Original Article

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Comparisons of Methods and Outcomes of Warfarin Guideline-based Management in Patients on Warfarin Therapy whose International Normalized Ratio (INR) is Higher than Target INR at Vachiraphuket Hospital

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Abstract:

Objective: To compare the methods and management outcomes based on the warfarin guidelines of Vachiraphuket Hospital in patients receiving warfarin whose international normalized ratio (INR) is higher than target INR at Vachiraphuket Hospital.

Material and Methods: Retrospective analytic studies were conducted. The data were collected from retrospective outpatient medical records from 1st January 2012-9th September 2016.

Results: Sixty-seven patients with a total number of 178 events of INR higher than the target were reported. All events were divided into 84 events and 94 events which dealt and did not deal with the management method according to the warfarin guidelines of Vachiraphuket Hospital, respectively. After treating patients based on the hospital management guidelines, 33 events (39.3%) achieved target INR and 51 events (60.7%) were out of the target INR range. In the cases of patients who were not treated based on the hospital guidelines, 39 events (41.5%) were in the target INR and 55 events (58.5%) were out of INR range. Comparing the management methods and their outcomes, there was no statistically significant difference in achieving target INR between the patients treated with the hospital guideline-based method or the non-guideline-based method (odds ratio=0.913, p-value=0.765).

Conclusion: According to the warfarin guidelines of Vachiraphuket Hospital, the management for patients with INR higher than target INR was probably unsuccessful for everyone. Therefore, the management of each individual patient should be carefully considered.

Keywords: guideline-based management, INR, taget INR, warfarin, warfarin guidelines

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Introduction

Warfarin is an oral anticoagulant drug for the prevention and treatment of thromboembolism. Warfarin is a high-alert medication in many hospitals because it has a narrow therapeutic index, and may cause serious adverse drug reactions, i.e., cerebral hemorrhage. The anticoagulant effect of warfarin is measured by the international normalized ratio (INR). Its value targets are between 2.0 and 3.0 for general indications and between 2.5 and 3.5 for mechanical prosthetic mitral valve.[1] Due to its narrow therapeutic range and the wide variability of patient responses, it is difficult for physicians to manage warfarin therapy.[1]

At present, the management of oral anticoagulants for patients with INR outside of target INR refers to 'Warfarin Guidelines for Anticoagulant Patients' 2010 by The Heart Association of Thailand under Royal Patronage. Management methods, including increased and decreased drug dose, hold drug, and vitamin K_1 or fresh frozen plasma prescription, are all considered related to patients' INR values. In a previous study, Tuntiviyavanit et al.[2] reported that one of the frequent prescription errors (36.2%) of warfarin usage in Pattanee Hospital was dosage adjustment without considering patients' INRs. In addition, Leasinoudom et al.[3] revealed that 27 patients from 85 patients (31.8%) receiving warfarin were treated by dosage adjustment which was not based on the warfarin guidelines developed by Srinagarind Hospital. These non-guideline based management methods included excessive dose adjustment (20.0%) and under dose adjustment (11.8%), leading to INR lower or higher than target INR. According to our knowledge, the study of the management methods and outcomes in patients whose INR is over the target INR range have not been investigated in order to compare the management methods of complied with and did not comply with the 'Warfarin Guidelines for Anticoagulant Patients' 2010 by The Heart Association of Thailand under Royal Patronage.[1]

Vachiraphuket Hostipal is a tertiary care center in Phuket province where a warfarin clinic was established. The pharmacists at the clinic are responsible for warfarin follow-up and intervention. The warfarin guidelines of Vachiraphuket Hospital were developed based on 'Warfarin Guidelines for Anticoagulant Patients' 2010 by The Heart Association of Thailand under Royal Patronage and first used in 2011. Data from the warfarin clinic between October 2014 and September 2015 show that there were 126 events in which the patients had INR higher than target INR. In addition, a study of patients' knowledge and drug-related problems (DRPs) on warfarin use was conducted by Jittsue et al.[4] at Vachiraphuket Hospital. However, there has been no research on methods and management outcomes in patients with INR over target INR in cases of management methods that were related and unrelated to the warfarin guidelines of Vachiraphuket Hospital. The objective of our study was to compare management methods based on Vachiraphuket Hospital's warfarin guidelines and their outcomes in patients receiving warfarin whose INR was higher than the target INR.

Material and Methods

An analytical retrospective cohort study was conducted from June 20, 2016 to September 9, 2016 at Vachiraphuket Hospital, Thailand. The data were collected from retrospective outpatient medical records between 1st January 2012 and 9th September 2016. The inclusion criteria were patients with age of ≥18 years, continuously using a stable warfarin dose for at least 1 month, and having INR higher than the target between 1st January 2012 and 9th September 2016, as well as their complete information involving warfarin management established in medical records. The data collection was performed as the number of events when patients' INR was over their target INR. Our form consisted of 4 parts: part 1, general information of the participants; part 2, information of warfarin utilization; part 3, the management methods and outcomes in patients receiving warfarin with INR over the target INR, and part 4, the comparison between Vachiraphuket

Hospital warfarin guideline-based and non-guideline-based management methods and outcomes.

Terms

International normalized ratio (INR) is a standardized value showing the level of anticoagulants of warfarin utilization.[1]

INR higher than target INR is INR with a higher level than the target therapeutic INR range. Therapeutic INR is different based on indications. Generally, therapeutic INR should be in the range of 2.5±0.5, except in patients with mechanical prosthetic valves which should be in the range of 3.0±0.5.[1]

Adverse drug reaction (ADR) is an unintentional and harmful reaction of the human body. It is caused by a typical drug dosage for prevention, diagnosis, intervention or alteration of body processes. However, the reaction of drug abuse, or accidents or intentional drug overdose is excluded.[5]

Hemorrhage is an adverse drug reaction of warfarin utilization. It often occurs, especially when patients' INR is over their target INR. The severity of hemorrhage is different and is divided into 2 types. First, major bleeding is harmful in some parts of the body, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular pericardial, and intramuscular hemorrhage. It may result in a drop in hemoglobin of 1.24 or more mmol/L, or 2 or more units of necessary blood transfusion. Second, minor bleeding is not harmful or occurred in some important parts of the body, and it is not necessary to have a blood transfusion for patients who have some symptoms, such as petechial hemorrhage, epistaxis, gum bleeding, and so on.[6,7]

The stable dose of warfarin is the stable therapeutic warfarin dosage, leading to target INR and is continuously used for at least 3 months.

Management methods include dose adjustment, drug withdrawal or vitamin K_1 prescription according to Vachiraphuket Hospital's management guidelines, which were developed from the warfarin guidelines issued by the Heart Association of Thailand under Royal Patronage.[1]

Management outcome is the INR value at the following appointment, after the management methods for patients with INR higher than target INR, whether based on the hospital's guidelines or not.

Statistical analysis

The demographic characteristics of patients, warfarin utilization, management methods, and outcomes were presented in percentage. The relationships between factors and management methods including outcomes were tested using chi-square. The comparisons of the management methods and outcomes were analyzed using logistic regression. The study protocol was approved by the Ethics Committee of the Faculty of Pharmacy, Srinakharinwirot University: approval number 016/M2559, issued on June 24, 2016.

Results

Part 1: Demographic characteristics

After warfarin administration, 67 patients with a total number of 178 events of INR over target INR were selected for our study. Of these 67 patients with an average age of 65.9±15.2 years, 61.2% were male. With different indications, most patients (65.7%) received warfarin for atrial fibrillation, followed by 16 patients (23.9%) for ischemic stroke/embolic stroke. In addition, most of them (91.0%) had their target INR in the range of 2-3. Some of the patients had comorbidities, including hypertension (58.2%), dyslipidemia (43.3%), and diabetic mellitus (20.9%). Only 5 patients (2.8%) smoked. The 178 events of patients with INR higher than target INR were divided into 2 groups, as the Vachiraphuket Hospital warfarin guideline based management group and the non-hospital guideline based management group. The number of events in the groups was 84 and 94, respectively, with non-significant differences between both groups. Except for the profile

Table 1 Demographic characteristics of the patients and the number of events that complied with the Vachiraphuket Hospital warfarin guideline-based management and non-guideline-based management

Demographic characteristics	Number (%) (N=67)	Event (%) (n=178)	
		Guideline-based management (n=84)	Non-guideline-based management (n=94)
Gender			
Male	41 (61.2)	43 (51.2)	54 (57.5)
Female	26 (38.8)	41 (48.8)	40 (42.6)
Indication for warfarin			
Atrial fibrillation	44 (65.7)	58 (69.1)	65 (69.2)
Ischemic stroke/embolic stroke	16 (23.9)	21 (25.0)	22 (23.4)
Valvular disease	8 (11.9)	11 (13.1)	11 (11.7)
Mechanical heart valve replacement	5 (7.5)	6 (7.1)	4 (4.3)
Pulmonary embolism	3 (4.5)	5 (6.0)	7 (7.5)
Ischemic cardiomyopathy	3 (4.5)	3 (3.6)	4 (4.3)
Thrombosis	2 (3.0)	3 (3.6)	1 (1.1)
Other	6 (9.0)	3 (3.6)	8 (8.5)
International normalized ratio (INR) target			
2.0-3.0	61 (91.0)	77 (91.7)	84 (89.4)
2.5-3.5	6 (9.0)	7 (8.3)	10 (10.6)
Comorbidities			
Hypertension	39 (58.2)	55 (65.5)	50 (53.2)
Dyslipidemia	29 (43.3)	44 (52.4)	41 (43.6)
Diabetes mellitus	14 (20.9)	15 (17.9)	16 (17.0)
Chronic heart failure	11 (16.4)	17 (20.2)	11 (11.7)
Chronic kidney disease	8 (11.9)	12 (14.3)	10 (10.6)
Chronic obstructive pulmonary disease (COPD)/asthma	7 (10.5)	6 (7.1)	15 (16.0)
Gout	3 (4.5)	5 (6.0)	6 (6.4)
Thyroid disease	1 (1.5)	2 (2.4)	3 (3.2)
Other	-	6 (7.1)	16 (17.0)
Smoking			
Yes	5 (2.8)	5 (6.0)*	0*
No	62 (97.2)	79 (94.1)	94 (100.0)

N=a number of patients, n=a number of events, *p-value<0.05

of smoking, the number of patients who smoked in the hospital guideline based management group was significantly higher than in the non-hospital guideline base management group (Table 1). On patients' INR, the average INR values before and after management methods were represented as 4.5±1.6 and 2.7±1.4, respectively. Additionally, the average warfarin dosage causing INR over target INR was 23.4±11.1 milligrams per week, at baseline. After management methods, the average dosage was 19.1±9.9 milligrams per week with an average dose reduction of 18.1±16.8%.

Part 2: Utilization of warfarin

At the beginning of our study, the 178 events of patients' baseline INR over target INR were divided into 4 groups according to INR ranges, with ranges of 3.01-3.59, 3.60-4.99, 5.00-9.00, and 9.01-13.50. The number of events were 59 (33.2%), 75 (42.1%), 39 (21.9%) and 5 (2.8%), respectively in each group.

Concerning the signs and symptoms of the patients whose INR was higher than target INR (Table 2): only 99 events (55.6% of all 178 events) were reported involving the signs and symptoms in the medical records. Of 99 events, 62 events (62.6%) were reported as without any signs or symptoms, whereas 37 events were reported as with signs and symptoms. These signs and symptoms can be divided into 3 groups: minor bleeding, major bleeding, and others with 33, 4 and 1 event, respectively in each groups. Of the 37 events of patients with signs and symptoms, the most frequently found was petechial hemorrhage (18 events), followed by gum bleeding (6 events). The aspect of major bleeding: 3 events of patients who needed blood

Table 2 Signs and symptoms of the patients with international normalized ratio over target international normalized ratios

Signs and symptoms	A number of events (%) (n=99)
Without signs and symptoms	62 (62.6)
With signs and symptoms	37 (37.4)
A. Minor bleeding	33 (33.3)
Petechial bleeding	18 (18.2)
Gum bleeding	6 (6.1)
Epistaxis	3 (3.0)
Hematuria	3 (3.0)
Hemoptysis	2 (2.0)
Melena	1 (1.0)
B. Major bleeding	4 (4.0)
Bleeding needed blood transfusion with PRC ≥2 units	3 (3.0)
Intramuscular bleeding	1 (1.0)
C. Others	
Leg swelling	1 (1.0)

PRC=pack red cell

transfusion with packed red cells (PRC), 2 units or more, and 1 event of intramuscular bleeding were reported. In terms of the reasons why INR values were higher than targeted INR, the reason for the 168 events (94.4% of all 178 events) appears unknown. The most probable reason was the changes of clotting factor metabolism (6 events of all 178 events, 3.4%), of which 4 and 2 events were reported as patients had a high fever and hyperthyroidemia, respectively during the week of INR monitoring. Another reason for 2 events (1.1%) was warfarin-non-steroidal anti-inflammatory drugs (NSAIDs) drug interactions. Moreover, the changes of warfarin metabolism were reported in 1 patient (0.6%) with congestive heart failure, as well as non-compliance in another one.

Part 3: The management methods and outcomes in patients receiving warfarin with their INR over the target INR

Our study included 178 events in which patients' baseline INR was higher than their target INR range. Then we investigated the management methods: whether they complied with the Vachiraphuket Hospital warfarin guidelines, as well as the outcomes of target INR range. We reported that the management methods consisted of 5 procedures: non-management, dose reduction, holding dose, vitamin K administration, and blood transfusion. The number of events in each procedure were 9 (5.1%), 95 (53.4%), 58 (32.6%), 11 (6.2%), and 5 (2.8%), respectively (Table 3). Furthermore, the number of events of all the above management methods were divided into 4 subgroups, depending on patients' baseline INR. Of all 59 events in the patients' INR range of 3.01-3.59 subgroup, 43 events (72.9%) were treated with dose reduction, 8 events (13.6%) with holding dose and the other 8 events with non-management. The frequent management methods for patients with INR ranges of 3.60-4.99, 5.00-9.00 and 9.01-20.00 were dose reduction (60.0%), holding dose (53.9%) and vitamin K administration (60.0%), respectively.

All the above mentioned management methods were considered as part of the Vachiraphuket Hospital guideline-based management methods, and the others as non-hospital guideline-based management methods. Of all 178 events, the number of events in each group were 84 (47.2%) and 94 (52.8%) events, respectively. Depending on patients' baseline INR, there were 47.5% (28 of 59 events), 34.7% (26 of 75 events), 66.7% (26 of 39 events) and 80.0% (4 of 5 events) of the patients with INR of 3.01-3.59, 3.60-4.99, 5.00-9.00 and 9.01-20.00, respectively, who received hospital guideline-based management methods.

After receiving these management methods according to the hospital guidelines or non-hospital guidelines, only 72 events (40.5% of all 178 events) were in the target INR range, but 106 events (59.6%) were out of INR range. In cases of INR outside target INR range, all 106 events were categorized into 2 groups: a group with INR lower than target INR range in 54 events (50.9%) and a group with INR higher than target INR range in 52 events (49.1%).

Regarding all 94 events of which management methods complied with the non-hospital guidelines, we represent the details of management methods and the outcomes depending on target INR and patients' INR in Table 4. Target INR was divided into 2 groups: a group with target INR range of 2.0-3.0 and another with 2.5-3.5. When target INR range was 2.0-3.0 and patients' INR was in the range of 3.01-3.59, most events (23 of all 31 events, 74.2%) were treated by a dose reduction of 11.0-20.0%. This was different from the hospital guideline-based management, which recommended a dose reduction of 5.0-10.0% with or without holding drug for 1 day.

Table 3 Management methods and its outcomes in patients whose international normalized ratio over target international normalized ratio range

Patients' INR	The number of events (%)								
	Management methods (n=178)					Complied with hospital guideline based management (n=178)		Management outcomes# (n=178)	
	Non-management	Dose reduction	Holding dose	Vitamin K administration	Blood transfusion	Complied	Non complied	INR within target INR range	INR outside target INR range
3.01-3.59 (n=59)	8 (13.6)	43 (72.9)	8 (13.6)	0	0	28 (47.5)	31 (52.5)	31 (52.5)	28 (47.5)
3.60-4.99 (n=75)	1 (1.3)	45 (60.0)	28 (37.3)	1 (1.3)	0	26 (34.7)*	49 (65.3)	29 (38.7)**	46 (61.3)
5.00-9.00 (n=39)	0	7 (18.0)	21 (53.9)	7 (18.0)	4 (10.3)	26 (66.7)*	13 (33.3)	9 (23.1)**	30 (76.9)
9.01–20.00 (n=5)	0	0	1 (20.0)	3 (60.0)	1 (20.0)	4 (80.0)	1 (20.0)	3 (60.0)	2 (40.0)
Total	9	95	58	11	5	84	94	72	106

*significant differences to Non complied with hospital guideline based management, p-value<0.05

**significant differences to INR outside target INR range, p-value<0.05

#Management outcomes, resulting from Vachiraphuket Hospital guideline-based management methods or non-hospital guideline-based management methods

INR=international normalized ratio

Table 4 Management methods and outcomes that complied with the non hospital guidelines

Non hospital-guideline based management method	The number of events (n=94) (%)	Management outcomes		
		INR within target INR range (n=39) (%)	INR lower than target INR range (n=23) (%)	INR higher than target INR range (n=32) (%)
Target INR 2.0-3.0				
INR 3.01-3.59 (dose reduction 5.0-10.0% ± hold 1 day*) (n=31)				
Dose reduction 11.0-20.0%	23 (74.2)	11 (47.8)	7 (30.4)	5 (21.7)
Dose reduction 21.0-30.0%	1 (3.2)	1 (100.0)	0	0
Dose reduction >30.0%	2 (6.5)	1 (50.0)	0	1 (50.0)
Hold drug 1 day + dose reduction 11.0-20.0%	3 (9.7)	1 (33.3)	0	2 (66.7)
Hold drug >1 day + dose reduction	2 (6.5)	1 (50.0)	0	1 (50.0)
INR 3.60-4.99 (dose reduction 10.0-20.0% ± hold 1 day*) (n=43)				
Continue same dose	1 (2.3)	0	0	1 (100.0)
Dose reduction <10.0%	9 (20.9)	4 (44.4)	0	5 (55.6)
Dose reduction 21.0-30.0%	11 (25.6)	6 (54.6)	2 (18.2)	3 (27.3)
Hold drug 1 day + dose reduction 21.0-30.0%	1 (2.3)	0	0	1 (100.0)
Hold drug >1 day + dose reduction	20 (46.5)	8 (40.0)	7 (35.0)	5 (25.0)
Hold drug + dose increment	1 (2.3)	0	0	1 (100.0)
INR 5.00-9.00 (Hold drug 1-2 dose or vit K 1-2 mg IV*) (n=10)				
Dose reduction 10.0-20.0% without hold drug	3 (30.0)	1 (33.3)	1 (33.3)	1 (33.3)
Dose reduction 21.0-30.0% without hold drug	2 (20.0)	2 (100.0)	0	0
Dose reduction >30.0% without hold drug	1 (10.0)	0	0	1 (100.0)
Hold drug >2 days	3 (30.0)	1 (33.3)	2 (66.7)	0
Vitamin K 2 mg IV + FFP + PRC + hold drug	1 (10.0)	0	0	1 (100.0)
Target INR 2.5-3.5				
INR 3.51-4.09 (dose reduction 5.0-10.0% ± hold 1 day*) (n=2)				
Hold drug 1 day + dose reduction 11.0-20.0%	1 (50.0)	0	1 (100.0)	0
Hold drug 1 day + dose reduction 21.0-30.0%	1 (50.0)	1 (100.0)	0	0
INR 4.10-5.49 (dose reduction 10.0-20.0% ± hold 1 day*) (n=5)				
Dose reduction 21.0-30.0%	1 (20.0)	0	0	1 (100.0)
Hold drug >1 day + dose reduction 11.0-20.0%	2 (40.0)	0	0	2 (100.0)
Hold drug >1 day + dose reduction>30.0%	2 (40.0)	0	2 (100.0)	0
INR 5.50-9.50 (hold drug 1-2 dose or vit K 1-2 mg IV*) (n=2)				
Hold 3 days + dose reduction 40.0%	1 (50.0)	0	1 (100.0)	0
FFP + vitamin K 5 mg oral	1 (50.0)	0	0	1 (100.0)
INR >9.50 (vit K 3-5 mg IV*) (n=1)				
Hold drug 3 days + dose reduction 46.0%	1 (100.0)	1 (100.0)	0	0

*Management methods based on hospital guideline

INR=international normalized ratio, FFP=fresh frozen plasma, PRC=pack red cell

Part 4: Comparison between Vachiraphuket Hospital warfarin guideline-based and non-guideline-based management methods and the outcomes

For the comparison between management methods and the outcomes, our study revealed that in 84 events receiving Vachiraphuket Hospital warfarin guideline-based management, 33 events (39.3%) achieved target INR, whereas 51 events (60.7%) did not. On the other hand, in 94 events receiving non-guideline based management, 39 events (41.5%) achieved target INR, whereas 55 events (58.5%) did not. The number of events to achieve target INR were not significantly different whether the management methods complied with hospital warfarin guidelines or not (odds ratio=0.913, p-value=0.765), as shown in Table 5.

Consideration of the relationship among the various factors, the management methods and the outcomes, our results reveal the relationship of only 2 factors as the baseline of patient INR over target INR and the comorbidities with methods and outcomes. First, patients with at least 1 event of their baseline INR over the target INR significantly affected whether outcome achieved target INR ranges (p-value<0.05). Second, their comorbidities of congestive heart failure and asthma/chronic obstructive pulmonary disease (COPD) significantly affected their achievement of target INR (p-value<0.05).

Discussion

Our present study investigated the management methods and the outcomes for patients whose INR was over target INR range at Vachiraphuket Hospital. From the retrospective data collection of medical records, a total of 178 events of 67 patients with INR higher than target INR were categorized into 2 groups: 84 events in the group receiving the Vachiraphuket Hospital warfarin guideline-based management methods and 94 events in the group receiving the non-hospital guideline-based management methods. Consistent with studies by Silaruks et al.[1] and Jittsue et al.[4] most indications of warfarin in our patients included atrial fibrillation, ischemic/embolic stroke, and valvular heart disease. There were non-significant differences between the demographic data of both groups, except five patients who smoked in a group receiving the hospital guideline-based management methods. Theoretically, chronic smoking causes significant interaction with warfarin by increasing warfarin clearance, leading to the reduction of the warfarin therapeutic effect and patients' INR value. To confirm smoking-warfarin interaction with clinical outcomes, Nathisuwan et al. conducted a pool analyses of multivariate studies and indicated that smoking was associated with a 12.1% (95% confidence interval= 6.999-17.265; p-value<0.001) increase in warfarin dosage

Table 5 The comparisons of management methods and outcomes

Management methods complied with hospital guideline	Achievement of INR to target INR range		
	Yes	No	Total
Yes	33	51	84
No	39	55	94
Total	72	106	178

Odds ratio estimate=0.913, p-value=0.765, INR=international normalized ratio

requirement compared with nonsmoking.[8] As mentioned above, smoking was probably one of the factors influencing INR value changes in our study.

Regarding the abnormal symptoms of patients with supratherapeutic INR, 44.4% of all the 178 events went unreported in medical records. Bleeding, an important and harmful symptom related to high INR level, as well as other symptoms need to be managed. Therefore, we suggest that it is essential to convince physicians, as well as medical staff, to investigate and address all unusual symptoms related to warfarin usage in the medical records in order to treat patients with the appropriate management methods. In additions, of these 99 recorded events, most symptoms were bleeding (37.4%), in accordance with the study conducted by Palareti et al.[9] which indicated a relationship between higher INR level and more bleeding. Among all 37.4% of the bleeding events, minor bleeding was more frequently reported than minor bleeding as 33.3% and 4.0%, respectively. The minor bleedings events were often described as petechial bleeding (18.2%), gum bleeding (6.1%), epistaxis (3.0%), and hematuria (3.0%). Our results were consistent with studies by Tantiviyavanit et al.[2] and Jittsue et al.[4] in which most of the adverse drug reactions were minor bleeding, especially petechial bleeding. Furthermore, we also suggest that it is important to inform patients using warfarin about the risk of bleeding and how to take action in case of bleeding.

Concerning the causes of patient INR over target INR: most (94.4% of all 178 events) had an unknown cause. It was probably due to the limitation of our retrospective methodology which was unable to collect enough patient information involving drugs or food lists, dosage adjustments, and patient compliance. Of the rest of the 10 events, the most common cause was metabolic changes of coagulation factors; it is established in medical records that in 4 events patients had a high fever during the week of INR monitoring, including 2 events with hyperthyroidism. As described by Tonna et al.[10] hyperthermia (pyrexia) and hyperthyroidism[11] accelerate the inactivated metabolic rate of clotting factors, leading to an incremental change of the warfarin anticoagulant effect. Moreover, 2 events of warfarin-NSAIDs drug interaction were reported, which mainly resulted from pharmacodynamics interaction by reducing platelet aggregation. It was probably a pharmacokinetic interaction by displacement of warfarin from its plasma protein binding, resulting in an increased amount of free drugs.[10] Our finding was related to the study by Leasinoudom et al.[3] which indicated that aspirin/NSAIDs was the drug with the second most interaction with warfarin. Another cause was metabolic changes of warfarin; as noted, there was 1 event of congestive heart failure (CHF). As described by Jaffer et al.[11] CHF led to hepatic congestion of blood flow, followed by inhibition of warfarin metabolism. The last cause was patient non-compliance. As mentioned above, many factors affected warfarin activity and INR range, including pharmacokinetics, pharmacodynamics interaction, and non-compliance, as well as patient comorbidities. Therefore, pharmacists have an important role to play in patient counseling, as well as monitoring adverse drug reactions and screening for drug interactions, in order to ensure that patients receive effective and safe warfarin treatment.

Regarding the management methods for the patients with supratherapeutic INR: dose reduction was the most common method used for patients with baseline INR of 3.01-3.59. Dose reduction and drug holding were the most common methods for patients with baseline INR of 3.60-4.99. In addition, drug holding and vitamin K_1 administration were the most common methods for patients with baseline INR ≥5.00. Our results were in conjunction with the study by Leasinoudom et al.[3] who found that the major management method for patients with INR of less than 5 without major bleeding was dose reduction, and those for the patients with INR of 5-9 without major bleeding were drug holding and vitamin K administration.

Consideration of the concordance of management methods with Vachiraphuket Hospital warfarin guidelines: patients who received the management methods were divided into 2 groups, the hospital's guideline-based group and the non-hospital's guideline-based group, resulting in 84 and 94 events (47.2 and 52.8%), respectively. Differences with the study by Leasinoudom et al.[3]: they reported that most management methods complied with the warfarin use guidelines of Srinagarind Hospital. Depending on patients' baseline INR, it seemed like the higher the level of patients' baseline INR, the greater the number of management methods that complied with the hospital guidelines. In our opinion, when baseline INR is minimally over the target (INR range of 3-5), physicians are able to consider the management methods depending on their experience, patient compliance, signs of bleeding and hospital guidelines together. In contrast, baseline INR greatly over the target (INR range ≥5) increases the risk of serious bleeding. These factors affect physician ability to make judgments; therefore, they follow only the hospital guidelines.

Concerning the management outcome results from both hospital and non-hospital guideline based management: of all 178 events, 40.5% of patients had INR within the target INR. In the other 106 events (59.6%) of the patients, INR outside the target INR was divided into two groups: 54 events (50.9%) for the patients with subtherapeutic INR and 52 events (49.1%) for the patients with supratherapeutic INR. Our findings indicated that the number of events with subtherapeutic INR was not different than the number with supratherapeutic INR. We suggested that it was resulted from inappropriate management methods, including dose adjustments that were too low or high. This was contrary to the study by Leasinoudom et al.[3] who found that only 24.7% of patients achieved their INR goal, as well as the other 42.4% and 18.8% who had INR less or more than target INR, respectively. They suggested that one of the main reasons was inappropriate drug starting and adjustment. In this study, the patients' baseline INR was high and their INR outcome after the management methods tended to be significantly out of the target range.

The comparison of management methods and outcomes of INR values showed that the number of events that achieved the target INR were not significantly different whether or not the management methods complied with hospital warfarin guidelines. This might be an indication that hospital guidelines could be modified for individual patients, based on several factors, such as age, social history, INR value, sign and symptoms of bleeding compli cations, and comorbidities, as well as patient compliance.

The relationships between patient factors, management methods, and INR outcomes after management were discussed. Our results showed that baseline INR values significantly affected INR outcomes after management. Higher baseline INR led to a higher proportion of patients with INR out of the target range. This finding was partly in accordance with the study by Tai et al. which demonstrated that when the baseline INR value was high, INR result after management tended to be significantly out of range.[12] In terms of comorbidity, CHF and asthma/COPD significantly affected on INR outcome after management. Exacerbation of CHF was supposed to impact warfarin absorption.[13]

Conclusion

In Vachiraphuket Hospital, the management of patients with supratherapeutic INR using warfarin guideline-based or non-guideline-based methods showed no significant differences in INR outcomes. We suggest that when patients experience INR over the target range, management methods based on the hospital's guidelines should be carefully applied for individuals, taking into consideration patients' baseline INR and target INR range, as well as comorbidities.

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