based on their baseline TTR (by quintile). A follow-up TTR was calculated every 15 days (see Figure 1). These TTRs were summarized as median and interquartile range and plotted. We also assessed the separation between the baseline groups, expressed as the c statistic from a multiclass receiver operator characteristics curve.[8] We also calculated the proportion of the variance that was explained (R^2) by baseline group membership as a categorical variable in linear regression.

Finally, we assessed the probability to obtain a good TTR (a TTR ≥70%) based on a previous TTR. For this analysis, we used 2 consecutive periods of the same length (see Figure 1). The TTR over the first period was binned (in bins with a width of 5%); for every bin, we obtained the percentage of subjects who achieved a TTR ≥70% in the second period. We constructed 95% confidence intervals (CIs) using a binomial test.

All analyses were performed in R version 3.6.1 (2019-07-05) using the pROC package.[9] We primarily report the analyses with a target range of 2.0-3.0; a target range of 2.5-3.5 is reported only in Appendix S1 because there were fewer patients in this target range.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are summarized in Table 1. Patients in the different strata were similar in the distribution of age, sex, indications, dose, and experience with VKAs (Table S1). Table S1 also includes patient characteristics for the auxiliary analyses on a target range of 2.5-3.5.

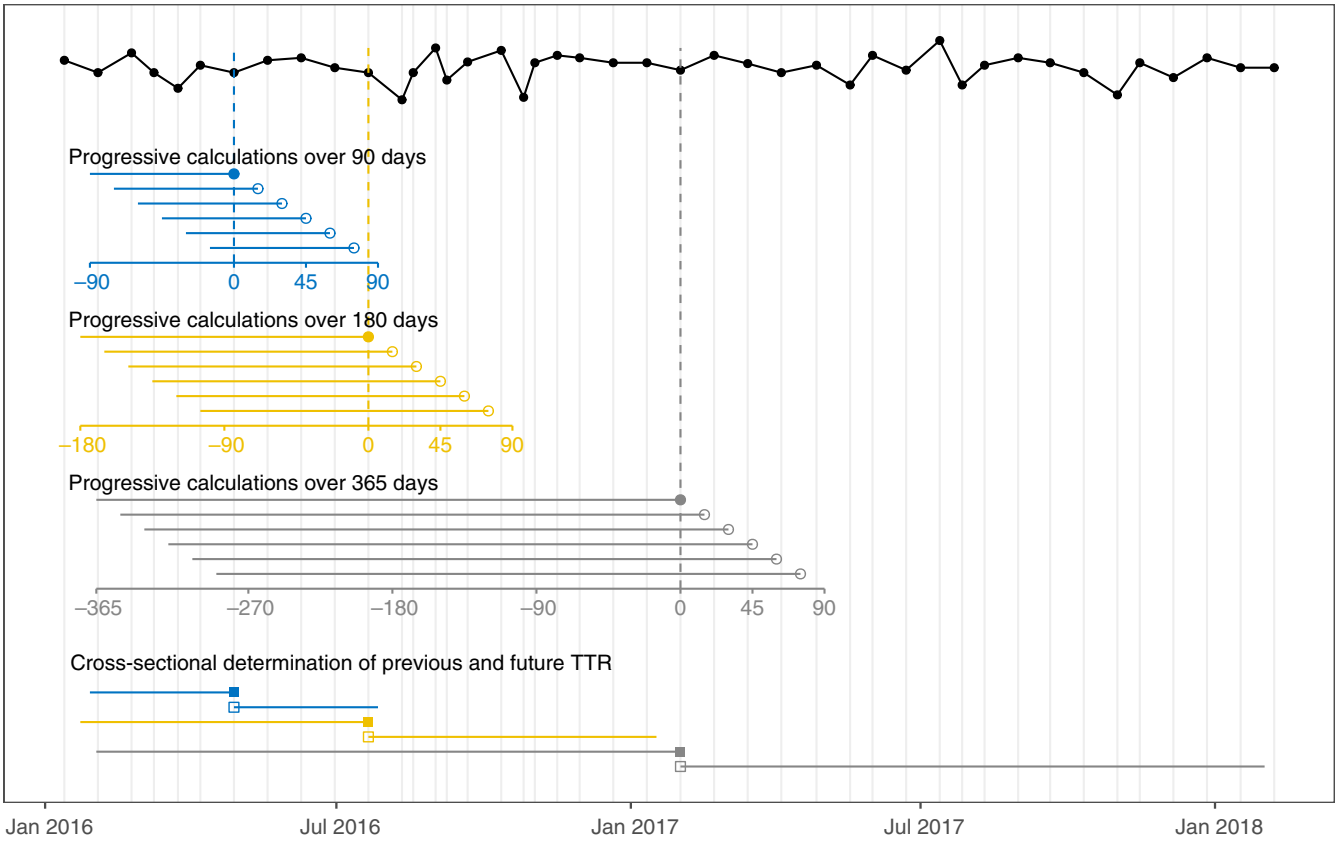

FIGURE 1 Periods for calculations. At the top, an example of an individual TTR. Periods marked with solid circles and squares were used as predictors; hollow symbols indicate outcome data. TTR, time within the therapeutic range

TABLE 1 Baseline characteristics of the patients included in the 180-day analyses

N	18 031
Age, years, mean (SD)	78.1 ± 11.1
Female sex, n (%)	8855 (49)
VKA experience, years, mean (SD)	5.6 ± 5.2
Atrial fibrillation, n (%)	15 267 (85)
VTE, n (%)	3119 (17)
Mechanical valve, n (%)	139 (1)
Mean acenocoumarol dose, mg, mean (SD)	2.2 ± 1.0
Follow-up duration in days, median (IQR)	690 (450-705)
TTR >70%, n (%)	7602 (42)
Time within range, %, median (IQR)	66 (51-80)
Time below range, %, median (IQR)	7 (0-18)
Time above range, %, median (IQR)	21 (9-36)

3.2 | Stability of the therapeutic range

The correlation between baseline TTR and later TTR was weak: for TTRs calculated over 90 days, the correlation coefficient *r* was 0.25 (95% CI, 0.24-0.26). For TTRs over 180 days, *r* was 0.25 (95% CI, 0.24-0.26); for TTRs over 365 days, it was 0.34 (95% CI, 0.32-0.35).

Baseline groups initially clearly differed in TTRs: the c statistics were 1.0 (by definition). There remained some variation in TTR within the groups, but most of the variance was explained: the proportion of variance explained was 94% for a calculation over 90 days, 92% over 180 days, and 91% over 365 days.

However, the groups became increasingly similar over time, as illustrated in Figure 2. A full period later, the c statistic for the analysis over 90 days had decreased to 0.60. The c statistic was 0.61 for the analysis over 180 days and 0.63 for that over 365 days, indicating poor discriminatory performance. Likewise, the proportions of variance explained were only 6%, 7%, and 10%, respectively.

A prognosis by baseline TTR expires over time. When there is a 1-year gap between the baseline period and the outcome period, the c statistic decreases to 0.54 for the 90-day analysis and 0.56 for the 180-day analysis. For the analysis over 1 year, we only had enough data to calculate the c statistic with a gap of 145 days; the c statistic then decreased to 0.62. The respective proportions of variance explained were 1%, 3%, and 8%.

The correlations between baseline TTR and the later TTR were 0.08 (95% CI, 0.07-0.10), 0.16 (95% CI, 0.14-0.18) and 0.30 (95% CI, 0.28-0.32).

There were no clear differences between males and females, or between different age groups.

The image in target range 2.5-3.5 was similar (Appendix S1).

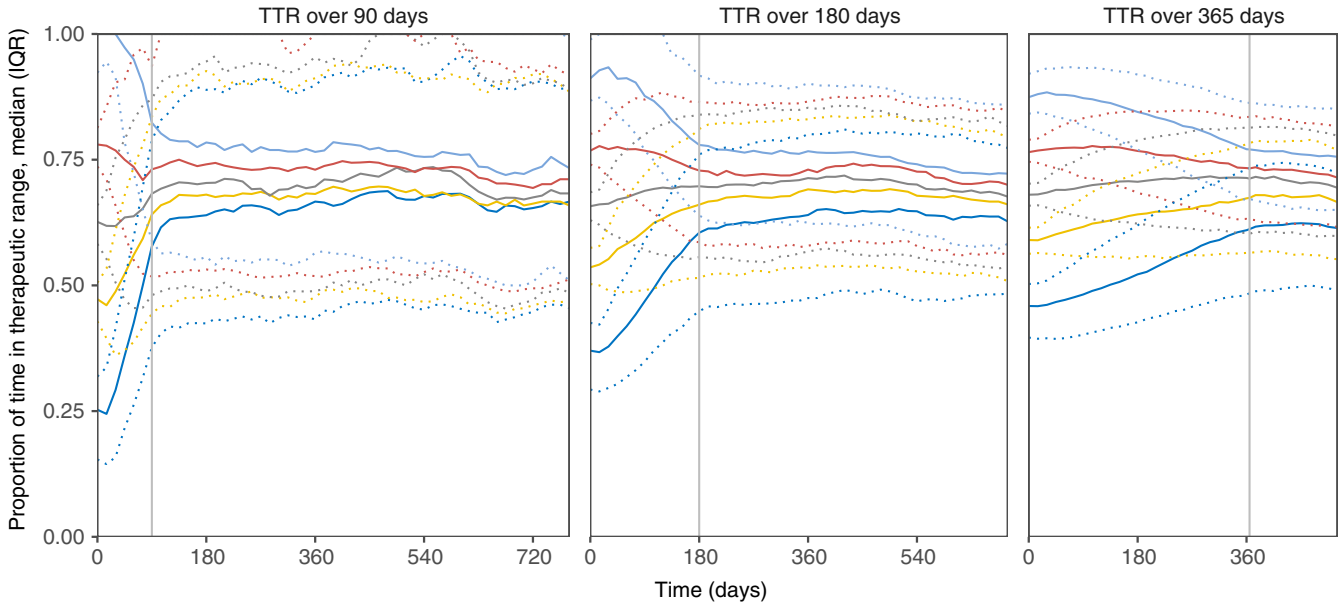

FIGURE 2 Median (IQR) of TTR by baseline TTR group, over time. The panels indicate the duration of TTR calculation; the vertical line indicates when no INRs overlap between current TTR and baseline TTR. IQR, interquartile range; TTR, time within the therapeutic range

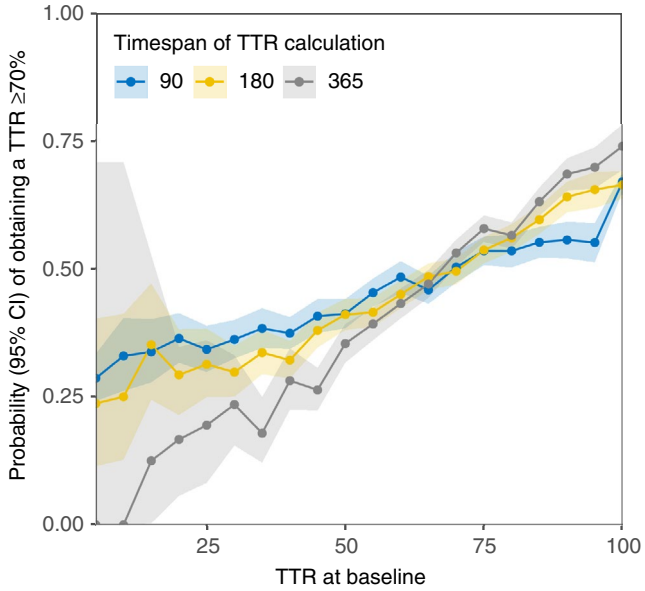

FIGURE 3 Probabilities to obtain a time in the therapeutic range (TTR) ≥70%, conditional on baseline TTR. CI, confidence interval; TTR, time within the therapeutic range

3.3 | Probabilities to obtain a good TTR

Patients with a baseline TTR ≥70% were not guaranteed to maintain a high TTR: only 60% achieved a TTR ≥70% in the adjacent period. However, these patients had a higher probability than patients with a lower TTR, as the probability to obtain a good TTR (≥70%) increased with baseline TTR (Figure 3). This relationship was also present in target range 2.5-3.5 (Figure S2).

Irrespective of TTR duration, a baseline TTR of approximately 67% resulted in a 50% probability to obtain a good TTR over the same period in the future. Of patients with a perfect TTR of 100%, these probabilities were 60%, 65%, and 74% over 90, 180, and 365 days, respectively. A TTR of 50% resulted in a TTR ≥70% in only 44%, 42%, and 36% cases.

Here, too, there were no clear differences between males and females, nor between different age groups. In the target range of 2.5-3.5, the probability to obtain a good TTR was lower across the baseline TTR groups (Figure S2).

4 | DISCUSSION

We found that the TTR's capability to predict future TTR is very limited. Groups separated by baseline TTR obtain increasingly overlapping TTRs over time. However, for an individual patient, a lower baseline TTR predicts a lower probability to obtain a good TTR later on. Nevertheless, even patients with a TTR of 70% maintain a good TTR in only half of the cases. This probability was even lower in the target range of 2.5-3.5, reflecting a more volatile INR pattern in a smaller group of patients (Appendix S1). We infer that a previous TTR might be less helpful for predicting future anticoagulation control than we initially thought.

Our findings are in line with a previous study, where only 56% of patients with a baseline TTR ≥70% maintained a TTR ≥70% over the following year.[10] In contrast to that study, which focused on patients with a good TTR, we looked at patients with a poor TTR because events cluster in this group and less in the "gray area" of mediocre TTR.[2] We aimed to identify a TTR below which therapy became unfeasible. How one defines "unfeasible therapy" depends on the availability of improvements or alternative anticoagulants. For example, if we strive for at least a 50% probability to obtain a TTR ≥70% in the future, patients in the target range 2.0-3.0 should have at least a baseline TTR

of 70%. For the target range of 2.5-3.5, there was more uncertainty: Only patients with a TTR of ≥90% over 1 year had a ≥50% probability (Appendix S1). Shorter periods had no realistic cutoff for this certainty.

It has proven difficult to predict TTR. Extremes in INRs, such as extreme over-anticoagulation[11] or successive subtherapeutic INRs[12] show an increased risk of worse TTR, but the effects are not very strong. The addition of clinical parameters might augment the prediction of TTR. Indeed, many clinical characteristics have been linked to VKA control.[13-18]

Some clinical decision tools are used to distinguish groups that differ in mean TTR.[16-18] This can be problematic because even significant differences between groups allow for considerable overlap (eg, in our data set, analysis of variance for TTR by strata resulted in a *P* value <.01 for all time points in Figure 2). Furthermore, these tools do not provide a probability for a certain TTR, making them less clinically useful.[19]

Other tools that predict an individual's TTR[14] or the probability to obtain a TTR <70%[15] report limited proportions of variance explained of approximately 7%.

Most of these tools use clinical parameters obtained at the start of anticoagulation therapy. This complicates their use during patient follow-up. Moreover, models that use only data available at treatment inception cannot incorporate events that occur during treatment.

The outcome of this study can be explained by a combination of several mechanisms: First, anticoagulation clinics strive to obtain a high TTR in all patients. If a patient obtains an inadequate TTR, dose adjustment and more frequent monitoring are employed to increase TTR. Second, a poor TTR could be caused by temporary factors, such as comorbidities and their treatment. When these are under control, TTR could improve again. A third factor would be "regression to the mean," the phenomenon where patients with a high TTR tend to decrease, and those with a low TTR increase as natural variation. The weight of these 3 factors depends on the time period used to calculate a TTR. If the TTR is poor over a whole year, it is less likely that this is just a temporal variation; instead, this may be due to a more profound cause.

Our study benefits from a large number of patients. The anticoagulant studied (acenocoumarol) could be a limitation because warfarin is the most widely used VKA. It is controversial whether a longer-acting VKA causes a higher TTR. A French randomized controlled trial found no difference in TTR between patients on acenocoumarol or warfarin.[20] Even if warfarin leads to higher TTRs than acenocoumarol, this does not necessarily invalidate our findings about the stability of a TTR over time. While this study would, of course, benefit from external validation, we believe that the VKA effect is generalizable. This is supported by similarities in outcomes with a Danish study using warfarin.[10]

Another limitation is that we lacked data on clinical events. Because of this, we can only make indirect inferences about the risk of a current TTR and the risk of thrombosis and bleeding. Clinical decisions based on TTR could have introduced bias in our analyses. If patients were more likely to continue or withhold VKA based on their TTR, this could affect follow-up time and could cause an overrepresentation of patients with a low TTR whom their physicians considered likely to improve. We lack the data to assess this bias. If the effect of this bias were large, this would "flatten" the association between baseline TTR and the probability of obtaining a good TTR. However, it is unlikely that this has markedly influenced our results: The large majority of physicians do not request TTR calculations from the thrombosis service, and those who do lack information about the predictive value of a current TTR.

These data allow physicians to tailor their counseling to their individual patient. Patients with a lower TTR are unlikely to obtain a good TTR in the future and should thus be counseled on alternatives such as DOACs. However, DOACs are contraindicated in mechanical valves and the antiphospholipid syndrome, and there is insufficient experience with venous thromboembolism outside the limbs and lungs. Furthermore, when therapy inadherence is the expected cause of a low TTR, DOACs might not be the right choice because adherence might decline and can no longer be assessed. In the most extreme cases, when the expected benefits no longer outweigh the bleeding risk, physicians and their patients should consider stopping anticoagulation altogether. Based on these data, we cannot give strong advice regarding patients with a high TTR. They are more likely, but not guaranteed, to maintain a high TTR. A decrease in TTR would put them in a gray area, where the TTR is suboptimal but the incidence of adverse events is only mildly increased.[2] In a previous study, we found no evidence to advise against switching patients with a high previous TTR to a DOAC.[21]

5 | CONCLUSION

We conclude that a current TTR hardly predicts a future TTR. Even patients with a perfect TTR are at risk of obtaining a suboptimal TTR. Physicians and patients should deliberate together which probabilities to accept, take measures to improve TTR, and consider potential alternatives.

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RELATIONSHIP DISCLOSURE

JHAvM and NJGMV report nothing to disclose. KM reports travel support from Baxter; grants, travel support, and speaker fees from Bayer; grants and speaker fees from Sanquin; grants from Pfizer; speaker fees from Boehringer Ingelheim; speaker fees from BMS; speaker fees from Aspen; consulting fees from Uniqure; and grants from Federatie van Nederlandse Trombosediensten, all outside the submitted work.

AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of the data and approved the final version of the manuscript. Additionally, JHAvM

designed the study, performed the analyses, and drafted the manuscript. NJGMV and KM critically revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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