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Using a personalized decision support algorithm for dosing in warfarin treatment: A randomised controlled trial

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ABSTRACT

Background: Vitamin K-antagonists such as warfarin treatment remain the mainstay to prevent thromboembolic events in various conditions. The quality of the treatment is reflected through time in therapeutic (INR) range (TTR) with a threshold at ≥70% indicating 'good quality'; achieving this quality is not trivial. We conducted a randomised controlled trial to assess the impact of decision aiding model on treatment quality in a high quality vitamin K-antagonist treatment setting.

Methods: We investigated if algorithm-suggested warfarin dosing was superior to standard dosing in a high-quality setting involving self-managing warfarin patients. Patients were initially allocated to either algorithm-suggested warfarin dosing or to standard care treatment, and were crossed over after three months. The trial period was a total of six months, and the primary endpoint was TTR; we also investigated a secondary endpoint of log-transformed INR variability.

Results: A total of 191 patients contributed to the main analysis with a mean follow-up time of 140 days; 75% were males and the mean age was 65 years old. The intervention arm achieved a TTR of 81.6, while the placebo arm attained a TTR of 80.9 (difference [intervention arm minus placebo arm]: 0.67 (95% confidence interval −2.93 to 4.27). The difference in INR variability was 0.30 (0.14 to 0.47), favouring the placebo arm in terms of lower log transformed variability.

Conclusions: We found no difference between the two trial-arms in a high-quality warfarin treatment setup. However in general, the model performed similarly as to routine patient self-management care. (ClinicalTrials.gov number: NCT02705976)

1. Introduction

Oral anticoagulant (OAC) treatment is effective in preventing thromboembolic events in patients at an increased risk such as atrial fibrillation [1]. However, the drawbacks of treatment with vitamin K-antagonists (VKA) involve drug-food interaction and International Normalised Ratio (INR) monitoring. Alternative treatment options (often referred to as non-vitamin K antagonists oral anticoagulants) are now available, i.e. direct Xa inhibitors or factor II inhibitor [2]. Nevertheless, VKA treatment remains the mainstay to prevent thromboembolic events in various conditions e.g. mechanical heart valve replacement, atrial fibrillation, and secondary prevention of venous thromboembolisms (VTE). Additionally, end-stage renal disease is a contraindication for use of direct Xa inhibitors or factor II inhibitor due to clearance pathways.

The quality of VKA treatment is often reflected through time in therapeutic (INR) range (TTR) with a threshold at ≥70% indicating 'good quality' [3]. In a well-managed Swedish cohort of VKA treated patients with various indications for treatment, the event rates of thromboembolism and major bleeding were around 2%/year [4]. Obtaining a high quality VKA treatment is not trivial. The highest quality is found when patients are assigned to patient self-management (PSM) or patient self-testing [5]. The lowest quality is found in conventional management performed by the general practitioner or a hospital department, and intermediary quality is found in a highly specialized anticoagulation centre [6–9]. Computerized dosing algorithms for warfarin has been developed to maintain warfarin dose, and also to aid in the initial dosing phase [10–13]. However, only few dosing algorithms have been tested in randomised clinical trials and not in high quality settings reflected through high TTR levels [14,15].

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We previously developed an individual dosing algorithm for warfarin maintenance dosage, which was demonstrated to be safe in a retrospective setting [13,16]. The main advantage of this developed model is use of patient specific parameters, which allow for personalized dosing suggestions. However, the model has not yet been tested in a prospective study design. Therefore, we conducted a randomised controlled trial to assess the impact of the model on treatment quality in a high quality VKA treatment setting.

2. Methods

2.1. Trial design

The trial was a pragmatic, single-blinded, cross-over, randomised, controlled trial designed to investigate if algorithm-suggested warfarin dosing was superior to standard dosing in a high-quality setting involving PSM patients in warfarin treatment. The study was approved by the hospital department and the protocol was approved by the National Ethics Committee [ref. N-20140036]. The trial was conducted in accordance with the principles of the Helsinki Declaration. The head of centre and chief physician (TBL) was in charge of clinical safety matters during the trial period. Data were collected by the investigators (PBN and MM) and analysed by a statistician (SLC).

Patients were initially allocated to either algorithm-suggested warfarin dosing (intervention arm) or to standard care treatment (placebo arm). After duration of three months, the involved participants were crossed-over to the other study arm for an additional three months, see Fig. 1. The cross-over design was chosen to reduce between-patient variation and with the intention of reducing potential learning bias, as participants were introduced to a new computerized dosing system (see Trial Procedure description).

The primary study outcome measure was TTR evaluated after six months comparing intervention versus placebo. A secondary study measure was the log-transformed INR variability calculated according to Fihn's method [17]. This method attempts to describe the degree to which each individual's INR value varies relative to his/hers previous INR value. Lower (negative) values correspond to more stable INR variability.

2.2. Trial participants

From September 2014 to November 2014 we enrolled study participants at a single centre in Aalborg, Denmark. Eligible participants were patients with an indication for warfarin treatment who were in steady-state PSM treatment at the Aalborg Thrombosis Centre, Department of Cardiology, Aalborg University Hospital. The patient training has been described previously [18]. In short, patients were educated in monitoring the INR values and to adjust the warfarin treatment accordingly to achieve a designated target INR range. Participants were required to be compliant with the online system used at the department (CoaguCheck Link, Roche Diagnostics, Switzerland); hence eligible participants were deemed comfortable in using IT-systems for reporting on INR values as well as warfarin treatment adherence. Patients with severe co-morbidity, pregnancy, and patients who lacked the ability to handle the interface on the web-based system used in the trial were excluded; see Supplemental Table 1 for detailed inclusion and exclusion criteria. All patients used the portable coagulometer CoaguChek, CoaguChek S or the CoaguChek XS (Roche Diagnostics, Switzerland) equipped with CoaguChek PT-test strips. Inclusion occurred only after a face-to-face meeting with a study investigator (MM); during this meeting the patients were introduced to the (new) online system used in the trial. All patients gave written informed consent before taking part in the trial.

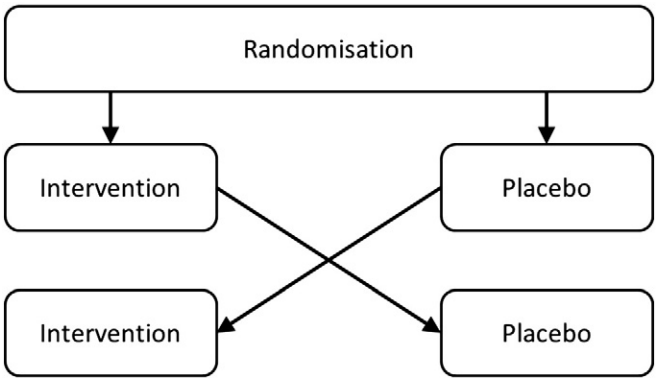

Fig. 1. Trial procedure after randomisation. After three months duration, patients are crossed to opposite trial arm relative to initial randomisation.

2.3. Trial procedure

Enrolled participants were block randomised, in a 1:1 ratio consisting of 20 participants in each block, to (initially) either receive algorithm-suggested warfarin dosing or standard treatment. We intended to analyse data from a total of 200 patients. Patients declining to participate after the meeting with a study investigator were still assigned to the specific block randomisation; hence more than ten randomisation blocks (20 participants × 10 blocks) were applied in the recruitment of participants.

Each enrolled participant was provided a personal log-in to an online, web-based system for which they were instructed to use during the trial period. When agreeing to participate, the study investigator typed in contemporary warfarin dose (last 14 days of warfarin tablets), and two most recent INR measurements. This was done to instantiate the model's ability to produce feasible predictions of INR values and subsequently warfarin dose [13,16].

When logging in to the web-based system, participants were given two options: 1) display the most recent dosage suggestion; 2) add new data into the system. When selecting the latter option, participants were required to type in the number of consumed tablets of warfarin each day since the last data registration. Additionally, they could choose to type in an INR value measured in the timespan from last login and the current day. Next, participants were presented a suggestion of the next week's number of warfarin tablets; this suggestion could be approved or altered. If a participant was allocated to intervention, he/she would receive an algorithm-calculated dosage suggestion. In contrast, the dosage suggestion in the placebo-arm would equal last week's dose of warfarin. The trial arm allocation was blinded for the participants, but recorded in the database holding trial data. After confirmation of 'planned' warfarin dose, a detailed scheme of tablets per day was displayed to the participant. Next time the participants typed data into the system, they were asked to confirm the actual number of tablets taken (each day) since last login. If this number was different from the registered planned warfarin dose, a 'non-compliant' registration was made in the database. Participants were instructed to use the system approximately once a week (routine care), but no requirement on frequency of use was applied. Three months after the initial trial-arm allocation, the web-based system would automatically switch the participant to the other trial arm.

No follow-up visits were made, but participants were encouraged to contact the clinic if they had any doubts or questions concerning the trail procedures, the web-based system, or the treatment in general. Additionally, a safety mechanism was built into the system on the intervention arm: if a calculated dosage suggestion would exceed a threshold of 20% difference relative to last week's dosage, the participant would not be presented this suggestion. Instead, the system would display a message instructing the participant to contact the clinic by telephone. The study investigator would tell the dosage suggestion, and in agreement with the participant, a 'planned' warfarin dosage would be typed into the system by the study investigator.

2.4. Statistics and outcome measures

The algorithm is based on a model, which is designed to handle time series of daily warfarin intakes and INR values measured at designated time points [16]. Based on these inputs the model is able to suggest a warfarin maintenance dose to achieve target INR value. Model parameters are initially set to population values and gradually, as data is entered into the model, these parameters become patient specific.

The primary study endpoint, TTR, was calculated according to the Rosendaal method [19]. Hereby the frequency of the INR measurements and the actual values are incorporated assuming that changes between consecutive INR measurements are linear over time. As a measure of INR variability we used log of the variance growth rate (logVGR) defined by Fihn et al. [17] This quantifies the variability between patient's INR values taking into account the time between INR measurements

A sample size calculation was done with a power of 0.8 to detect a TTR difference of 5% between the control and intervention in an unpaired comparison. The standard deviation (SD) in TTR was based on Nielsen et al. [13] A sample size calculation corresponding to paired comparisons was impossible due to the lack of an estimate of the SD of change in TTR between dosing algorithms and standard care. We expected a drop-out rate of 5% in this trial.

Paired comparisons of TTR and INR variability between treatments were done by paired *t*-tests. To accommodate for potential non-normality confidence intervals were calculated by means of bootstrap. The comparisons were repeated when stratified on INR target, randomization order and warfarin dose groups. Non-compliance, i.e. substantial difference between suggested and administered warfarin intake was specified to imply additional analyses of (i) 'reasons' and (ii) 'consequences' of a non-compliance registration.

All analyses were performed with the use of STATA software, version 13 (StataCorp LP, TX).

3. Results

A total of 211 patients were screened and deemed suitable for inclusion, while 191 patients contributed to the main analysis and randomised to either intervention or placebo. The main reasons for dropout ($n = 12$) were lack of compliance to the web-based system or patient preferences due to worsening of health-related conditions. Initially, 113 patients were assigned to the intervention arm, while 86 patients were randomised to the placebo arm. A total of 191 patients were crossed-over and completed at least 90 days of follow-up. The mean follow-up time in the trial was 140 days.

Most of the patients were males (75%) and the mean age was 65 years, see Table 1. The majority of the patients had atrial fibrillation ($n = 103$) as indication for warfarin treatment, while 39 patients had venous thromboembolism as primary indication. The average dose of warfarin (based on an average of 14 days steady-state warfarin intake before study start) was 5.5 mg/day.

Table 1
Patient characteristics.

Variable	Number (%)
Number of participants	191
Mean age (SD)	65 (8.2)
Sex, male	144 (75%)
Indication for treatment	
Atrial fibrillation	103 (54%)
Venous thromboembolism	39 (20%)
Heart valve replacement	41 (22%)
Other*	8 (4%)
Years in VKA treatment (SD)	2 (1.6)
Target INR range	
2.0 to 3.0	178 (93%)
2.5 to 3.5	13 (7%)
Average warfarin dose (IQR)	5.5 mg/day (5.0–7.5)

SD: Standard deviation. VKA: Vitamin K-antagonist. INR: International normalised ratio. IQR: Interquartile range.
* Sinus thrombosis; myocardial infarction/aneurism; stroke; polycythaemia.

3.1. Primary study outcomes

The TTR was overall comparable in the two trial arms during the study period, see Table 2. The intervention arm achieved a TTR of 81.6, while the placebo arm attained a TTR of 80.9 (difference [intervention arm minus placebo arm]: 0.67 (95% confidence interval [CI] −2.93 to 4.27). The number of INR measurements were 11 (approximately once every 8 days) in each randomisation allocation and was similar in the two arms, i.e. a difference of 0.03 (−0.49 to 0.54); while the number of days contributed in the study period was markedly higher in the intervention group: 19.57 (15.90 to 23.24), mainly due to the block randomisation design. The logVGR was different in the two study arms: 0.30 (0.14 to 0.47), favouring the placebo arm in terms of lower logVGR according the method of Fihn's.

The primary result of comparable TTR in the two trial arms was observed across all stratified analyses including warfarin dosing regimen (low; middle; high), INR target range, and initial randomisation allocation [Table 2]. The intervention arm achieved a higher TTR in the high dosing regimen compared to the low dosing regimen, 84.4 and 74.9, respectively. We found no difference in TTR according to initial randomisation allocation, which indicated that a learning bias was not present in this study.

3.2. Additional analysis

The number of 'non-compliant' registrations (disagreement with dosage suggestion) was different in the two trial arms, average 15% per participant in the intervention arm and 6% in the placebo arm. As described previously, this triggered additional analyses to investigate the *reason* for non-compliance as well as the *consequence* (i.e. effect on following INR measurement). Non-compliance was specifically calculated as a difference between suggested and taken dose of warfarin higher than 15% of the suggested dose. Hereby we deemed discrepancies <0.8 mg/day (in average) to be compliant. Of note, in this analysis we excluded patients who underwent bridging ($n = 5$), or patients who preferred a different therapeutic target ($n = 3$) than the primary indication (e.g. an atrial fibrillation patient preferred a target range of 2.5 to 3.5 rather than 2.0 to 3.0).

In Table 3 we focused on the period prior to an INR measurement leading to potential non-compliance – i.e. the '*reason*' for a non-compliant registration. The three panels cross tabulates the frequency of non-compliance based on the previous-to-current INR value (trend or the direction of change) minus the target INR value and the suggested changes in weekly dose categorized as 1) *taken dose > recommended dose*; 2) *no dose discrepancy*; and 3) *taken dose < recommended dose*. In 95.6% of the cases when the INR values were within target range, no dose discrepancy was observed in the placebo arm. When the INR values had a trend moving below target range, 11.4% of the cases the dose taken was higher than the recommended dose. The dose was left unchanged in the majority of these cases (88.6%), which reflects some conservatism towards dosage changes in the participants. For the intervention arm a somewhat similar pattern was observed. However, when a trend of increasing INR values was observed (1 or more above INR range), the taken warfarin dose was higher than the algorithm-suggested dose in 22.4% of the cases. Correspondingly, in 27.8% of the cases, when the trend of changes was towards 0.5 below INR target range, the taken dose was below the algorithm-suggested warfarin dose.

Table 4 shows the '*consequence*' on the following INR value relative to the chosen dose compliance or non-compliance. The INR values are grouped in five levels as being in therapeutic range, being 0.5 above or below, and >1 above and below. For the placebo arm, there was no

Table 2
Study outcomes according to trial study arms.

		Control	Intervention	Difference, 95% CI
Days in follow-up		60.7 (26.6)	80.3 (16.4)	19.57 (15.90 to 23.24)
Number of INR measurements		11.3 (2.8)	11.3 (3.0)	0.03 (−0.49 to 0.54)
TTR (SD)		80.9 (24.0)	81.6 (18.5)	0.67 (−2.93 to 4.27)
logVGR		−3.7 (1.2)	−3.4 (0.9)	0.30 (0.14 to 0.47)
Warfarin dosing regimen				
Low (n = 42)	TTR	82.3 (22.3)	74.9 (23.8)	−7.5 (−16.12 to 1.23)
	logVGR	−3.7 (1.1)	−3.2 (0.9)	0.53 (0.20 to 0.86)
Middle (n = 111)	TTR	80.0 (25.0)	83.1 (17.2)	3.18 (−1.42 to 7.77)
	logVGR	−3.7 (1.3)	−3.5 (0.9)	0.20 (−0.03 to 0.43)
High (n = 38)	TTR	82.1 (23.2)	84.4 (13.4)	2.31 (−5.29 to 9.91)
	logVGR	−3.5 (1.3)	−3.1 (0.9)	0.34 (−0.10 to 0.79)
INR target range				
2.0–3.0 (n = 178)	TTR	80.5 (24.3)	81.7 (18.4)	1.22 (−2.52 to 4.97)
	logVGR	−3.5 (1.0)	−3.4 (0.9)	0.13 (−0.01 to 0.28)
2.5–3.5 (n = 13)	TTR	87.2 (18.0)	80.3 (20.7)	−6.92 (−20.21 to 7.04)
	logVGR	−3.5 (1.0)	−3.0 (1.0)	0.46 (−0.12 to 1.04)
Initial randomisation allocation				
Control first (n = 84)	TTR	80.5 (26.3)	80.4 (17.6)	−0.10 (−6.30 to 6.09)
	logVGR	−3.6 (1.3)	−3.3 (0.8)	0.35 (0.04 to 0.67)
Intervention first (n = 107)	TTR	81.2 (22.0)	82.5 (19.1)	1.27 (−3.02 to 5.56)
	logVGR	−3.7 (1.1)	−3.4 (1.0)	0.26 (0.01 to 0.52)

INR: International normalised ratio. TTR: Time in therapeutic range. SD: Standard deviation. VGR: Variance growth rate. CI: Confidence interval.

clear consistency between the dose compliance or non-compliance and the effect of the following INR value. A similar non-consistency between dose selection and consequence on INR value was observed in the intervention arm.

In general, as displayed from the results presented in Tables 3 and 4, we were not able to identify a clear pattern of behaviour from the participants according to neither *reason* nor the *consequence* in relation to non-compliance of warfarin dosage suggestions.

4. Discussion

In this randomised controlled, cross-over designed trial we observed similar TTR in routine PSM care and in patients who received an additional warfarin dosage suggestion. The INR variability expressed as the logVGR was slightly higher in the intervention group, indicating that the serial INR values fluctuated more compared to that of the placebo group. We also observed a higher degree of 'non-compliance' to dosage suggestion in the intervention group, but no pattern of the reason for this behaviour could be detected.

In general, the TTR in both groups was very high (>80%) indicating excellent quality of the OAC treatment. The patients included for randomization were all in steady-state warfarin treatment, and were educated in PSM of the treatment. In this education programme, they were instructed to be reluctant towards changes in dose despite INR values being out of target range. The main reason for this was to avoid an 'oscillating' effect, but instead await dose changes until a clear trend in serial INR values was observed [20]. In the current study, the included patients had good access to clinical sparring with trained caretakers in OAC treatment. Specifically, they were instructed to make telephone contact or use online communication (standard email or message service in CoaguChek Link) if assistance in warfarin dosing was required. We were not able to investigate if use of the algorithm-based dosage suggestion improved the TTR compared to before commencing the study.

Indeed, high quality of OAC treatment reflected by TTR is pivotal to reduce the risk of bleeding and thromboembolic events [3]. We have previously shown in retrospective investigations that the developed model could potentially improve TTR [13]. However, due to the retrospective nature of these studies, it was not possible to ascertain if the magnitude of these warfarin dose suggestions would be too high/low and thus cause risks of serious adverse events. We therefore conducted this trial in a selected cohort of well-trained OAC-PSM patients to minimize safety aspects, as the patients per se are reluctant to (large) dose changes. Clearly, the proposed algorithm is not to be used in an excellent quality setting in the future. However, as we obtained positive results in this prospective trial, it appears safe to investigate if the model may perform similarly in a setting with lower OAC quality, e.g. in general practice. In routine OAC settings in general practice, the frequency of INR measurement are often lower compared to PSM settings, and the treating physician may have limited expertise in optimal dose adjustments of warfarin to maintain stroke prophylaxis.

Use of coumarin dosage suggestion is being used in different settings to either maintain INR target and/or to provide guidance in dosing to obtain steady-state treatment. Computer aided dosing has been shown to make dosing easier and more efficient in the Swedish national quality registry, Auricula [21]. This system is based on >700 (hidden) dosing rules. A commercially available system (DAWN AC) has been tested in a multicentre setup and improved the TTR from 63.4% to 66.8% during the investigation period [15]. However, in a randomised comparison between a simple decision rule for warfarin dosing vs the DAWN AC, the maintenance control of INR was similar [22]. In general, most investigations on use of computer aided coumarin dosing has been shown to be safe and effective as well as cost-effective [14,23,24].

The quality of OAC treatment with vitamin K-antagonists is often measured by TTR. However, it has been shown that TTR correlates

Table 3
Cross-tabulated '*reason*' for non-compliance to a warfarin dosage suggestion for the two trial arms. Each cell indicates the frequency of compliance (no dose discrepancy) or non-compliance according to changes from previous-to-current INR-deviation relative to INR-target – i.e. the trend of change in INR values.

	Taken > recommended	No dose discrepancy	Taken < recommended	INR measurements
Placebo arm				
1 or more above	0%	70%	30%	54
0.5 above	2.0%	94.0%	4.0%	151
Within range	2.2%	95.6%	2.2%	1251
0.5 below	11.4%	88.6%	0%	70
1 or more below	60.0%	40.0%	0%	5
Intervention arm				
1 or more above	22.4%	65.7%	11.9%	67
0.5 above	2.2%	91.2%	6.6%	226
Within range	2.5%	86.1%	11.4%	1637
0.5 below	9.2%	63.0%	27.8%	119
1 or more below	50.0%	50.0%	0%	6

Table 4
Cross-tabulated '*consequence*' of non-compliance to warfarin dosing suggestion for the two trial arms. Each cell indicates the frequency of compliance (no dose discrepancy) or non-compliance to dose suggestion and the effect on the following INR measurement.

	1 or more above	0.5 above	Within range	0.5 below	1 or more below	INR measurements
Placebo						
Taken > recommended	0%	18.4%	68.4%	13.2%	0%	38
No dose discrepancy	2.5%	10.2%	82.9%	4.4%	0.4%	1378
Taken < recommended						
Intervention						
Taken > recommended	5.6%	8.5%	77.5%	7.0%	1.4%	71
No dose discrepancy	4.0%	11.3%	79.2%	5.4%	0.1%	1639
Taken < recommended	2.3%	7.1%	80.1%	8.5%	0.9%	224

poorly with clinical endpoints [25]. In the current study, we did not investigate if the algorithm dosing resulted in fewer clinical events. Nevertheless, we acknowledge that TTR as a surrogate of OAC quality may not directly translate into clinical value. Other groups have reported that INR variability is also an important measure when assessing quality of OAC treatment. Razouki et al. investigated the addition of logVGR to predict adverse events in 40,404 anticoagulated patients [26]. With an overall TTR of 64% they observed a log INR variability of −3.41. They concluded that INR variability adds important information on top of TTR when predicting adverse events. The reported INR variability from Razouki et al. is comparable to our results [Table 2], while we obtained a markedly higher TTR. One explanation of the weak correlation between variability and TTR could be the frequency of measurements and the different observation time between the two studies. Naturally, we were not able to evaluate if the INR variability could have been lower in our study, if the patients were required to comply with the warfarin dosage suggestions.

Our study has some limitations that should be emphasized. The online system used in the study was affected by periodically malfunction during the first three initial weeks. The reason for the malfunction was detected and corrected, and sensitivity analyses by excluding this period was performed but did not affect our results [data not shown]. We imposed an intention-to-treat analysis on the main outcome. Hence, we did not assess if the comparisons was affected by bridging periods or patient's target preferences. The non-compliance option in the study design caused us to be unable to determine if the algorithm performs optimal in all dosage regimens and levels of INR values. As seen from the additional analyses [Tables 3 and 4], we were therefore not able to evaluate any reasons of non-compliance to dosage suggestions. We only included long-term VKA treated, steady-state PSM patients in this study, which could impose a selection bias. As such, our results of excellent OAC quality by use of the dosing algorithm could be hypnotised not apply to other settings with lower (baseline) OAC quality.

In conclusion, we found no difference between the two trial-arms in a high quality OAC setup, however in general, the model performed similarly as to routine PSM care. We could not assess if higher quality of treatment was obtainable in patients were mandated to follow algorithm dosing suggestions. Further studies are needed to assess if the model is a feasible tool for patients managed in settings with expected overall lower quality of OAC treatment with warfarin.

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TBL has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim and has been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Takeda and Boehringer Ingelheim. PBN: Speaker for Boehringer Ingelheim. Other authors: None declared.

Role of the authors

All authors made important contributions to all processes of the study and the manuscript preparation. PBN: This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. PBN designed the study; undertook data collection; analysed the data; wrote the first draft of the manuscript. SLC designed the study; analysed the data; revised the manuscript. MdvM designed the study; undertook data collection; revised the manuscript. TBL undertook clinical interpretation of the results; made critical revision of the intellectual content; revised the manuscript.

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