ผลของการจัดการผู้ที่ได้รับยาวาร์ฟารินโดยเภสัชกร ณ โรงพยาบาลมโหสถ สาธารณรัฐประชาธิปไตยประชาชนลาว
Effects of Pharmacist-Managed Warfarin Therapy at Mahosot Hospital, Lao PDR

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบผลลัพธ์ของการจัดการผู้ป่วยที่ได้รับยาวาร์ฟารินโดยเภสัชกรกับการดูแลแบบปกติที่แผนกผู้ป่วยนอก โรงพยาบาลมโหสถ สาธารณรัฐประชาธิปไตยประชาชนลาว **วิธีการศึกษา**: เป็นการทดลองแบบสุ่มและมีกลุ่มควบคุม ณ แผนกผู้ป่วยนอก ศูนย์หัวใจลาว-ลักเซมเบิร์ก กลุ่มตัวอย่าง คือ ผู้ป่วยได้รับยาวาร์ฟาริน 1 เดือนขึ้นไป และรับยาต่ออีกอย่างน้อย 4 เดือน มีผลตรวจค่า INR ทุกครั้งที่มาติดตามการรักษา ผู้ป่วยจะถูกสุ่มเข้ากลุ่มทดลอง (มีเภสัชกรจัดการการได้รับยาวาร์ฟาริน) และกลุ่มควบคุม (รับการดูแลแบบปกติ) วัดผลลัพธ์ทางคลินิกได้แก่ ผลลัพธ์ด้านประสิทธิภาพ ประกอบด้วย 1) ช่วงเวลาที่ค่าไอเอ็นอาร์อยู่ในช่วงรักษา (TTR) 2) ค่า INR 3) คะแนนความรู้ 4) ปัญหาจากการใช้ยา (ขนาดยาต่ำกว่าขนาดที่ควรได้รับ ขนาดยาสูงกว่าขนาดที่ควรได้รับและปฏิกิริยาระหว่างยาวาร์ฟาริน) 5) ภาวะลิ่มเลือดอุดตัน 6) ความร่วมมือในการใช้ยาของผู้ป่วย ส่วนผลลัพธ์ด้านความปลอดภัย คือ อาการไม่พึงประสงค์จากการใช้ยา (อาการเลือดออกชนิดรุนแรง หรืออาการเลือดออกชนิดไม่รุนแรง) วิเคราะห์ข้อมูลโดยใช้สถิติ student *t*-test, Mann-Whitney *U* test repeated-measure ANOVA test, Chi-squared test, Fisher's exact test และ Cochran's test **ผลการศึกษา:** ผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 72 คน (กลุ่มละ 36 คน) ค่า TTR ของผู้ป่วยในกลุ่มทดลองเท่ากับ 63.3 ± 35.5% ซึ่งสูงกว่าค่า TTR ในกลุ่มควบคุม (45.3 ± 39.9%) อย่างมีนัยสำคัญทางสถิติ (*P*-value = 0.046) คะแนนความรู้ระหว่างกลุ่มทดลองและกลุ่มควบคุมที่การติดตามครั้งที่ 3 ต่างกันอย่างมีนัยสำคัญทางสถิติ (13.2 และ 7.0 ตามลำดับ, *P*-value = 0.013) ปัญหาจากการใช้ยาที่พบมากที่สุด คือ ขนาดยาต่ำกว่าขนาดที่ควรได้รับ (30 ครั้งในกลุ่มทดลอง) และพบปัญหาจากการใช้ยา ณ การติดตามครั้งที่ 4 ในกลุ่มทดลองจำนวน 6 ครั้งเมื่อเปรียบเทียบกับกลุ่มควบคุมพบจำนวน 15 ครั้ง **สรุปผลการศึกษา:** ผู้ป่วยในกลุ่มทดลองมีผลลัพธ์ที่ดีกว่าเมื่อเปรียบเทียบกับกลุ่มควบคุม การจัดการการได้รับยาวาร์ฟารินโดยเภสัชกรสามารถช่วยเพิ่มผลลัพธ์ทางสุขภาพของผู้ป่วย ซึ่งผลลัพธ์เหล่านี้จะนำไปสู่การจัดตั้งคลินิกวาร์ฟารินโดยเภสัชกรในระยะยาวต่อไป ณ โรงพยาบาลมโหสถ และโรงพยาบาลอื่น ๆ

คำสำคัญ: เภสัชกร, ยาวาร์ฟาริน, ช่วงเวลาที่ค่าไอเอ็นอาร์อยู่ในช่วงรักษา, TTR, ความรู้

Abstract

Objective: To determine the effects of warfarin clinic serviced in patients receiving pharmacist-managed warfarin therapy and those receiving usual care at out-patient department, Mahosot Hospital, Lao PDR. **Methods**: A randomized controlled trial was conducted at the out-patient department, Lao Luxembourg heart center. To be eligible, patients had to receive warfarin for at least 1 month, continue warfarin for a minimum of 4 months, and have the INT result for each visit. Patients were randomized either to the pharmacist-managed warfarin therapy (test group) or the usual care (control group). Efficacy outcomes were 1) time in therapeutic range (TTR), 2) INR 3) knowledge scores 4) DRPs (sub-therapeutic dosage, over dosage, and drug interactions) 5) thromboembolism events 6) patient adherences. Safety outcomes were adverse drug reactions (major bleeding or minor bleeding). A student *t*-test, a Mann-Whitney *U* test, a repeated-measure ANOVA test, a Chi-squared test, a Fisher's exact test and a Cochran's test were used statistical analysis. **Results**: From a total of 72 patients (36 in each group), TTR was 63.3 ± 35.5% in the test group and 45.3 ± 39.9% in the control group with statistical significance (*P*-value = 0.046). Knowledge scores about warfarin therapy were significantly different between the test and control groups at 3rd visit (13.2 and 7.0 points, respectively, *P*-value = 0.013). The most common DRPs identified were sub-therapeutic dosage (30 cases in the test group). At 4th visit, 6 and 15 DRPs were found in the test and control groups, respectively. **Conclusion:** Patients receiving pharmacist-managed warfarin therapy had better outcomes than those receiving usual care. These results then lead to the long-run establishment of warfarin clinic led by pharmacist at Mahosot Hospital, and other hospitals.

Keywords: pharmacists, warfarin, time in therapeutic range, TTR, knowledge

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Introduction

Warfarin remains the most widely available anticoagulant in most healthcare settings and is the one of oral anticoagulants (OACs) in the World Health Organization model list of essential medicines.[1] Warfarin is indicated for treating blood clots such as in deep vein thrombosis (DVT) and pulmonary embolism, and preventing ischemic stroke in

patients with atrial fibrillation (AF), valvular heart disease, and artificial and mechanical valve replacement (MVR).[2] The prevention of stroke and systemic embolism in AF patients is established by warfarin therapy but it could possibly lead to bleeding. In addition, inadequate or excessive amount of warfarin could lead to death.[3] Warfarin has a narrow therapeutic window and is associated with a vast array of drug-drug and drug-food interactions. Its use is heavily relied on frequent monitoring of international normalized ratio (INR) test. Hence, physicians and pharmacists need to adjust warfarin regimens based on INR results. Furthermore, patients need to recognize and understand the INR values to make a discussion with healthcare providers when the INR value is out of the target range. For most indications, the target INR range is 2 – 3[2], with a target range of 2.5 – 3.5 for mechanical heart valve replacement (MVR) as suggested by the American Heart Association.[4] The optimal target INR could be achieved mainly by the close supervision of physicians. However, the role of pharmacists in taking care of patients using warfarin has been more evident.

More studies showed that patients getting better therapeutic outcomes when pharmacist-managed warfarin therapy is provided. With this pharmacist-managed warfarin therapy, pharmacists are responsible for 1) providing education, 2) assessing patients' adherence, 3) reviewing medications, comorbidities, nutrition and drug interactions, 4) screening side effects of thromboembolism or bleeding, 5) adjusting warfarin dose, and 6) scheduling INR test. Previous studies showed that patients receiving pharmacist-managed warfarin therapy were more likely to achieve better outcomes that those receiving usual care, including higher percentages of time within the therapeutic range (TTR), improvement of patients' knowledge, and significant reduction of bleeding complication and lower risk of minor hemorrhage.[5-7]

Lao People's Democratic Republic (Lao PDR) is a low-middle incomes country, located in Southeast Asia. By 2017, life expectancy of men and women were 65.4 and 68.6 years old, respectively.[8] Stroke was the third leading cause of death, followed by coronary heart diseases and infectious diseases. According to WHO ranking of mortality by stroke in 2017, Lao PDR was ranked the 37th of the world with a mortality rate of 9.99% (i.e., 4,273 stroke-related deaths and 42,773 all-causes deaths) which was higher than 9.01% in 2011.[9] As stated in the Laos National Essential Medicines List, heparin, enoxaparin, warfarin and dicoumarol were only 4 anticoagulants listed.[10] In 2018, warfarin is an only OAC drug used in Lao PDR. Mahosot Hospital is a tertiary teaching hospital with 450 beds located in Vientiane, the capital city of Lao PDR. The central cardiology center is also located in Mahosot Hospital. According to warfarin dispensed in the central cardiology center, the amount of warfarin prescribed had been increasing from 2015 to 2016 and 2016 to 2017 by 38.09 % and 38.61 %, respectively.[11] In the central cardiology center, on each usual visit, physicians prescribed and adjusted dose of warfarin and nurses provided basic knowledge on warfarin and concerns about food interaction, while pharmacists dispensed warfarin with no consultation with the patient on warfarin use.

Since 2002, Mahosot Hospital has performed the heart valve replacement surgery. Nowadays, patients with MVR still needed follow-ups and received warfarin from the hospital. A cross-sectional descriptive study on patients using warfarin therapy at out-patient department, Lao-Luxembourg Heart Centre, Mahosot Hospital was conducted between September 2017 and January 2018. Among the 272 patients using warfarin, 48.16% of them had their INR within the target range, while 25.36% were with the INR over therapeutic range.

It had been known that 89.33% of the patients receiving warfarin at Mahosot Hospital also took other medications such as acetaminophen, simvastatin, aspirin, and omeprazole.[12] An individual interview to investigate the patients' views on pharmacists' interventions was conducted between February and March 2018 with 10 patients on warfarin at the out-patient department. The report showed that the patient needed more information on the benefit and side effects of warfarin therapy because they had never known about such matters.[13]

To help patients recognize the signs and symptoms of bleeding or clotting associated with warfarin use, understanding on warfarin is needed. Healthcare professional including physicians, nurses and pharmacists should work together in order to monitor, rehabilitate and prevent the incidence of bleeding or clotting and unnecessary use of warfarin. All pharmacist interventions from the result of the interview study were based on collaborations among healthcare professionals that needed pharmacists to be a part of warfarin therapy at Mahosot Hospital. To better prepare the pharmacist for the future role in warfarin therapy, expectations on pharmacist's role by healthcare professionals was used in a part of the lesson to train the pharmacist.

The practical intervention model was discussed and accepted by all healthcare professionals. First, the process of pharmacist-managed warfarin therapy at the end of the service, i.e., after the dispensing of medications, was accepted. Second, pharmacist's roles accepted by all healthcare professionals at Mahosot Hospital included medication review, drug-related problems (DRPs) checking, patient adherence checking, screening for bleeding or thromboembolism events, and education for the patients.

As a consequence, this randomized controlled trial (RCT) aimed to evaluate the effect of pharmacist-managed warfarin therapy on patient's clinical outcomes. For the primary research question, we aimed to compare the duration or time that the INR was within therapeutic range (TTR) between patients receiving the pharmacist-managed warfarin therapy (test group) and those receiving the usual care (control group). We stated that %TTR in the test group was different from that in the control group, as an alternative hypothesis.

Methods

A randomized controlled trial was conducted to compare clinical outcomes in patients receiving pharmacist-managed warfarin therapy with those receiving usual care at out-patient department, Mahosot Hospital, Lao PDR.

Population of this study was patients who were receiving warfarin therapy. The sample was patients who were receiving warfarin therapy at the out-patient department, Lao Luxembourg Heart Center, Mahosot Hospital, Lao PDR during February to May 2019. Patients included in this study met the following requirements: 1) age of 18 years old or older, 2) receiving warfarin for at least 1 month and being expected to continue warfarin for a minimum of 4 months, 3) having INR result for each visit, 4) being able to communicate with Lao language, and 5) being willing to participate and voluntarily provide written informed consent. Patients having any of the following conditions were excluded from this study: 1) active cancer 2) hearing impairment, or having no caregiver.

Sample size of this study was based on the work of Wilson et al. (2003).[14] With $Z_{\alpha/2}$ of 1.96, Z_{β} of 0.84, and a dropout rate 20%, a total of 30 patients for each group were required. To ensure comparable numbers of patients in the two groups, block randomization with a block size of 4 and consequently 6 permuted blocks was carried out.

Research instruments

The patient data collection form and questionnaire on the patients' knowledge were validated by two researchers (WA and PK) with an Index of Item Objective Congruence of 1 for all questions. The questionnaire contains 15 questions and was translated from English version of Lakshmi et al[15] to Lao language by the researcher (VS). These 15 questions were (1) What is warfarin? or Why have you been prescribed warfarin? (2) What is your current dose of warfarin?, (3) Who is responsible for adjusting your warfarin dose?, (4) What is the important of INR testing?, (5) What is your target INR?, (6) How frequently should you check your INR?, (7) When should warfarin be taken and why?, (8) What will you do in case of a missed dose?, (9) What will happen when you take double dose of warfarin?, (10) What will you do in case of surgery, dental work, or some type of invasive procedures while on warfarin?, (11) Which types of foods affect warfarin therapy?, (12) Do you know what drugs, alcohol, herbs can affect warfarin's action?, (13) What will you do in case of bleeds from nose/gum?, (14) What should you do if you plan to go on holidays?, and (15) What are the possible side effects of warfarin?[15]

Lao language version form was validated by two experts working in the health care field. The internal consistency reliability of questionnaire was assessed in 20 patients comparable to the prospective participants from the out-patient department. The questionnaire had a high internal consistency reliability with a Cronbach's alpha coefficient of 0.8444.

Study procedure

In the **test group**, the patients the received usual care followed by the intervention led by pharmacists. On the first visit (month 0 or baseline), demographic and clinical data of the patients were obtained including gender, age, indication of warfarin use, target therapeutic INR, INR results, warfarin prescription, comorbidities, other medications, food-drug-herb interaction with warfarin, thromboembolism event, patient adherence, and major and minor bleedings warfarin ADR. The patients were then asked about warfarin therapy using the questionnaire of 15 questions. The total score was considered to be the patient's baseline score.

The intervention by pharmacist was provided by means of in-person counselling with individual patients using warfarin educational materials including how to use warfarin,

precaution and how to monitor and manage adverse events, if any. The researcher identified the patient's drug related problems and notified physicians accordingly.

On the second, third and fourth visits (month 1, 2, and 3), the patient was asked about warfarin therapy to assess the patient's knowledge. Warfarin therapy consultation was then provided by the pharmacist for each patient in each of all visits. Each visit was scheduled one month apart and took about 15 minutes. The study profile is shown in Figure 1.

In the **control group**, the patient received usual care followed by the questionnaire identical to that in the test group. On the first visit (month 0 or baseline), demographic and clinical data of the patients in the control group were obtained. They were also required for another 3 visits where each visit was scheduled one month apart and took about 5 minutes to complete. The patients were also asked to answer the questionnaire for baseline knowledge (first visit) and at the fourth visit.

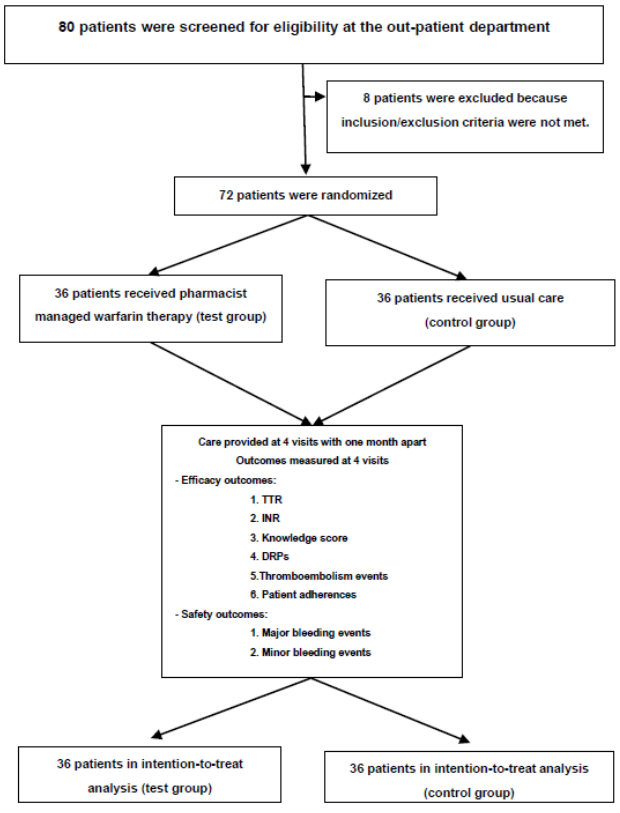

Figure 1 Study profile. **Note:** TTR = time that INR was within target therapeutic range; DRP drug related problems,

Outcomes assessments

Time in therapeutic range (TTR) was estimated as suggested by Rosendaal method. [16] To calculate the percentage of time spent within the therapeutic range, the number of days with INR in therapeutic range divided by a total number of days from first to third visit, and multiplied by 100. To calculate TTR in this study, three INR results after baseline visit were used. There have been two types of TTR; one is based on INR in the exact therapeutic range of 2 -3 for AF and DVT and 2.5 - 3.5 for MVR, and another is based on the INR therapeutic ranges with an extension of ±0.2. This study TTRs based on both the exact and expanded therapeutic range as mean ± SD. We also determined the proportions of patients whose INRs were within their target therapeutic range at each of all visits. INR values at each of all visits in both groups were obtained.

The knowledge scores on warfarin therapy in both groups by questionnaire were obtained at each of all visits from patients in the test group; while scores only at visit 1 (baseline) and visit 4 were obtained from those in control group.

Drug related problems (DRPs) assessment was modified from Hepler and Strand's criteria. [17] However, we identified three main categories of DRPs including the actual and potential DRPS associated with sub-therapeutic dosage, over dosage and drug interaction. For, sub-therapeutic dosage, we assessed the physician's prescription for patients whose INRs were below therapeutic range in each visit; while those over therapeutic range were subject to assessment for over dosage in the prescription. For drug interactions, all well established drug-drug, drug-food, drug-herb and drug-alcohol interactions were identified from the prescription and the consultation. [18] For drug-drug interactions, only interactions with significance level 1 and 2 stated in Drug Interaction Facts 2012 were investigated. [19] A well known reference was used to identify interactions between warfarin and food, herbs and other dietary supplements. [20] DRPs were identified in all visits for the test group; while only in the last visit for the control group.

Thromboembolism event was defined as the physician diagnosis of thromboembolism events documented in the medical chart. Patient who had sub-therapeutic dosage of INR value might have a risk to have thromboembolism event more than those with INR within therapeutic range. Main cause of thromboembolism event for patients with warfarin therapy was patients' adherences and drug-interaction with warfarin which could decrease the drug effect. Diagnosis of thromboembolism event was identified at each of all visits.

For safety outcomes, **major bleeding** was determined based on the physician's diagnosis including a severe

bleeding requiring blood transfusion, intracranial bleeding, intraspinal bleeding, intraocular bleeding or retroperitoneal bleeding. For **minor bleeding**, it was identified by the pharmacist assessment on the interview such as bruising, nose bleeding, gum bleeding, and bleeding in urine or stool. These signs and symptoms of bleeding within the past month prior to the visit consultation were acquired by the pharmacist at each visit.

The patient's **medication adherence** was assessed by the Morisky et al. questionnaire of 4 items.[21] Scoring the questionnaire was defined as 1- Yes and 0- No with Yes indicated an undesirable behavior. In accordance, patients with good adherence were those who got a score of zero points from the questionnaire; while those with scores of 1 to 4 points were considered having poor adherence. Medication adherence based on Morisky et al. scale was assessed at each of all visits in both groups. Pill count method was also done at 2nd, 3rd and 4th visits in both groups.

In terms of the **protection of study participants**, the study protocol was approved by the National Ethics Committee for Health Research (NECHR) from Lao PDR (approval number: 17/NECHR) and Mahasarakham University Ethics Committee for Research Involving Human Subjects (Approval number: No 079/2019).

Data analysis

Intention- to- treat analysis was performed. Kolmogorov-Smirnov test was used to test for normal distribution. Continuous variables were presented as mean ± SD when data were normally distributed. A student *t*- test or Mann-Whitney *U* test for independent samples were used to compare the mean or median values between groups, respectively. For within groups comparisons, a repeated measure ANOVA test was used. Categorical variables were presented as numbers and percentages. For categorical variables, a Chi- squared test or Fisher's exact test was used to compare differences between groups, as appropriate. Cochran's test was used to compare within group differences for categorical variables. Statistical analysis was performed using STATA software version 14. A type I error (α) of 5% was set as a significance level (i.e., *P*-value < 0.05).

Results

Of the 72 eligible patients, there were 36 in each group. Average age in the test group was slightly higher than that in the control group (53.1 ± 14.6 and 50.8 ± 14.0 years old, respectively). About three quarters of women were in two groups comparably (72.2% and 75.0% in test and control groups, respectively). Regarding indication of warfarin therapy, more patients in the test group on warfarin for atrial fibrillation than in the control group (50.0% and 38.9%, respectively); while the opposite was true for mitral valve replacement (47.2% and 58.3%, respectively). For patients requiring a therapeutic INR of 2 – 3, a slightly higher proportion of those within the target INR was found in the test group (52.8% and 41.7%, respectively). However, for those requiring a target INR of 2.5 – 3.5, the control group (58.3%) had a higher fraction than those in the test group (47.2%). Somewhat comparable proportions of co- morbidities were found in the two groups with hypertension as the most frequently found illness (22.2% vs13.9% in test and control groups, respectively).

Table 1 Patient demographic and clinical characteristics (N = 72).

Characteristics	N (%)	
	Test group (n = 36)	Control group (n = 36)
Age (mean ± SD)	53.1 ± 14.6	50.8 ± 14.0
Gender: female	26 (72.2)	27 (75.0)
Indication of warfarin therapy		
Atrial fibrillation	18 (50.0)	14 (38.9)
Mitral valve replacement	17 (47.2)	21 (58.3)
Deep vein thrombosis	1 (2.8)	1 (2.8)
Therapeutic INR range		
2 - 3	19 (52.8)	15 (41.7)
2.5 - 3.5	17 (47.2)	21 (58.3)
Comorbidities		
Hypertension	8 (22.2)	5 (13.9)
Diabetes	2 (5.6)	3 (8.3)
Rheumatic heart disease	1 (2.8)	1 (2.8)
Heart failure	1 (2.8)	1 (2.8)
Gout	2 (5.6)	0
Embolic stroke	0	1 (2.8)

For **time in therapeutic range**, TTR in the test group (63.3 ± 35.5%) was significantly higher than that in the control group (45.3 ± 39.9%) (*P*-value = 0.046) (Table 2). Once the expanded therapeutic range was considered, TTR in the test group (77.3 ± 34.1%) was also higher than that in the control

group (67.3 ± 36.5%) but with no statistical significance (*P*-value = 0.225). In terms of the proportion of patients with the TTR more than 60% of the time, the proportion in the test group (21 of 36 patients or 58.3%) was higher than that in the control group (12 of 36 patients or 33.3%) with statistical significance (*P*-value = 0.033). Once the expanded therapeutic range was considered, the proportion in the test group was also greater than that in the control group but with no statistical significance (72.2% and 62.1%, respectively, *P*-value = 0.317) (Table 2).

Table 2 Time of INR within therapeutic range (TTR) between test and control groups (N = 72).

Outcomes	Test group (n = 36)	Control group (n = 36)	*P*-value
Percentage of time that patients' INR values were within the therapeutic range (mean ± SD)			
• within the EXACT therapeutic range	63.3 ± 35.5	45.3 ± 39.9	0.046[a]
• within the EXPANDED therapeutic range	77.3 ± 34.1	67.3 ± 36.5	0.225[b]
Number of patient having TTR within the therapeutic range > 60% of the time (number (%))			
• within the EXACT therapeutic range	21 (58.3)	12 (33.3)	0.033[c]
• within the EXPANDED therapeutic range	26 (72.2)	22 (62.1)	0.317[c]

[a] Student *t*-test, [b] Mann-Whitney *U* test, [c] Chi-squared test.

In terms of **the number of patients with INR within their target range**, there were 19 and 15 patients in the test and control groups, respectively, who needed the target INR of 2 – 3 (Table 3). Of these patients, the number of patients with INR in the exact therapeutic range for the test group at baseline was not different from that at second visit (63.2% each); however, the number increased to 78.9% and 89.5% at the third and fourth visits, respectively, with no statistical significance.

In the control group, there was also an increase of number of patients whose INRs were in the exact target range from baseline (40.0%), to 66.7%, 66.7%, and 73.3% at the other three consecutive visits with no statistical significance (Table 3).

Table 3 Number of patients with the target INR of 2 – 3 whose INRs were in such exact target range (N = 34).

	Number (%) of patients by visit				Mean	*P*-value
	1st (baseline)	2nd	3rd	4th		
Test group (n = 19)	12 (63.2)	12 (63.2)	15 (78.9)	17 (89.5)	56 (73.7)	0.161[a]
Control group (n = 15)	6 (40.0)	10 (66.7)	10 (66.7)	11 (73.3)	37 (61.7)	0.208[a]
P-value	0.300[b]	1.000[b]	0.462[b]	0.370[b]	-	-

[a] Cochran's test for within-group comparison.

[b] Fisher's exact test, between test and control groups at each visit.

In terms of difference between groups, the proportions of patients with INR within their exact target range were slightly higher in the test group at each of all visits, with no statistical significance (Table 3).

Prortions of patients achieving their target INR

There were 17 and 21 patients in the test and control groups, respectively, who needed the target INR of 2.5 – 3.5 (Table 4). Of these patients, there was also an increase of number of patients whose INRs were in the exact target range from baseline (5.8%), to 52.9% at each of the other three consecutive visits with a statistical significance (*P*-value = 0.011). In the control group, there was also an increase of number of patients whose INRs were in the exact target range from baseline (14.3%), to 38.1%, 57.1%, and 61.9% at the other three consecutive visits with a statistical significance (*P*-value = 0.003).

In terms of difference between groups, the proportions of patients with INR within their exact target range were somewhat similar between the two groups at each of all visits, with no statistical significance (Table 4).

Table 4 Number of patients with the target INR of 2.5 – 3.5 whose INRs were in such exact target range (N = 38).

	Number (%) of patients by visit				Mean	*P*-value
	1st (baseline)	2nd	3rd	4th		
Test group (n = 17)	1 (5.8)	9 (52.9)	9 (52.9)	9 (52.9)	28 (41.2)	0.011[a]
Control group (n = 21)	3 (14.3)	8 (38.1)	12 (57.1)	13 (61.9)	32 (38.1)	0.003[a]
P-value	0.613[b]	0.513[b]	1.000[b]	0.743[b]	-	-

[a] Cochran's test for within-group comparison.

[b] Fisher's exact test, between test and control groups at each visit.

Regarding the patient's **knowledge on warfarin therapy**, the mean baseline score in the test group was only 5.2 points of the total of 15 points (Table 5). The score in the test group increased to 9.4, 13.4 and 13.2 points at the 2nd, 3rd and 4th visits, respectively with a statistical significance (*P*-value = 0.001). In the control group, the mean score at baseline (7.1 points) was similar to that at 4th visit (7.0 points).

In terms of difference between groups, the mean score at baseline in the test group (5.2 points) was significantly lower than that in the control group (7.1 points) (*P*-value = 0.013). However, at the 4th visit, the mean score in the test group (13.2 points) was much higher than that in the control group (7.0 points) with a statistical significance (*P*-value = 0.001).

Table 5 Patient's knowledge about warfarin therapy (N = 72).

	Knowledge scores by visits, mean ± SD				*P*-value
	1st (baseline)	2nd	3rd	4th	
Test group (n = 36)	5.2 ± 2.6	9.4 ± 2.5	13.4 ± 2.1	13.2 ± 1.4	0.001[a]
Control group	7.1 ± 3.7	-	-	7.0 ± 3.6	0.628[b]
P-value**	0.013[c]	-	-	0.001[d]	-

[a] Repeated-measure ANOVA test for within test group comparison.

[b] Paired t-test for within control group comparison.

[c] Student t-test, between test and control groups at.

[d] Mann-Whitney U test, between test and control groups.

In terms of DRPs, there were 20 DRPs in 16 patients in the test group at baseline. The number of DRPs were more likely to decrease with 6, 8 and 6 DRPs at the 2nd, 3rd and 4th visits. On the other hand, there were as high as 15 DRPs in the control group at the last visit.

Of the 20 DRPs found in the test group at baseline, the majority were sub-therapeutic dosage, at baseline (12 of 20 DRPs or 60.0%) followed by drug interaction (8 or 20 DRPs or 40.05). Sub-therapeutic dosage could also be the majority of DRPs in the test group at 2nd visit (6 of 6 DRP or 100.0%), 3rd visit (6 of 8 DRPs or 75.0%), and 4th visit (6 of 6 DRPs or 100.0%).

Of the 15 DRPs found in the test group at the 4th visit, the majority were drug interaction (10 of 15 DRPs or 66.7%), followed by sub-therapeutic dosage (5 of 15 DRPs or 33.3%).

Table 6 Number of drug related problems (%) (N = 72).

	Number of DRPs (%)by visits*			
	1st (baseline)	2nd	3rd	4th
Total DRPs				
Test group (n = 36)	20 DRPs in 16 patients	6 DRPs	8 DRPS	6 DRPS
Control group (n = 36)	-	-	-	15 DRPS
Sub-therapeutic dosage				
Test group	12 of 20 (60.0)	6 of 6 (100.0)	6 of 8 (75.0)	6 of 6 (100.0)
Control group	-	-	-	5 of 15 (33.3)
Over dosage				
Test group	0	0	1 of 8 (12.5)	0
Control group	-	-	-	0
Drug interaction				
Test group	8 of 20 (40.0)	0	1 of 8 (12.5)	0
Control group	-	-	-	10 of 15 (66.7)

* DRPs were identified in all visits for the test group and only in the last visit for the control group.

For **thromboembolism event**, none of the patients in both groups experienced the event at any visits during study period.

On the safety side, major and minor bleedings were as follows. For **major bleeding**, none were found in both groups. **Minor bleeding**, on the other hand, decreased from 11.11% in the first visit (baseline) to 0% in fourth visit. A total of 6 minor bleeding cases in 6 patients in the test group and 9 cases in 9 patients in the control group.

In terms of **patient's medication adherence**, the proportion of patients with good adherence in the test group was 69.4% at baseline (visit 1) and increased to 100.0% in the last visit; while in the control group, it increased from 88.9% at baseline to 97.2% at the last visit (Table 7). At each of all visits, no statistically significant differences between the two groups.

Table 7 Patient's medication adherence by Morisky et al. questionnaire (N = 72).

	Number of patients with good adherence (%) by visits			
	1st (baseline)	2nd	3rd	4th
Test group (n = 36)	25 (69.4)	35 (97.2)	36 (100.0)	36 (100.0)
Control group (n = 36)	32 (88.9)	36 (100.0)	36 (100.0)	35 (97.2)
P-value*	0.079	1.000	1.000	1.000

* Fisher's exact test, for between-group comparisons at each visit.

Based on the pill count method, percentage of pills taken increased from the 2nd visit to the highest value at 3rd visit, followed by a decrease at the 4th visit, in both groups (Table 8). By average from the three visits, percentage of pills taken in the test group (87.3%) was higher than that in the control group 81.8%) with no statistical significance.

Table 8 Patient's medication adherence by pill count method (N = 72).

	Percent of pills taken (mean ± SD) by visits			
	2nd	3rd	4th	Mean
Test group (n = 36)	86.4 ± 25.1	97.8 ± 24.9	77.7 ± 16.1	87.3 ± 16.9
Control group (n = 36)	77.3 ± 23.9	88.5 ± 32.7	79.6 ± 25.3	81.8 ± 15.7
P-value*	0.249	0.076	0.945	0.207

* Mann-Whitney U test, for between-group comparisons at each visit.

Discussions and Conclusion

In this randomized controlled trial examining the effects of pharmacist-based warfarin management compared with the usual care, all patients were successfully followed up for the

total of 3 months. The patients in the two groups were comparable regarding age, indications of warfarin therapy (AF, MVR and DVT), gender, target therapeutic INR range, and co-morbidity. The fact that hypertension was the most found co-morbidity raised a concern. Certain antihypertensive drugs could react with warfarin which could lead to various problems. [22] The problem could be considerable since hypertension was found in 22.0% and 13.9% in the test and control groups, respectively. Other co-morbidities with fewer patients included diabetes, rheumatic heart disease, heart failure, gout and stroke. These patients needed a large number of medications which could pose potential drug interactions with warfarin among these patients. Pharmacist could have a major role in preventing drug interactions. Bungard et al. showed that most comorbidities were non-communicable diseases (e.g., hypertension, heart failure and diabetes mellitus) [23] which were similar to our study. The potential drug interaction between warfarin and other drugs is still of concern even though our study did not find any of such drug interactions.

Our participants were in there 50 of age with 53.1 and 50.8 years in the test and control groups, respectively. This finding was consistent with the work of Verret el al. [24] where the age of 58.4 and 57.0 years were found in the pharmacist intervention and control groups, respectively. Age is of concern since it is one of the risk factor of cardiovascular diseases where higher age was associated with a higher risk of AF or MVR which was found the most indications in our study.

The indications of warfarin found in our study was somewhat different from other studies. Chan et al.[25] found that the most common indications for warfarin therapy were atrial fibrillation (53.0%) followed by deep vein thrombosis (12%), pulmonary embolism (7.0%) and mechanical valve replacement (1.8%). In our study, MVR was as high as 47.2% and 58.3% in the test and control groups, respectively; while AF was found in 50.0% and 38.9% in the test and control groups, respectively. This could be due to the fact that Mahosot Hospital is the only hospital in Lao that provides MVR operation. On the other hand, a very low number of DVT patients could be due to a short duration for warfarin therapy for DVT which led the patients to missing the study period.

In our study, pharmacists only identified DRPs and notified physician if found. No warfarin dose adjustment was conducted. intervention on this study only educate patient and assess DRPs to notified with physicians if DRPs were found. There was no dose adjustment activity by pharmacist. However, a systematic review by Saokaew et al. [6] and Manzoor et al. [26] revealed that pharmacist activities such as dosage adjustment, bridging assessment, and next INR appointment or follow-up could be indirectly educational to the patients. Every service the pharmacist provided could improve clinical outcomes when compared with services not including the pharmacist. This is generally in accordance with our findings.

Pharmacist' s activities in warfarin therapy could be different from study to study depending on the actual and potential responsibilities of the pharmacist at the given hospitals or countries. Our study showed the development of pharmacist responsibility in warfarin management at the out-patient department of Mahosot Hospital. Wilson et al[14] compared pharmacists in the anticoagulation clinics with family physicians. More elaborate services by the pharmacist provided standardized educational package consisting of the indication for therapy, the importance of complying with the regimen, the need for the close monitoring, the potential risk of taking other medications, dietary considerations and the importance of self-monitoring for evidence of bleeding or thromboembolic complications. The better way to educate the patient was face-to-face discussion for individual patients with the support materials for the patient to view later.

Findings from our study could be different from other studies due to the length of follow-up. Our study had a total of 4 visits within a 3-month period. Wilson et al., Jackson et al., and Chan et al. had the same length of follow up of 3 month as our study[25,25-→27]; while Lalonde et al had a 6-month follow up[28] and Katemateegaroon had a 10-month follow up.[29]

Our study showed that warfarin therapy provided by pharmacist could result in a better coagulation control when compared with the usual care. A systematic review and meta-analysis of Hou et al. which included 8 RCTs and 9 observational cohort studies with 9,919 patients showed that TTR control in the pharmacist-led management group was significantly better than the control group (*P*-value = 0.007).[5] This was consistent with our study where %TTR in the intervention group (63.3 ± 35.5%) was significantly higher than that in the control group (45.3 ± 39.9%) (*P*-value = 0.046). Furthermore, Wilson et al. showed that the percentage of time that patients' INR values of those managed by anticoagulation clinics was within the expanded therapeutic range by 82%

(95 % confidence interval [CI] of 78% - 85%) versus 76% (95% CI of 72% - 80%) in patients taken care of by family physicians (*P*-value = 0.034).[14] A higher value in Wilson et al. could possibly due to more new warfarin users.

In Thailand, Saokaew et al. found that at the end of follow-up period, patients in the pharmacist intervention group had significantly higher actual TTR (48.3% and 40.1%, respectively, *P*-value < 0.001) and expanded TTR (62.7% and 53.9%, respectively, *P*-value < 0.001) than those receiving usual care. [30] The TTR results from our present study were higher than those in Saokaeow et al. study. The different TTRs from our study could mean that patients from both countries had different culture and different eating behaviors which could affect INR. However, there have been no studies to prove this different contributing factors. Our findings could have been slightly higher than a few more studies since TTR in European ancestries that the exact expanded therapeutic INR ranges were 40 - 64%.[31]

The analysis of the outcome of patients who were randomized to warfarin therapy in the SPORTIF III and V studies indicated that the risk of death and stroke or embolic events was lower in patient with TTR ≥ 60% than in those with TTR < 60%.[32] Patients with high %TTR had low risk of death or stroke. Our TTR outcomes showed the percentage of patients who had TTR within exact therapeutic range > 60% was 58.3% in the test group which was higher than 33.3% in the control group. It has been know that TTR > 60% in pharmacist-managed warfarin therapy was associated with a lower risk of death and stroke.

The definitions of expanded INR value in a therapeutic range in various studies were different. In our study, it was defined as INR ± 0.2 which was similar to Chan et al.[25] It was defined as INR ± 0.3 by Verret et al.[24] and ± 0.5 by Bungard et al.[23] The expansion is very useful for real practice of adjusting warfarin dosage**.** Aiming at ± 0.2 could better prevent the thromboembolism events or stroke and bleeding.

The number of patients with INR in therapeutic range 2-3 was not statistically significant difference in 4 visits in each of the two groups. The percentage of patients' INR in therapeutic range in the test group was higher than that in the control group (73.7% and 61.7%, respectively). The percentages that we found were still low. The length of the follow-up should be extended for awareness of ADRs along with major bleeding, minor bleeding and thromboembolism events.

The intervention of pharmacist consultation improved the patient's knowledge in warfarin therapy as the knowledge scores in the test groups increased dramatically from 5.2 to 13.2 points after the intervention. The intervention also offered a better knowledge when compared with the usual care as indicated by the scores from the last assessment where the test group had 13.2 points and the control group had 7.0 points (*P*-value = 0.001). Several studies reported that patients' knowledge outcomes improved after the patient's education becomes a part of pharmacist intervention.[33-35] However, our study results were in contrast with the study of Hasan et al. where there were no significant differences between pharmacist and non-pharmacist that run anticoagulant clinic.[35] This could be due to the differences in the emphasis of knowledge. Hasan et al. focused on the patients' knowledge on the mechanism of action of warfarin, the interaction between warfarin and alcohol, side effects of warfarin; our study focused mainly on the patient's behavior toward warfarin therapy.

The most found DRPs were sub-therapeutic dosage which consisted of 30 cases in the intervention group, followed by drug interactions (9 cases). Our finding was not consistent with the study of Jittsue el al. where the most found DRPs were drug interaction (33.6%), followed by adverse drug reactions (28.2%), and sub-therapeutic dosage (16.0%).[36] This could be attributable to the fact that Mahosot Hospital did not have the protocol for warfarin dosage adjustment therefore leaving the physicians to adjust the dosage by their routine experience based on INR value. In addition, due to the awareness of bleeding events, physicians were more likely to adjust the dosage lower than recommended. However, no huge concern was not apparent since no reports of thromboembolism events in this study despite as prevalent sub-therapeutic dosage.

No thromboembolism events were found both in intervention and control groups. This could be due to a relatively short duration of follow-up and a small number of patients. In addition, more factors were influencing these beneficial outcomes.

The patient's adherence assessed by the questionnaire of Morisky and colleagues was good in both groups at all follow-up visits. However, no significant differences between groups at all follow-up visits were found. Pill count method offered a similar result. However, level of adherence seemed to be higher with the 4-question scale of Morisky et al. Both

methods were generic for assessing warfarin adherence warfarin and could be practically done at each visit. Both methods were better than physician assessment as suggested by Parker et al. [37] They found that clinicians judged participants to be adherent at 82.8% of visits and the patient self-reported perfect adherence at 77.9% of the time. Their findings were similar to our study. Another study in patients with prosthetic heart valves in 1981 found that adherence to warfarin was about 90% [38] which was close to 87.3% in the intervention group with pill count method. Kimmel et al. also reported 92% adherence[39] which was consistent with our study.

Even though major bleeding events were not found in our study, minor bleeding events were found. All patients who faced such events had already counselled by pharmacists, including how to manage the existing events and prevent the future events. Study of Wilson et al. also emphasized the pharmacist's responsibility in managing and preventing bleeding related to warfarin.[14]

Our study had some limitations. Since no electronic medical records in the study hospital, some information was recorded in the patient patient's book. Missing information sometimes could happen since the patient forgot to bring the book to the follow-up visit. In addition, ADR or DRPs of warfarin were not recorded in the patient's book. Some significant information could lose. We recommended recording such information in the patient's book. With a lack of patient's information recorded, researchers could not be certain about the number of all warfarin patients, and the number of follow-up patients in each month.

Furthermore, with a small number of patients included in the study, significant comparisons could be more difficult to find; for example, number of patients with INR within therapeutic range. In addition, with a small number of patients, rare events such as thromboembolism event and major bleeding were hard to find. If we could have more patients, we could increase the chance of finding thromboembolism event and major bleeding. In addition, the follow-up period was relatively short. A longer follow-up period was recommended to better understand the patient's adherence, efficacy and safety outcomes, and any issues relevant to warfarin.

For future research, more studies on agreement toward warfarin dosage adjustment guideline among all health care professionals, especially physicians, are needed. This could encourage the acceptance of pharmacist's role in warfarin clinic.

In conclusion, warfarin therapy by pharmacist-managed consultation resulted in a better outcome when compared with usual care. This result could be useful in decision making on implementing warfarin clinic to benefit professionals and patients themselves. The pharmacist's role in warfarin clinic should be enhanced to meet the expectation of all parties in healthcare service.

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