OUTPATIENT MANAGEMENT OF ORAL ANTICOAGULATION THERAPY IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

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Abstract

Due to heightened risk for thromboembolic complications, nonvalvular atrial fibrillation (NVAF) presents an absolute indication for long-term oral anticoagulation therapy. This was an observational, analytical, randomised, one-year clinical study, conducted in the Blood Transfusion Institute Sarajevo, Bosnia & Herzegovina. The aim of this study was to present the oral anticoagulation treatment in terms of International normalised ratio (INR) monitoring and warfarin/acenocoumarol dose titration in 117 patients with NVAF. INR values, the doses of warfarin and acenocoumarol, as well as the tendency and adequacy of their changes were monitored. Percentages of the therapeutic INR values were 51,77% and 53,62%, subtherapeutic 42,84% and 35,86%, and supratherapeutic 5,39% and 10,53% for the warfarin and acenocoumarol treatment, respectively. The average total weekly doses (TWD) which most frequently achieved the therapeutic INR values were 27,89±12,34 mg and 20,44±9,94 mg, for warfarin and acenocoumarol, respectively. The dose changes with the INR values 1,7 or lower/3,3 or higher were omitted in 13,46% and 15,63%, and with the INR values 1,8-3,2 were noted in 8,62% and 13,48% of all the check-up visits in the warfarin and acenocoumarol group, respectively. The annual dose changes were noted in 24,65% and 31,41%, and the daily dose changes in 74,43% and 73,36% of all the check-up visits of warfarin and acenocoumarol group, respectively. We can conclude that the management of the oral anticoagulation treatment in our country is in accordance with the relevant recommendations, but with the present tendency toward underdosing and unnecessary frequent dose changing.

KEY WORDS: nonvalvular atrial fibrillation, warfarin, acenocoumarol, INR, dosing

Introduction

Vitamin K antagonists, warfarin and acenocoumarol are oral anticoagulant drugs currently available for the long-term prevention of stroke in patients with non-valvular atrial fibrillation (NVAF). In due to height-ened risk for thromboembolic complications, these patients suffer from stroke 5,8 times more often than people without arrhythmia (1). Numerous studies have shown that warfarin and acenocoumarol are un-derused drugs in patients with atrial fibrillation (2, 3). The latest recommendations for wide use of oral antico-agulation drugs for patients with NVAF, based on the control of INR values, have been published by Ameri-can College of Chest Physicians (ACCP, 8th Edition) (4, 5, 6). The anticoagulation effects are measured by the prothrombin time (PT), which is according to the recommendation of the World Health Organization stated as International normalised ratio (INR) (7). The target INR range (2,0-3,0) is achieved in only 50-60% of patients (8). The dosing is regularly adjusted to the age of the patient, gender, clinical variables which influ-ence mechanism and metabolism of the drug, and the individual risk of haemorrhage and thrombosis (9). Ac-cording to the latest studies, two genes mutation–gene for cytochrome P450 (CYP2C9 and CYP4F2) and gene for vitamin K epoxide reductase complex (VKORC1) are responsible for one third of all variations of the to-tal weekly doses (TWD) of warfarin (10, 11, 12, 13). Management of the anticoagulation treatment is very complex due to a number of issues such as (14): the narrow therapeutic index, the tendency toward un-predictable INR fluctuations, the significant interin-dividual and intraindividual variations in the patients' response, the regular obligatory laboratory testing of INR and the dose adjustments. Therefore, the aim of this study was to present the oral anticoagulation treat-ment in terms of the INR monitoring and warfarin/acenocoumarol dose titration in patients with NVAF. The analysis of the relevant databases has not provided any information with regards to whether this kind of problem has ever been addressed and researched in our country. This is the first study of the manage-ment of the oral anticoagulation treatment in B&H.

Patients and Methods

Study design
This was an observational, analytical, randomised, bidi-rectional (prospective and retrospective), one-year clini-cal study, conducted in the Blood Transfusion Institute Sarajevo, Bosnia & Herzegovina. Study was conducted according to the GCP (Good Clinical Practise), GLP (Good Laboratory Practise) and local ethical principles. All patients who were using warfarin/acenocoumarol therapy and were monitored by medical team in this Institute were eligible. The patient inclusion criteria were, as follows: the age of 40-80, diagnosed NVAF, CHADS2 index score ≥2 (12), the planned long-term treatment with warfarin/acenocoumarol started at least 2 months prior to the observational period and a signed informed consent. Diagnose of NVAF, indica-tion for oral anticoagulant treatment and target INR range were determined in competent specialised in-stitutions and adequately documented by medical records. In order not to be biased, included patients were separated by the method of centralized computer randomisation into two parallel groups of 60 patients. Groups were homogenized according to the antico-agulation therapy (warfarin/acenocoumarol) as well as the gender and age. The duration of the observational period was 12 months. Retrospectively, the previous 6 months from the day of screening were observed, and prospectively, the following six months. The INR values, the doses of warfarin and acenocoumarol, as well as the tendency and adequacy of their changes were monitored. The control visits were on a monthly basis, or even more frequently, whenever necessary.

Data collection and analysis
Anamnestic data collected at screening visit (age, gen-der, weight, height, CHADS2 index score, comorbodi-ties, smoke and alcohol use) are gathered in a study sheet. Data gathered in the especially designed Patient's Diary were as follows: dates of measurements, INR values and the daily warfarin/acenocoumarol doses, collected via retrospective chart review of monthly pa-tient organisers (retrospective data for 6 months prior to enrolment) and prospectively for the following six months. In prospective part of study, additional data (the adherence to the treatment, temporary or per-manent interruption of the treatment, and the use of concomitant drugs) were assessed and collected. The data were collected in the Microsoft Office Excel da-tabase and statistically analysed by MedCalc for Win-dows program, Version 10.1.2.0 (MedCalc Software, Mariakerke, Belgium). Descriptive statistical analysis presented as arithmetic mean value and standard de-viation (SD) was performed. Quality of treatment was expressed as percentages of therapeutic, subthera-peutic and supratherapeutic INR values, and average doses were expressed as arithmetic mean value ± SD.
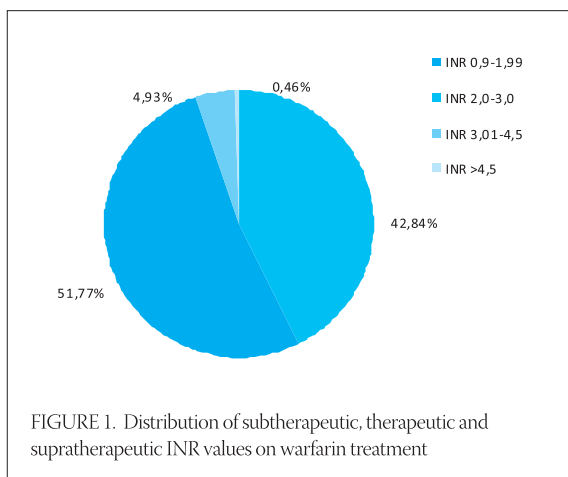
FIGURE 1. Distribution of subtherapeutic, therapeutic and supratherapeutic INR values on warfarin treatment
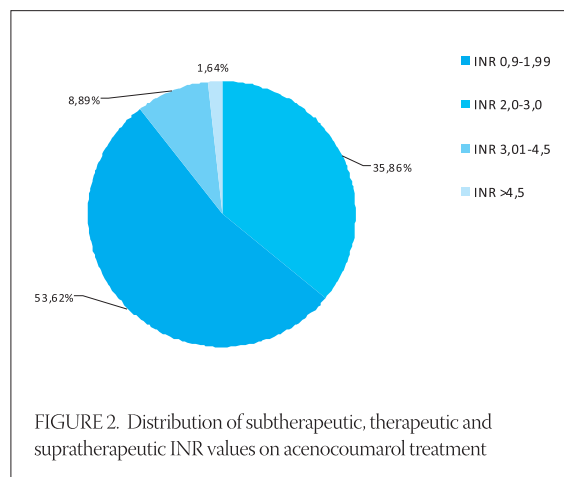

FIGURE 2. Distribution of subtherapeutic, therapeutic and supratherapeutic INR values on acenocoumarol treatment

INR measurement

In order to measure INR values, the blood samples were taken in the morning, by the venepuncture of the cubital vein. The blood has been taken into a 3,2 sodium citrate test-tube (Vacutainer, Becton Dickinson, Great Britain). All INR measurements were conducted in the same laboratory, on the fresh plasma obtained from blood samples centrifuged at room temperature at 3000 g for 15 minutes (Laboratory centrifuge CENTRIC 322A, Slovenia). The automatic haemostasis scanner were used (CD-X, Switzerland), with liquid calcium rabbit thromboplastin (DiaPlastin-E, ISI=1,1). The measurement of INR values was done according to the following formulae: INR = (PT ratio) ISI (15).

Dosing

At each visit, The Patient's Diary was filled with the new INR value and prescribed dose regimen until the next scheduled visit, as follows:

— INR values in therapeutic range → dose is not changed → next visit in a months

— INR values 1,8-3,2 → dose is not changed → next visit in 7 days

— 1,7≥INR≥3,3 → dose is changed → next visit in 3 days

RESULTS

The total of 117 patients were monitored; 60 patients were treated with warfarin and 57 with acenocoumarol. Three patients from the acenocoumarol group were excluded from study in due to changed anticoagulation drug. Within one year of study, total of 649 and 608 INR values were measured, with 10,82±1,65 and 10,67±1,89 INR measurements per patient in warfarin and acenocoumarol group, respectively. The average INR values were in the both therapeutic groups within the therapeutic range (2,0-3,0), in warfarin group 2,12±0,61 and in acenocoumarol group 2,26±0,79. In respect to overall quality of treatment, percentages of the measured therapeutic INR values were 51,77% and 53,62%, subtherapeutic 42,84% and 35,86%, and supratherapeutic INR values 5,39% and 10,53%, for the warfarin and acenocoumarol treatment, respectively (Figures 1 and 2). 72,3% of all the subtherapeutic INR values in the warfarin, and 69,72% in the acenocoumarol group had the values of 1,5-1,99. Out of all supratherapeutic INR measurements, 57,57% in the warfarin
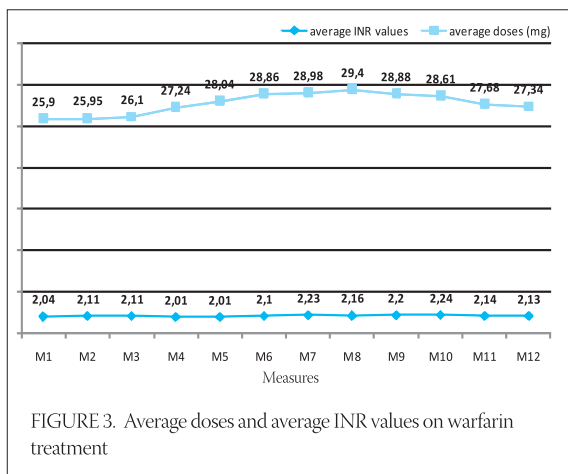

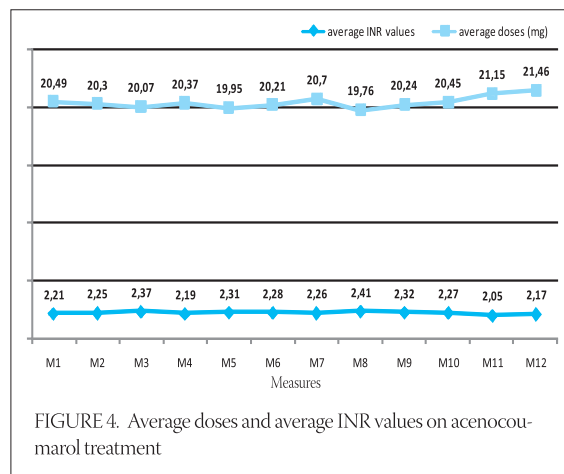FIGURE 3. Average doses and average INR values on warfarin treatment

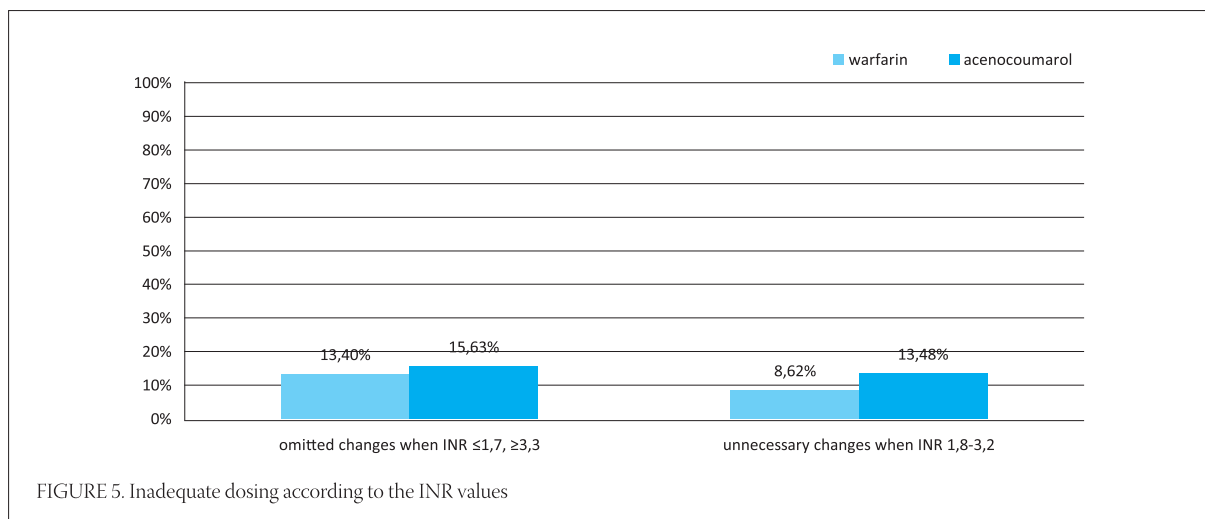FIGURE 4. Average doses and average INR values on acenocoumarol treatment

FIGURE 5. Inadequate dosing according to the INR values

group, and 56,45% in the acenocoumarol group had the values up to 3,5. The supratherapeutic states (INR>4,5) were insignificantly more frequent in the acenocoumarol group (1,64% of all measurements, compared to the 0,46% in the warfarin treatment). The average daily dose of warfarin was 3,72±1,7 mg, and of acenocoumarol 2,84±1,66 mg. The values of warfarin TWD were from the minimum of 3,25 mg up to 68,25 mg, and of acenocoumarol from the minimum of 3 mg up to 68 mg. The average total weekly dose of warfarin, which most frequently achieved the therapeutic INR values was 27,89±12,34 mg, and of acenocoumarol 20,44±9,94 mg. The changes in the warfarin and acenocoumarol dosing, when the INR values were 1,7 or lower/3,3 or higher were omitted in 13,40% and 15,63% of all the check-up visits, respectively (Figure 5). The changes in the dosing when the INR values were 1,8-3,2 were noted in 8,62% of the check-up visits in the warfarin, and in 13,48% of the check-up visits in the acenocoumarol group (Figure 5). Dosing changes on an annual basis were 24,65% (160 changes of all 649 check-up visits) in the warfarin,

and 31,41% (191 changes of all 608 of all the check-up visits) in the acenocoumarol group (Figure 6). The percentages of the daily changes were 74,43% (483 changes of all 649 check-up visits) and 73,36% (446 changes of all 608 of all the check-up visits) of warfarin and acenocoumarol doses, respectively (Figure 6).

Discussion

Homogenisation of both therapeutic groups in our study, based on the number of patients, gender and age, contributed to the reliability of our results. The average INR values in the therapeutic groups were within the target range (2,0-3,0), but with the clear tendency toward low therapeutic limit (2,12±0,61 and 2,26±0,79). Analysis of overall quality of treatment showed that portion of therapeutic INR values in this study was 51,77% and 53,62% in warfarin and acenocoumarol group, respectively. Similar data has been published with the therapeutic INR values achieved in 55-60% of all measurements in specialized anticoagulation clinics (16). Our results concerning the total quality of the antico-
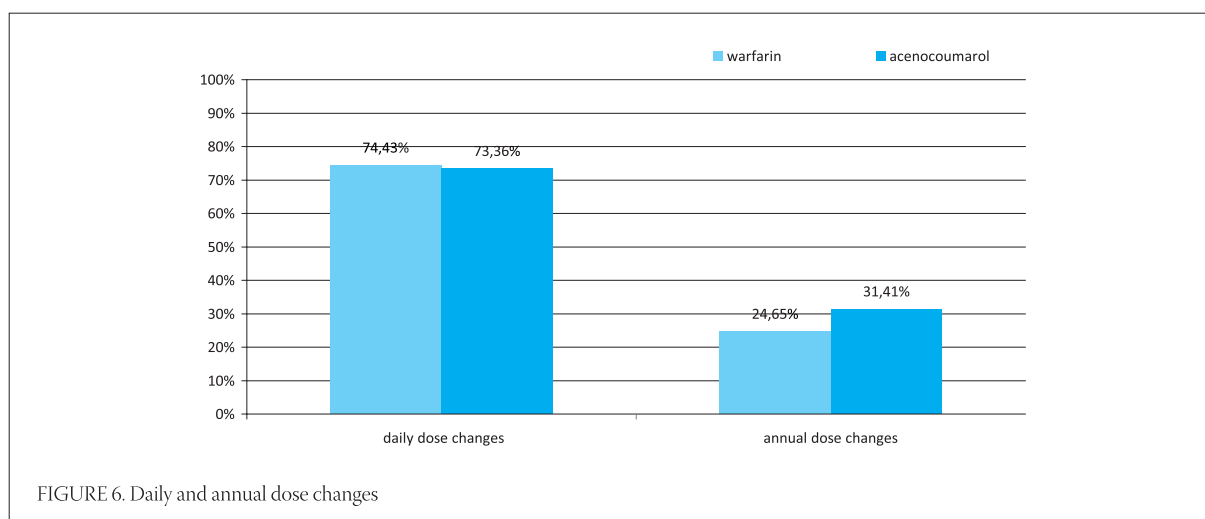

FIGURE 6. Daily and annual dose changes

agulation treatment was lower compared to the results of the most of other studies with therapeutic INR values achieved in two thirds of all measurements (5,17,18). Mostly dominating non-therapeutic INR values in our study were the subtherapeutic values indicating a clear tendency toward keeping the INR values closer to the lower therapeutic limit (Figures 1 and 2). Influence of low compliance, as one of the most common reasons for the subtherapeutic INR values were excluded in this study, since our patients have shown almost absolute compliance and adherence to the treatment. That confirms the results of other studies that despite the good compliance, a significant number of patients have an inadequate treatment (19). The influence of the genetic and other factors (co-medications) can be considered as some of the reasons for the instability of the treatment, but according to our results the main reason is underdosing and inadequate dose changing. Although the subtherapeutic values were more common, the supratherapeutic states (INR>4,5) were also noted in this study. More frequent supratherapeutic states in the acenocoumarol treatment can be explained by the fact that acenocoumarol has a stronger effect, so even lower doses can lead to higher INR values, compared to those of warfarin. Similar data has been published by other studies (20, 21). The daily doses of warfarin to achieve the therapeutic INR values are usually from 0,5 to 20 mg (22). Analysis in this study showed that the average daily doses of warfarin (3,72±1,7 mg) and acenocoumarol (2,84±1,66 mg) were in recommended range but with the tendency toward low therapeutic dose level. Taking into account that the average INR values in the both therapeutic groups were within the therapeutic range, with more than a half therapeutic INR values, we can suggest that majority of our patients achieved the therapeutic INR values with low warfarin doses. This warfarin doses were significantly lower and acenocoumarol doses were slightly higher compared to the SPORTIF-III study (5,03±1,99 mg of warfarin, and 2,5±1,3 mg of acenocoumarol) (17). Since the average ages of our patients were 66 years in warfarin and 68 years in acenocoumarol group, findings confirmed from previously published literature (23, 24) that elderly patients need smaller TWDs of these drugs, can be taken as a relevant explanation for the occurrence mentioned above. Due to the homogenisation of the group and the subsequent elimination of other significantly important influences, we can also conclude that the other reasons for low dose levels of warfarin in this study can be either CYP2C9 polymorphism with genetically higher sensitivity to warfarin or exposition to interacting co-medications which are

known to increase the anticoagulation effects. Approximately 10-20% of patients who have 1 or 2 polymorph allele for CYP2C9, can achieve the therapeutic INR value with the dosing of 1,5 mg/day (25). The analysis of the average INR values and related average TWDs of warfarin has shown, that during the winter, the maintenance of the stable INR values requires higher doses of warfarin (Figure 3). It has been mentioned in earlier medical literature as the seasonal variations in the oral anticoagulation treatment (26). We did not notice any effects of the seasonal variations in the acenocoumarol treatment (Figure 4). The ratio of average weekly doses of warfarin and acenocoumarol which needs to be taken into consideration when thinking about a possible change of treatments, in our study was 1,36. It means that approximately 1,3 times higher warfarin dose is needed in the same patient than those of acenocoumarol. It is significantly lower transition factor compared to 1,8 and 2,18, results from the other studies (17, 27).

The doses should be adjusted so that the total dose from the previous week is increased or decreased for 5-20% (28). The results of our study have shown that, in order to move from the subtherapeutic (0,9-1,99) to therapeutic (2,0-3,0) INR values, a similar increase of 20,94% of the TWD of warfarin is required. Expressed in milligrams, the change mentioned above was around 5,85 mg of warfarin. The most of INR values (72,3%) used in the evaluation of the described necessary changes of warfarin dosing were 1,5-1,99 INR values. Based on the same data concerning acenocoumarol, and according to the results of this study, in order to move from the subtherapeutical to therapeutical INR values, the weekly dose of acenocoumarol should be increased for 9,05%, which in this study was around 1,85 mg. We examined the methods of the dosing titration in this study taking into consideration the study conducted by Rose et al. (29) and their suggestion that dosing should ideally be changed only in cases with the INR values 1,7 or lower/3,3 or higher. These authors suggest that in that case 74% of INR values will be possible to achieve within the therapeutic range. Both kind of dosing changes, when the INR values were 1,7 or lower/3,3 or higher and when the INR values were 1,8-3,2 observed in our study (Figure 5), represent an inadequate dosing titrations, each omitting and frequent, unnecessary changes. That unnecessary, less important changes were sporadic. Frequent underdosing, inadequate dose titration in terms of each omitted and unnecessary dose changes in patients with NVAF can be the main reason for frequent suboptimal INR values.

Even though it is recommended to keep the dosing scheme as consistent as possible – in order to obtain the stable INR values and to avoid or lower the patients' confusion (28, 30) – in this study, we noted down frequent changes (annual and daily) of the dosing of warfarin and acenocoumarol. Our results showed frequent dosing changes on an annual basis – in 24,65% and 31,41% of all the check-up visits in the warfarin and acenocoumarol treatment, respectively (Figure 6). The most frequent changes of the acenocoumarol doses can be explained by the frequent supratherapeutic INR values, compared to the treatment with warfarin – where doctors, due to their bigger fear of haemorrhage than of thrombosis, are more rapid and agile in deciding to decrease the dosing of the drug. Amián et al. (31) noted even more frequent annual dose changes in 27,5% and 33,62% of the check-up visits in the warfarin and acenocoumarol group, respectively. Fihn et al. (32) described annual acenocoumarol dose changes in 62% of the check-up visits, which is higher than in all other noted or published results so far, and which also explains the percentage of only 38% of the therapeutic INR values in this study. As Sanfelippo et al. (33), we also suggest to continue with the same dose without a single dose change and to repeat test in about two weeks. Marco et al. (34) suggested that patients, who take unequal doses of acenocoumarol every day, have significant fluctuations of INR values. The fact that the percentages of the daily changes of warfarin and acenocoumarol doses in our study were 74,43% and 73,36%, respectively (Figure 6), can be the reason for the lower INR quality noted in our study. According to numerous other studies, the therapy with oral anticoagulation drugs is often suboptimal, usually due to the doctors' fear of haemorrhage and them being too cautious when it comes to the dosing (3, 17, 18). The evaluation of the oral anticoagulation treatment in our study has clearly shown the tendency toward frequent dose changes, especially frequent daily dose changes, to underdose and to keep the INR values in low therapeutical levels.

Conclusion

Monitoring of the oral anticoagulation treatment in this study is in accordance with the relevant ACCP recommendations, but with the present tendency toward underdosing. As expected, this study suggests that the way of warfarin/acenocoumarol dosing titration may have significant influence on quality of oral anticoagulation treatment. Frequent underdosing, inadequate dose titration in terms of each omitted and unnecessary annual and daily dose changes in patients with NVAF can be the main reason for frequent suboptimal INR values. In order to maintain better INR monitoring we hope that, in near future, we will encounter models such as the computerised dosing and anticoagulation self-management in B&H.

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