An easy-to-use tool to flag patients at risk of poor INR control

van Miert, Jasper H.A.; Veeger, Nic J.G.M.; Meijer, Karina

Published in:
Thrombosis Research

DOI:
10.1016/j.thromres.2019.06.006

Publication date:
2019

An easy-to-use tool to flag patients at risk of poor INR control: a streak of subtherapeutic INRs

- Jasper H.A. van Miert, MD [*,†]
- Nic J.G.M. Veeger, PhD [‡]
- Karina Meijer, MD PhD [*]

* Department of Hematology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
† Certe Thrombosis Service Groningen, Groningen, the Netherlands
‡ Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Corresponding author:
J.H.A. van Miert
Department of Hematology
University Medical Center Groningen
Huispostcode: AA24
Postbus 30.001
9700 RB Groningen
the Netherlands

Email: j.h.a.van.miert@umcg.nl
Telephone: +31 50 36 10225
Fax: +31 50 36 11790

Word count manuscript: 2406
Word count abstract: 246 words

Essentials

- We present a simple way to flag higher risk of poor INR control
- We used INRs from patients using acenocoumarol from our anticoagulation clinic
- Four consecutive INRs < 2.0 increase the odds of poor INR control threefold
- This method can be used to flag patients at higher risk of poor INR control

Abstract

Introduction: Vitamin K antagonist therapy is safest and most effective with a high time within the therapeutic range (TTR). The TTR is difficult to calculate in the consultation room, therefore physicians need an easier-to-use tool to predict poor VKA control.
We explored the prognostic value of subtherapeutic INRs on future TTR in two settings:
(1) Clinical review setting, where a physician (bi)annually reviews a patient and uses the INRs since the last visit to predict the TTR up to the next visit;
(2) Day-to-day INR management setting, where every new INR measurement prompts a new prediction over the next 90 days.

Materials and Methods: Retrospective cohort of 17,711 patients from a dedicated thrombosis service, using acenocoumarol (target range 2.0-3.0), with a "streak" defined as four consecutive INRs <2.0.
(1) Odds ratios of any streak in the last 180 days or 1 year on a TTR <45% over the same period in the future;
(2) Odds ratio of a current streak on a TTR <45% over the next 90 days.

Results and Conclusions: Clinical review setting: The occurrence of any streak in the last 180 days or 1 year increased the odds of a TTR <45%: ORs 2.84 (95% CI 2.41-3.34) and 3.25 (95% CI 2.72-3.87), respectively.
Day-to-day INR management setting: A current streak increases the odds of poor TTR over the next 90 days 3.58 (95% CI 2.64-4.87) fold.
We conclude that a streak of four consecutive subtherapeutic INRs can aid physicians in flagging at-risk patients.

Keywords

- Anticoagulants
- Acenocoumarol
- Coumarins
- Decision Support Techniques
- Quality control

Introduction

Vitamin K antagonists (VKA) effectively treat and prevent thrombosis in different clinical scenarios, such as atrial fibrillation and venous thromboembolism. Specific ranges of anticoagulant activity (international normalised ratio; INR) are targeted to strike a balance between efficacy and bleeding risk. The VKA dose is adjusted to maximise the proportion of time a patient's INR is within the therapeutic range (TTR). Patients with a lower TTR experience more thrombosis and bleeding[1,2]. Furthermore, a recent TTR predicts future events[3,4]. Sadly, the TTR is under-used in clinical practice, because it is difficult to calculate in the consultation room.

Physicians need easier to obtain information to identify patients at risk of subsequent poor VKA control. An example is the -always adverse- event of an INR ≥ 8, which negatively affects future VKA control[5]. Subtherapeutic INRs might likewise predict poor VKA control. However, sometimes a low INR is intended, e.g. for surgery. Multiple, consecutive subtherapeutic INRs, on the other hand, are never intended. We, therefore, aimed to explore the prognostic value of consecutive subtherapeutic INRs to predict future VKA control, in two settings. First, the setting of physicians (bi)annually reviewing their patients. They need information on future VKA control to balance bleeding and thrombotic risk. Second, the setting of VKA dosing after a new INR measurement. Here, a streak could stratify patients for aggressive interventions to improve VKA control.

Methods

Patients

In the Netherlands, anticoagulation with VKA is managed by dedicated thrombosis services. We selected all patients from Certe Trombosedienst, the largest thrombosis service in the north of the Netherlands, who satisfied the following criteria: adults of at least 18 years of age, who were treated with acenocoumarol (the most common anticoagulant in this thrombosis service) with an INR target range of 2.0 - 3.0. We included all patients who were treated for at least 9 months between January 1st, 2016, and June 30th, 2018, excluding the first 3 months after initiation of VKA.

Study design

We retrieved all thrombosis service records for the patients who matched the criteria above. We determined whether they had a "streak" of four consecutive INRs below the target range (i.e. INR < 2.0). We chose this cutoff arbitrarily, based on our clinical intuition that four consecutive INRs below the target range "are no coincidence". Furthermore, this suggests a persisting problem for which intervention may be required.

We explored the predictive value of a "streak of lows" in two settings: the "clinical review setting" simulates a patient's (bi)annual visit to the outpatient clinic, where the bleeding and thrombotic risks are weighed and risks are minimised. Secondarily, we analysed the "day-to-day INR management setting". In this more practical, executive, setting, the last INRs are used only to determine the next acenocoumarol dosing scheme.

Statistical analysis

Clinical review setting

In our clinic, we see a patient every six months or every year. We check the INR measurements since the last visit, and use this information to predict INR control up to the next appointment.

We simulated a doctor's appointment on the date in the middle of the treatment period. We checked whether a streak of subtherapeutic INRs occurred anywhere in the preceding six months (and if so, how many days had since passed), and, alternatively, whether the TTR over the preceding six months was poor (less than 45%, because in this group more events occurred than in those with TTR 45-60% or >60%[3]). These predictors were used in a univariate logistic regression to predict a future poor TTR, and in a univariate linear regression to predict future TTR as a continuous variable. The same was done, *mutatis mutandis*, for a review every year. This method is summarised in Fig 1.

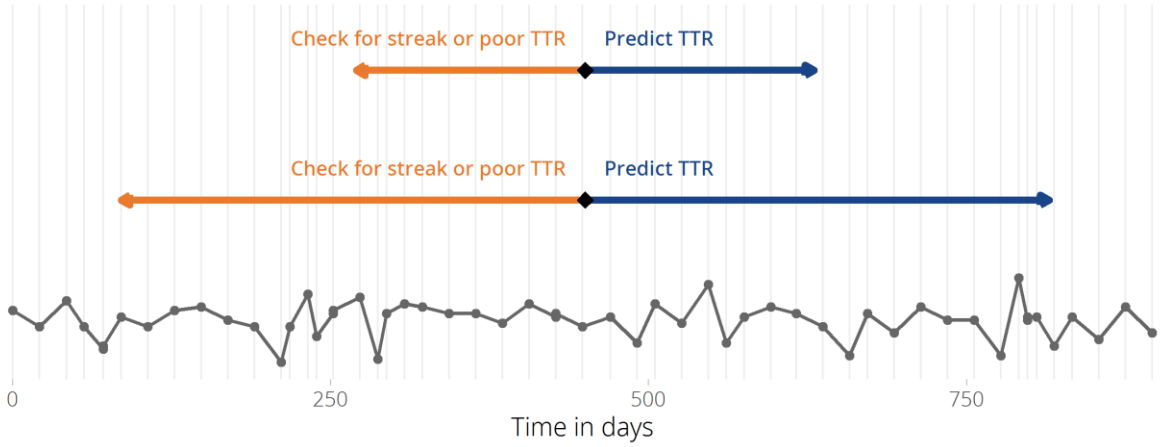

Fig. 1. Time periods for the calculations in the clinical review setting.

Day-to-day INR management setting

In the day-to-day INR management setting, every new INR offers an opportunity for reassessment. For every INR, we checked whether it formed a streak of lows with the three preceding INRs. This was used to predict a poor TTR (TTR < 45%, see above) over the next 90 days, using a univariate logistic regression as described below. Alternatively, we used the TTR over the last 90 days, including the current INR, as a predictor. TTR was categorised as poor (TTR < 45%, see above) or not.

Each patient contributed a different number of INR measurements to the overall dataset, because treatment duration varied and the period between INR measurements is based on the previous INRs. Furthermore, measurements of the same patient are correlated; not just because they concern the same subject, but also because the predictors overlap: one INR is included 4 times for the streak (because a streak is length 4); and a variable number of times for previous TTR. The latter depends on the number of times the INR was determined in the 90-day period. Due to these dependencies, normal linear or logistic regressions were not suitable. Instead, we performed a regression on a data subset that contained 1 randomly selected INR assessment date per patient. This procedure was repeated a 1000 times (bootstrapping) to construct an empirical confidence interval (the 2.5th and 97.5th percentile of the 1000 observations) and point estimate (median). The method for the day-to-day INR management setting is summarised in Fig 2.

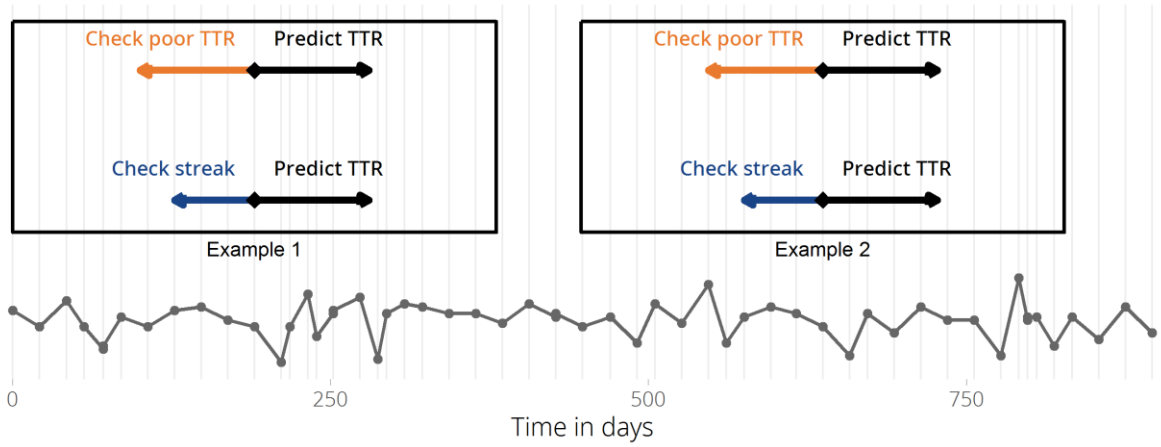

Fig. 2. Time periods for the calculations in the day-to-day INR management setting.

All analyses were performed in R. The TTR was calculated using the established Rosendaal method[6]. We report data as linear estimates (for continuous variables) or odds ratios (for binary variables), with their 95% confidence intervals.

Results

Patient selection and characteristics

We selected 17,711 patients who contributed 708,540 INR measurements. Patient characteristics of the included patients are outlined in Table 1. A streak occurred in 2750 (16%) patients at least once; 1119 (6%) had a poor TTR over the full study period. The mean time within the therapeutic range was 67% (SD 14), with 7832 (44%) patients having a TTR > 70%.

Table 1: Characteristics of the included patients (n = 17711)

age (years, mean (SD))	77.8 (11.2)
age below 50 years	349 (2%)
male sex	9017 (51%)
time within range (%, mean (SD))	66.9 (13.5)
time below range (%, mean (SD))	11.6 (9.2)
time above range (%, mean (SD))	21.5 (11.0)
poor TTR (%)	1119 (6%)
mean INR (median (IQR))	2.6 (IQR 2.5 – 2.7)
any streak	2750 (16%)
measurement period length (days, mean (SD))	774.9 (180.0)
atrial fibrillation	14537 (82%)
venous thrombo-embolism	2972 (17%)
heart valve	301 (2%)
other indication	1953 (11%)

Clinical review setting

Review every six months

When we looked back six months, 772 (5%) patients had a streak, and 2302 (14%) had a poor TTR. 406 (2%) had both.

Patients who had a streak in the previous six months, had a lower TTR in the next six months: 70% versus 58% (difference 12.5 (10.9 - 14.1)). For a previous poor TTR, the difference was 13.8 (12.8 - 14.7): 72% versus 58%.

The presence of a streak increased the risk of a poor TTR over the next six months: OR 2.84 (2.41 - 3.34). A poor TTR increased the odds 3.53 (3.18 - 3.91) fold.

As the streak happened longer ago, its predictive value diminished, as shown in Table 2.

Table 2: Influence of time since streak on continuous TTR and OR of poor TTR in the next six months.

Days since streak	TTR	OR of poor TTR
0 to 1 days	-21.7 (95% CI -26.5 to -16.8)	5.1 (95% CI 3.2 - 8.3)
1 to 30 days	-12.4 (95% CI -15.5 to -9.2)	3.4 (95% CI 2.4 - 4.7)
30 to 90 days	-12.7 (95% CI -15.7 to -9.8)	3.2 (95% CI 2.3 - 4.3)
90 to 180 days	-10.5 (95% CI -12.8 to -8.3)	2.1 (95% CI 1.6 - 2.7)

Absolute TTR difference in percentage points, or odds ratios. CI, confidence interval; OR, odds ratio; TTR, time within therapeutic range

Review every year

Over a period a year, more patients had a streak (now 949 (7%)) and fewer a poor TTR (986 (8%)), compared with the six month period. 287 (2%) had both a poor TTR and a streak.

A streak sometime in the last year predicted a lower TTR over the next year: 70% versus 61% (difference 9.6 (8.5 - 10.7)). A poor TTR did as well: 71% versus 56% (difference 14.2 (13.1 - 15.4)).

The odds ratios for a poor TTR over the next year were 3.25 (2.72 - 3.87) for a streak and 5.80 (4.95 - 6.80) for a poor TTR.

Here, too, the predictive value of a more recent streak was higher (see Table 3).

Table 3: Influence of time since streak on continuous TTR and OR of poor TTR in the next year.

Days since streak	TTR	OR of poor TTR
0 to 1 days	-12.8 (95% CI -17.3 to -8.2)	5.6 (95% CI 2.9 - 10.2)
1 to 30 days	-9.9 (95% CI -12.8 to -7.1)	3.3 (95% CI 2.1 - 5.2)
30 to 90 days	-12.1 (95% CI -14.9 to -9.3)	4.1 (95% CI 2.7 - 6.2)
90 to 180 days	-8.5 (95% CI -10.6 to -6.3)	3.7 (95% CI 2.6 - 5.1)
180 to 366 days	-8.9 (95% CI -10.4 to -7.4)	2.6 (95% CI 1.9 - 3.3)

Absolute TTR difference in percentage points, or odds ratios.
CI, confidence interval; OR, odds ratio; TTR, time within therapeutic range

Day-to-day INR management setting

The percentage of INR measurements that was part of a streak varied from bootstrap sample to bootstrap sample, and was on average 0.8 (0.7 - 1.0)%. When the last four INRs were all subtherapeutic, the odds of a poor future TTR increased 3.58 (2.64 - 4.87) fold. A poor TTR over the previous 90 days resulted in an odds ratio of 2.29 (2.13 - 2.45).

Discussion

Vitamin K antagonist therapy is safer and more effective when patients achieve a high time within the therapeutic INR range (TTR). The TTR is however under-used in practice because it is difficult to calculate (as it requires software that is unavailable in the consultation room). We explored the predictive value of a “streak” of four consecutive subtherapeutic INRs as an easier alternative to flag patients with a poor future TTR. We found that the presence of a streak predicts an approximately 10 percentage point reduction in future TTR over six months and a year, and a threefold increase in the odds of a TTR <45%. The effect of a streak was largest when the streak persisted at the time of clinical review, and diminished with increasing time since streak. Patients remained at increased risk, even when the streak occurred more than six months ago.

We compared a streak with the TTR over the preceding period, to properly value our new method of identifying patients at risk of poor VKA control. In the day-to-day INR management setting (where the presence of a streak or a poor TTR was assessed with every new INR measurement available) a streak outperformed a poor previous TTR in predictive power for a poor future TTR. An added benefit of a streak is that it is generally quicker in flagging a patient, because it only requires four measurements instead of 90 days. During a six month observation, the predictive power of a streak is equal to that of the poor previous TTR. Looking back over a longer period, the TTR outperforms a streak. This is not surprising: extending the screening period from six months to a year will cause more patients to be flagged by the streak (simply because more measurements lead to a higher chance of forming a streak). Those streaks have occurred 7-12 months ago; patients have since recovered and hence

obtained a better prognosis. These patients will dilute the prognostic effect. For a TTR the opposite is true: having a poor TTR over a period that is twice as long occurs less frequently. It indicates a longer lasting problem and therefore a worse prognosis. We stress that we were not looking for a replacement or a stronger alternative for the TTR, but just a measure that is easier to obtain and more likely to be actually used in practice.

Fewer patients are flagged by a streak than by a poor TTR. A streak and a poor previous TTR overlap to a limited extend. One reason for this is that a TTR can also be poor because the INR is too high. We focused on subtherapeutic INRs because the prognostic value of a high INR had already been established[5]. One should decide for oneself whether the lower flag rate is a strength or a weakness; this could differ from setting to setting. The flag rate depends on the cutoff used to define a streak. In this study we primarily used a streak of four consecutive subtherapeutic INRs. We also analysed different cutoffs: longer streaks predict a larger difference in TTR and odds for poor TTR, but occur less frequently (Fig 3).

How can the physician or thrombosis service act, after a patient has been flagged using a streak? An important cause of a subtherapeutic INR is poor medication adherence. This might be improved by patient education[7], devices that remind patients to take their medication, multi-dose drug dispensing[8], or lottery systems[9]. Another option would be to switch to longer-acting VKAs (e.g. phenprocoumon), which are less sensitive to occasionally forgetting a dose. If poor medication adherence is ruled out, non-VKA, or direct, oral anticoagulants (NOACs/DOACs) may be an option.

Strengths of this study are the pragmatic approach, as well as the large number of patients. INR measurements were prospectively collected by the thrombosis service, while we analysed the value of a streak retrospectively. This way, the thrombosis service could not have acted based on our hypothesis to abate the effect on poor TTR. The other way around, the increased risk that we found could also be the result of inadequate reactions to a streak. The high average TTR over the entire study period makes this unlikely. As always, this study would benefit from external validation. Because acenocoumarol is shorter-acting than warfarin or phenprocoumon, it is not clear whether our findings can be generalised to patients using these drugs. The same is true for alternative therapeutic ranges. The number of patients using VKA has dropped significantly after the introduction of the DOACs. This makes quality assessment for patients using VKA even more vital: those with a poor TTR might have more to gain by switching to a DOAC than those with a high TTR[10] (but data are indirect).

Conclusion

A streak of four consecutive subtherapeutic INRs can aid physicians to flag at-risk patients.

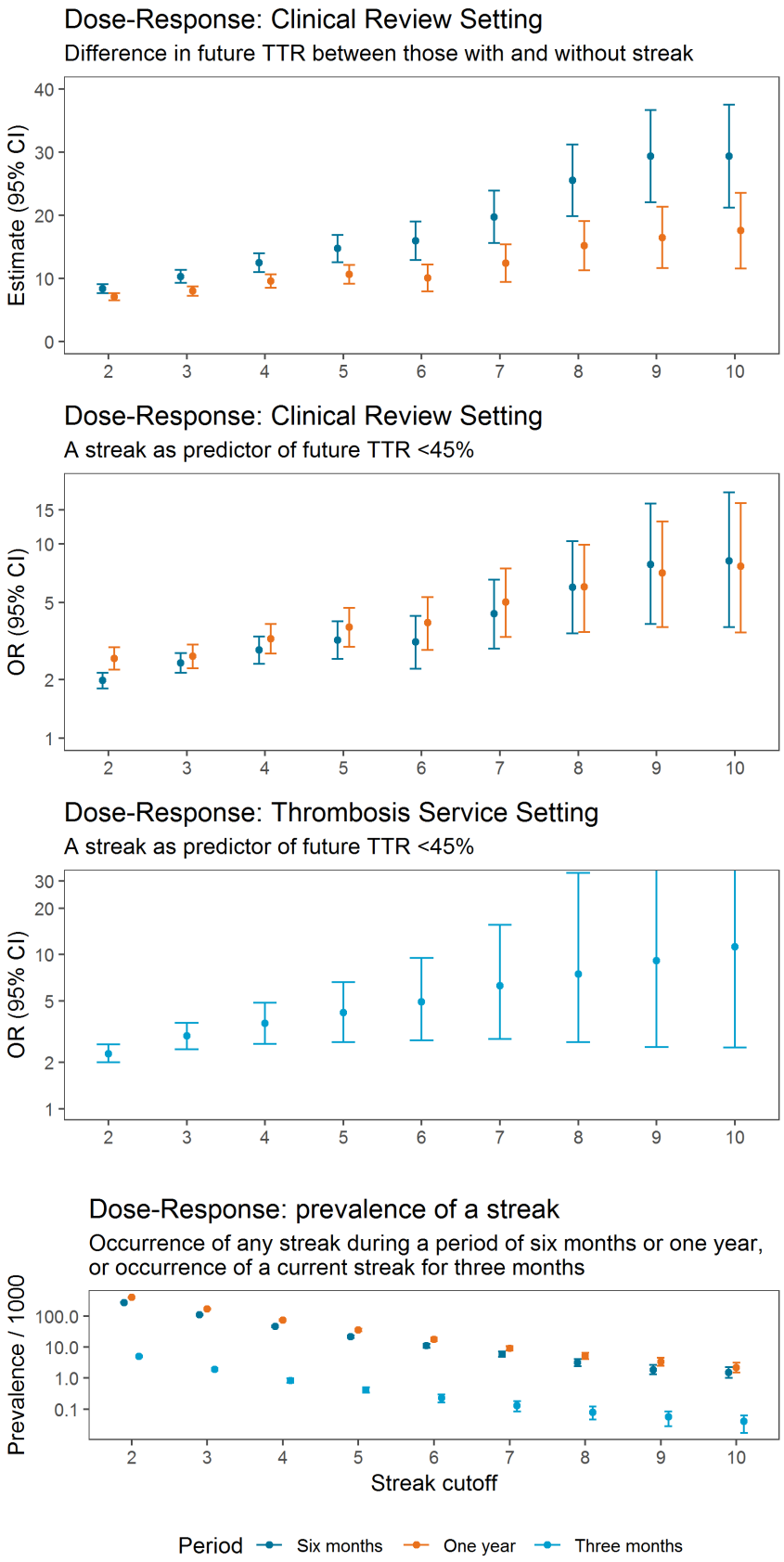

Fig. 3. Effect of different cutoffs for a streak.

Funding

No external funding was used for this study.

Author contributions

- Study conception: J.H.A. van Miert
- Study design: J.H.A. van Miert, N.J.G.M. Veeger, K. Meijer
- Data acquisition: J.H.A. van Miert
- Analysis: J.H.A. van Miert
- Interpretation: J.H.A. van Miert, N.J.G.M. Veeger, K. Meijer
- Drafting of manuscript: J.H.A. van Miert
- Critical revisions: N.J.G.M. Veeger, K. Meijer

Image captions

- Fig 1: time periods for the calculations in the clinical review setting
- Fig 2: time periods for the calculations in the day-to-day INR management setting
- Fig 3: effect of different cutoffs for a streak

Conflict of Interest

J.H.A. van Miert and N.J.G.M. Veeger have no potential conflicts of interest to disclose. K. Meijer reports grants from Bayer, Sanquin, Pfizer, and Federatie Nederlandse Trombosediensten; travel support from Baxter and Bayer; speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS, and Aspen; consulting fees from Uniqure, all outside the submitted work.

References

1 Björck F, Renlund H, Lip GYH, Wester P, Svensson PJ, Själander A. Outcomes in a Warfarin-Treated Population With Atrial Fibrillation. *JAMA Cardiol* American Medical Association; 2016; **1**: 172.

2 Sandén P, Renlund H, Svensson PJ, Själander A. Bleeding complications and mortality in warfarin-treated VTE patients, dependence of INR variability and iTTR. *Thromb Haemost* 2016; **117**: 27–32.

3 Veeger NJGM, Piersma-Wichers M, Tijssen JGP, Hillege HL, Van Der Meer J. Individual time within target range in patients treated with vitamin K antagonists: Main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol* 2005; **128**: 513–9.

4 Bonde AN, Staerk L, Lee CJ, Vinding NE, Bang CN, Torp-Pedersen C, Gislason G, Lip GY, Olesen JB. Outcomes Among Patients With Atrial Fibrillation and Appropriate Anticoagulation Control. *J Am Coll Cardiol* 2018; **72**: 1357–65.

5 Kooistra HAM, Veeger NJGM, Khorsand N, Kluin-Nelemans HC, Meijer K, Piersma-Wichers M. Long-term quality of VKA treatment and clinical outcome after extreme overanticoagulation in 14,777 AF and VTE patients. *Thromb Haemost* 2015; **113**: 881–90.

6 Rosendaal FR, Cannegieter SC, Meer FJ van der, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; **69**: 236–9.

7 Mazor KM, Baril J, Dugan E, Spencer F, Burgwinkle P, Gurwitz JH. Patient education about anticoagulant medication: Is narrative evidence or statistical evidence more effective? *Patient Educ Couns* 2007; **69**: 145–57.

8 Rein N van, Geus KSK de, Cannegieter SCS, Reitsma PHP, Meer FJF van der, Lijfering WWM. Multi-dose drug dispensing as a tool to improve medication adherence: A study in patients using vitamin K antagonists. *Pharmacoepidemiol Drug Saf* 2018; **27**: 46–51.

9 Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TEH, Laskin M, Brensinger CM, Meussner C, Volpp K. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. *Pharmacoepidemiol Drug Saf* 2016; **25**: 1219–27.

10 Piccini JP, Hellkamp AS, Lokhnygina Y, Patel MR, Harrell FE, Singer DE, Becker RC, Breithardt G, Halperin JL, Hankey GJ, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KAA, Califf RM. Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: Results from the ROCKET AF trial. *J Am Heart Assoc* 2014; **3**: 1–11.