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RESEARCH ARTICLE

Evaluation of the four mg warfarin initiation dose in patients with cardiovascular disease

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Abstract

Background: Warfarin is the most widely used oral anticoagulant for the prevention of stroke in patients with cardiovascular disease. In Indonesia, validation of the initiation dose of warfarin has never been carried out. **Objective**: To evaluate the efficacy and safety of 4 mg warfarin initiation dose in achieving therapeutic targets. **Methods**: It was a prospective observational study involving hospitalised and ambulatory patients administered a 4 mg warfarin initiation dose between days one and three. On day four, the INR was measured for three to seven days. Subsequently, the initiation dose was adjusted to the therapeutic INR. The INR level was measured every seven days until patients achieved therapeutic INR twice. **Results:** A total of 14 patients were included in this study, with a mean age of 62 years. The most common indication for using warfarin was non-valvular atrial fibrillation (85.7%), with a CHA2DS2-VASc score between one and three and a HAS-BLED score ranging from zero to two. The median time to achieve therapeutic INR was 22.2 days, and the predictive value of the day four INR for determining the maintenance dose had an r^2= 0.77. **Conclusions:** The initiation dose of 4 mg warfarin effectively achieved therapeutic INR within an acceptable time.

Introduction

Warfarin is the most widely used oral anticoagulant for the prevention of stroke in patients with cardiovascular disease, specifically atrial fibrillation (Chang *et al*., 2018). However, variations in the response of each patient with warfarin require careful monitoring to determine the initiation dose (Heneghan *et al*., 2010). The initial administration of warfarin to patients who receive therapy for the first time consists of an initiation dose, followed by a maintenance dose after the therapeutic target is achieved (Sridhar *et al*., 2014). In the initiation stage, selecting the right dose is crucial to maintain patients within their therapeutic range (Heneghan *et al*., 2010). Various studies proposed initiation doses ranging from ten milligrams, five milligrams and three milligrams (Sabry *et al*., 2022), considering lower doses such as 2.5 mg and one milligram for geriatric patients (Baglin *et al*., 2006). Consequently, the mean dose of warfarin initiation dose ranges from four to five milligrams daily for approximately two weeks, which allows patients to achieve the target INR (Sridhar *et al*., 2014; Gage *et al*., 2000; Siguret *et al*., 2005). In Indonesia, there is no protocol regarding warfarin initiation dose, which is a determinant of achieving efficient therapy and preventing the risk of excessive bleeding in patients. This study aimed to evaluate the application of the 4 mg warfarin initiation dose protocol to achieve the therapeutic target within the Indonesian population.

Methods

Design

This prospective observational study was carried out at Airlangga University Hospital, Surabaya between April

and October 2022. Data sources included medical records, laboratory examinations, and data collection sheets from patient interviews. Inclusion criteria were patients who were hospitalised or attended the cardiac polyclinic and had received oral anticoagulant warfarin for the first time with a 4 mg warfarin initiation dose at Airlangga University Hospital. However, patients with a history of bleeding or those who had previously used anticoagulant drugs were excluded. All patients who fulfilled inclusion and exclusion criteria between April and October were included as samples.

Assessment

All patients received 4 mg of warfarin on days one to three, and INR values were measured on day four to determine the next dose based on the warfarin initiation dose algorithm (Table I). Subsequently, the dose was adjusted according to the final INR level until each patient reached therapeutic INR. To monitor the process, the INR level was measured every seven days until patients reached the therapeutic target twice.

Data analysis

A normality test was conducted using Shapiro-Wilk. All statistical analyses were conducted using the JASP software.
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Ethical approval

The Research Ethics Committee of Rumah Sakit Universitas Airlangga approved this study under ethics approval number 041/KEP/2022.

Table I: Warfarin initiation dose algorithm

Day	INR value	Dose (mg)
Day 1	Do not measure	4
Day 2	Do not measure	4
Day 3	Do not measure	4
Day 4	< 1.3	5
	1.3 or 1.4	4
	1.5 or 1.6	3
	1.7 or 1.8	2
	1.9 or 2.4	1
	≥ 2.5	Measure INR daily and stop giving warfarin until INR <2.5, then give 1 mg

INR: International Normal Ratio

Results

This study included 14 screened from 17 patients who met the inclusion criteria. The patients were rejected because they had previously received anticoagulants.

The mean age of this study was 62 years. The most common indications for the use of warfarin were in patients with non-valvular atrial fibrillation (85.7%). Furthermore, the two most prevalent comorbidities were hypertension and heart failure (21.4%). The highest CHA2DS2-VAS score observed was two, namely 57.1% (eight patients), and the most common HAS-BLED found was one, representing 50% of the participants (seven patients). The additional demographic characteristics of the patients are listed in Table II.

Table II: Demographic and patient characteristics

Demographic and patient characteristics	N	%
Age means	62 (45-79)	
BMI means	25 (18.4-30.1)	
Gender		
Man	6	42.9
Woman	8	57.1
Warfarin indications		
Non-valvular atrial fibrillation	12	85.7
Valvular atrial fibrillation		
Heart valve disease		
Deep vein thrombosis		
Pulmonary embolism		
Other	2	14.3
Comorbidities		
Hypertension	3	21.4
Heart failure	3	21.4
CAD	1	7.1
Strokes/TIAs	1	7.1
CHA2DS2-VASc score		
0	0	
1	2	14.3
2	8	57.1
≥ 3	3	21.4
HAS-BLED score		
0	5	57.1
1	7	50
2	2	14.3
≥ 3	0	
Potential interaction		
Aspirin	1	7.1
Clopidogrel	1	7.1
Aspirin + clopidogrel	1	7.1
Blood Supplements	1	7.1

In this study, adjustments were made after administration of the predicted maintenance dose until the therapeutic target was achieved. Table III shows that the mean dose adjustments among 14 patients was 1.07 times, with the highest occurrence being four times for one patient.

Table III: Number of dose adjustments after predicted maintenance dose until the therapeutic target was reached

Patients	Number of dose adjustments
1	1 time
2	-
3	1 time
4	2 times
5	2 times
6	4 times
7	-
8	2 times
9	2 times
10	-
11	-
12	-
13	1 time
14	-
Mean	1.07 times

Correlation between the predicted maintenance dose on day four and the actual maintenance dose required to reach the therapeutic target (Table IV), using the Shapiro-Wilk non-parametric statistical test. The average time to reach the therapeutic target was 22.2 days, and the value of r^2= 0.77 was obtained. Based on the results, no incident of INR >3 values was observed on day four. However, INR > 3 values incidents occurred after examination without bleeding complications.

Table IV: Correlation of predicted maintenance dose and the actual maintenance dose and the time to achieve therapeutic target

Patients	Predicted maintenance dose (mg/week)	Actual maintenance doses (mg/week)	Time to achieve therapeutic targets (Day)
1	21	22	30
2	21	21	30
3	35	42	26
4	35	21	32
5	14	13	41
6	28	42	28
7	7	7	7
8	7	3	24
9	7	14	24
10	14	14	12
11	35	35	16
12	7	7	18
13	28	35	19
14	7	7	16
Mean	19	20.2	22.2
R	0.878		
r^2	0.77		

Discussion

To the authors' knowledge, this is the first study in Indonesia to evaluate the initiation dose of warfarin. It is very important to research because responses to warfarin may vary among different populations due to pharmacogenetic influence (Momary *et al*., 2007; Suriapranata *et al*., 2011; Bader & Elewa, 2016). Thus, this study yielded a new value, which implied that the 4 mg initiation dose was effective and safe. Secondly, the results of this study will be beneficial for future implementation in Indonesia.

In this study, the 14 included patients were predominantly dominated by women (57.1%) compared to men (42.9%), with an age mean of 62 years. The most prevalent diagnosis was non-valvular atrial fibrillation (85.7%). Similarly, previous investigations showed that out of 120 patients who received warfarin, the majority were women (59.2%) compared to men (40%) (Abdel-Aziz *et al*., 2015).

Patients who received warfarin initiation dose for the first time passed several examinations regarding the risk of stroke, bleeding, and baseline INR. Measurements related to stroke risk were examined using the CHA2DS2-VASc score. In this study, patients who received treatment had a CHA2DS2-VASc score of one to three, while measurements of bleeding risk were examined using a HAS-BLED score of zero to two. The results of the CHA2DS2-VASc and HAS-BLED scores are presented in Table I. For patients with a CHA2DS2-VASc score of one, antithrombotic therapy with oral anticoagulants or antiplatelet therapy was recommended. The CHA2DS2-VASc score of two indicated a recommendation for oral anticoagulation. For those with a score of ≥ 3, oral anticoagulant

administration should be followed by careful monitoring of stroke risk. Meanwhile, the HAS-BLED score of less than three was included in patients with a low risk of bleeding (Lane & Lip, 2012). Patients eligible for the 4 mg warfarin initiation dose were expected to have a baseline INR of ≤ 1.5 (Siguret *et al*., 2005). The therapeutic algorithm for administering the warfarin initiation dose is presented in Table I.

The mean dose adjustment was carried out 1.07 times. Specifically, there were one, two, and four adjustments in a total of two, three, and one patient, respectively. Meanwhile, no adjustments were made for some patients because their INR value reached the therapeutic target on day four. Proper monitoring related to the INR value was conducted, and dose adjustments were made according to the clinician's judgment based on experience and protocol.

Table IV shows that the mean predicted and actual maintenance doses were 19 and 20.2 mg, respectively. Based on the nonparametric Shapiro-Wilk statistical test, the correlation results between the predicted and actual dose were $r = 0.878$ and $r^2 = 0.77$. The difference between the predicted and actual maintenance dose was more than 1 mg in four patients. Specifically, patients three and nine differed approximately 7 mg, while numbers four and six were 14 mg. This difference occurred due to nonadherence when receiving a 4 mg dose for three days, leading to an inaccurate INR value on day four. Furthermore, there was a difference in the time each patient took to achieve the therapeutic target.

The mean time patients reached the therapeutic target was 22.2, ranging from seven to forty-one days. However, Sridhar *et al*. and Siguret *et al*. stated that patients with an initiation dose of 4 mg could achieve a therapeutic target in 11 days (≤ 14 days) (Siguret *et al*., 2005; Sridhar *et al*., 2014). Several factors, such as genetic variability, contributed to differences in dose values and duration for each patient. In Indonesia, it was found that Single Nucleotide Polymorphisms (SNPs) contributed to the variability of the dosage requirements for each ethnicity. The results indicated that 14.5% of the warfarin genetic variants were obtained from the variants of VKORC1 and CYP2C9 variants (Suriapranata *et al*., 2011). Furthermore, the majority of CYP2C9*2, CYP2C9*3, and VKORC1 -1639G allele variants were associated with increased sensitivity to warfarin, resulting in a lower actual maintenance dose and longer time to achieve the therapeutic target (Suriapranata *et al*., 2011; Fisch *et al*., 2013). Variations could also influence the time to achieve a therapeutic target in the frequency of the INR value. Studies showed that INR checks every three days identified factors such as obesity, infection, and hypo-albumin that could affect this target (Siguret *et al*., 2005; Sridhar *et al*., 2014; Kahlon *et al*., 2016).

In hypo-albuminous conditions, the risk of bleeding potentially increased due to the high protein binding of warfarin, particularly with albumin, leading to higher free fraction and enhanced anticoagulant effects (Kawai *et al*., 2019). In this study, no INR was greater than three events on day four, like previous results using a 4 mg warfarin initiation dose for three days (Sridhar *et al*., 2014). However, analysis after day four of the examination showed a 35% incidence of INR greater than three. This phenomenon could be attributed to risk factors associated with interactions between warfarin and other drugs. Several therapies that posed a risk of interacting with warfarin and influencing the therapeutic effect were aspirin, clopidogrel, clopidogrel-aspirin, blood-boosting supplements, and budesonide inhalation. Combinations of warfarin with antiplatelets (aspirin, clopidogrel) or DAPT increased the risk of bleeding without affecting the INR value (Janardan & Gibbs, 2018; Menditto & Antonicelli, 2020). Based on other studies, the combination of warfarin, aspirin and clopidogrel increased the risk of bleeding three times (Hansen *et al*., 2010). The action of aspirin was to inhibit irreversible platelet cyclooxygenation and the formation of thromboxane A2, preventing platelet adhesion. Clopidogrel's mechanism also prevented platelet aggregation and activation by irreversibly inhibiting the P2Y12 ADP receptor on the platelet surface. Consequently, combining clopidogrel and aspirin with warfarin can significantly increase the risk of bleeding due to impaired haemostasis (Ho & Brighton, 2002; Fisch *et al*., 2013). Another therapy that showed the potential to interact with warfarin was inhaled budesonide, a corticosteroid, by inhibiting the CYP450 enzyme (Choi *et al*., 2010). Generally, the administration of inhaled budesonide occurs due to an absorption process in the tracheobronchial area, leading to metabolic interaction with warfarin (Ajimura *et al*., 2018).

This study showed no major or minor bleeding side effects in all patients. Similarly, Sridhar *et al.* reported that a 4 mg warfarin initiation dose showed safety and effectiveness, particularly among elderly patients (Siguret *et al*., 2005; Sridhar *et al*., 2014). The therapeutic target achieved using this initiation dose showed a different pattern for each patient. To understand patients ' responses, several factors should be considered, including genetic variability, body weight, adherence, honesty, self-medication, and drug interactions. A study related to the implementation of counselling strategies through virtual patients mentions medications, especially high-risk medicines like DOACs (direct oral anticoagulants) and VKAs

(vitamin K antagonists), would have a positive effect a positive effect was observed on patient adherence and safety (Richardson *et al.,* 2021). Therefore, personalised dosing and monitoring were crucial to ensure the achievement of the therapeutic target and maintain safety in patients with a 4 mg warfarin initiation dose.

Conclusion

In conclusion, this study indicated that the 4 mg dose of warfarin initiation showed safe results in all patients, with a therapeutic target INR value (2.0 - 3.0) and no INR value > 3 occurrence. Therefore, the 4 mg warfarin initiation dose effectively achieved therapeutic INR within an acceptable time.

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Conflict of Interest

The authors declare that there are no conflicts of interest in this study.

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