นิพนธ์ต้นฉบับ

Effect of patient booklet and dosage adjustment protocol on oral anticoagulant therapy monitoring

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Abstract:

Effect of patient booklet and dosage adjustment protocol on oral anticoagulant therapy monitoring

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Songkla Med J 2003; 21(1): 33-43

Objectives: *This study was to determine the effect of patient booklet and the dosage adjustment protocol on oral anticoagulant therapy monitoring. The outcome measures were (1) number of International Normalized Ratio (INR) results/number of clinic visits (2) number of INR within therapeutic range (TR)/number of INR results (3) number of dosage adjustments following the protocol/number of INR outside TR (4) number of clinic visits/number of appointments (5) number of emergency room (ER) visits and/or hospital admissions associated with warfarin therapy.*

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Design: *Pre-post intervention study*

Materials and methods: *The study was divided into 3 phases. Phase 1 was a 10-month control phase (January - October 1997). During phase 1, patients received only anticoagulants as issued in the prescriptions without INR monitoring by pharmacists. Phase 2 was a 12-month counseling phase (November 1997 - October 1998) during which patients were interviewed and counseled by a pharmacist. Along with counseling, the pharmacist provided a warfarin leaflet to patients. Pharmacist counseling continued for every warfarinised patients in the heart clinic. Nurses in the heart clinic transferred OPD cards to the pharmacists by asking patients to carry the card with their prescriptions. Phase 3 was an 8-month study phase (November 1998 - June 1999). During the phase 3, patients received drug counseling similar to phase 2 but instead of a warfarin leaflet, patient booklets on warfarin with an INR record table were given. Twelve patients were interviewed for satisfaction with the booklet. Eleven of them (91.7%) were satisfied with the booklet, the other one had his own booklet from another hospital. In this phase, the investigator also provided the dosage adjustment protocol to every physician in the heart clinic. The investigator described the details of dosage adjustment protocol individually. The patients attending the heart clinic were divided into 2 groups. Group 1 was patients visi-ting the heart clinic before and during phase 1. Group 2 was those entering the heart clinic during phase 2.*

Results: *The study showed that, in group 1 patients (n = 38), the number of INR results in phase 3 was increased as compared to phase 1 and phase 2 ($p < 0.001$ and < 0.025, respectively). In group 2 patients (n = 24), the number of INR results in phase 3 was increased as compared to that of phase 2 ($p < 0.001$). The number of INR within therapeutic range (TR) in group 1 patients was significantly increased in phase 3 as compared to those of phase 1 and phase 2 ($p = 0.001$ and 0.005, respectively). The corresponding figures in group 2 patients were not different between phase 3 and phase 2 ($p > 0.05$). The number of dosage adjustments following the protocol when INR was outside the TR was not different between each phase in either group of patients. Except for group 1 patients, the number of dosage adjustments was increased in phase 3 as compared to that of phase 2 ($p < 0.05$). The number of clinic visits following appointments was not different between each phase in either group of patients. For group 1 patients, the number of hospital admissions and ER visits associated with warfarin therapy were 10, 2 and 4 in phases 1, 2 and 3, respectively. The corresponding figures in group 2 patients were 2 in both phases 2 and 3.*

Conclusion: *The results showed that the patient booklet increased patient compliance to clinic visit, according to the physician's appointment, to have INR tested. The dosage adjustment protocol could contribute to INR being in the TR in group 1 patients, but it had no effect in group 2 patients. The explanation may be that some of the group 1 patients had received dosage adjustments from specialty hospitals and had been recommended to keep the target INR similar to the dosage adjustment protocol in this study. But group 2 patients had received warfarin in Maharaj Nakhon Sri Thammarat Hospital, where physicians had different dosage adjustment protocols. The dosage adjustment protocol was not followed except for group 1 patients. This might be due to the variation in warfarin adjustment of individual physicians. Further study should focus on the consensus guideline agreement between physicians and pharmacists. Patients attending the clinic should be monitored more frequently and regularly.*

Key words: *patient booklet, dosage adjustment protocol, anticoagulant therapy, warfarin*

บทคัดย่อ:

วัตถุประสงค์: *การศึกษานี้มีวัตถุประสงค์เพื่อวัดผลการให้คู่มือการใช้ยาวาร์ฟารินแก่ผู้ป่วยและแนวทางการปรับขนาดยาวาร์ฟารินแก่แพทย์ต่อผลของการใช้ยาวาร์ฟารินในผู้ป่วยคลินิกโรคหัวใจ แผนกผู้ป่วยนอก โรงพยาบาลมหาราชนครศรีธรรมราช โดยมีตัวชี้วัด คือ (1) จำนวนครั้งของการวัดระดับ International Normalized Ratio (INR) ของผู้ป่วย/จำนวนครั้งของการมาโรงพยาบาล (2) จำนวนครั้ง*

ของค่า INR ที่อยู่ในช่วงของการรักษา/จำนวนครั้งของการวัดระดับ INR (3) จำนวนครั้งของการปรับขนาดยาของแพทย์/จำนวนครั้งของค่า INR ที่อยู่นอกช่วง INR เป้าหมายของผู้ป่วย (4) จำนวนครั้งของการมาโรงพยาบาล/จำนวนครั้งที่นัด (5) การมารับการรักษาที่แผนกฉุกเฉินหรือนอนโรงพยาบาลเนื่องจากภาวะแทรกซ้อนจากการใช้ยาวาร์ฟาริน

ชนิดของการวิจัย: *การประเมินผลก่อนและหลังการให้บริการสุขภาพ*

วัสดุและวิธีการ: *ระยะเวลาในการศึกษาแบ่งเป็น 3 ระยะ คือ ระยะที่ 1 เป็นระยะควบคุม ใช้เวลา 10 เดือน (มกราคม - ตุลาคม 2540) ระยะนี้ผู้ป่วยได้รับการจ่ายยาตามใบสั่งยาโดยได้รับคำแนะนำเฉพาะวิธีรับประทานยาตามแพทย์สั่ง โดยมิได้มีการติดตามดูค่า INR ระยะที่ 2 เป็นระยะการให้คำปรึกษาและแนะนำการใช้ยาแก่ผู้ป่วย ใช้เวลา 12 เดือน (พฤศจิกายน 2540 - ตุลาคม 2541) ระยะนี้ผู้ป่วยได้รับคำแนะนำเพิ่มเติมจากเภสัชกร โดยเภสัชกรสัมภาษณ์ผู้ป่วยและค้นหาปัญหาจากการใช้ยารวมทั้งให้แผ่นพับประกอบในการให้คำแนะนำ การให้คำแนะนำจะทำต่อเนื่องในผู้ป่วยคลินิกโรคหัวใจทุกรายที่ใช้ยาวาร์ฟาริน โดยให้พยาบาลประจำคลินิกโรคหัวใจช่วยแนบประวัติของผู้ป่วยมากับใบสั่งยาทุกครั้ง ระยะที่ 3 เป็นระยะศึกษา ใช้เวลา 8 เดือน (พฤศจิกายน 2541 - มิถุนายน 2542) ระยะนี้ผู้ป่วยจะได้รับคำแนะนำเช่นเดียวกับระยะที่ 2 แต่มีการให้คู่มือการใช้ยาที่มีการบันทึกผลของค่า INR โดยให้ผู้ป่วยนำมาทุกครั้งที่มาโรงพยาบาล มีการทดสอบความพึงพอใจในผู้ป่วย 12 ราย ในช่วงเริ่มต้นของระยะที่ 3 ผู้ป่วย 11 ราย (91.7%) พึงพอใจในคู่มือนี่ อีก 1 ราย มีคู่มือจากโรงพยาบาลอื่นแล้วจึงไม่ได้ใช้ และมีการให้แนวทางการปรับขนาดยาแก่แพทย์ประจำคลินิกโรคหัวใจทุกคน โดยผู้ศึกษาอธิบายรายละเอียดของแนวทางการปรับขนาดยาเป็นรายบุคคล ผู้ป่วยที่ศึกษาแบ่งเป็น 2 กลุ่ม กลุ่มที่ 1 คือ กลุ่มที่มารับการรักษาที่โรงพยาบาลมหาราชก่อนหรือในระยะที่ 1 และกลุ่มที่ 2 คือ กลุ่มที่เริ่มมารับการรักษาที่โรงพยาบาลมหาราชในระยะที่ 2 ของการศึกษา*

ผลการศึกษา: *ผลการศึกษาพบว่าผู้ป่วยกลุ่มที่ 1 (จำนวน 38 ราย) มีจำนวนครั้งของการวัดระดับ INR ในระยะที่ 2 มากกว่าระยะที่ 1 ($p < 0.001$) และในระยะที่ 3 มากกว่าระยะที่ 2 ($p < 0.025$) กลุ่มที่ 2 (จำนวน 24 ราย) มีจำนวนครั้งของการวัดระดับ INR ในระยะที่ 3 มากกว่าระยะที่ 2 ($p < 0.001$) โดยจำนวนครั้งของค่า INR ที่อยู่ในช่วงของการรักษาของผู้ป่วยกลุ่มที่ 1 เพิ่มขึ้นอย่างมีนัยสำคัญในระยะที่ 3 เทียบกับระยะที่ 1 และระยะที่ 2 ($p = 0.001$ และ 0.005 ตามลำดับ) แต่ผลไม่แตกต่างกันในกลุ่มที่ 2 ($p > 0.05$) ส่วนการปรับขนาดยาของแพทย์เมื่อระดับ INR อยู่นอกช่วง INR เป้าหมายไม่แตกต่างกันในแต่ละระยะของผู้ป่วยทั้ง 2 กลุ่ม ยกเว้นกลุ่มที่ 1 มีการปรับขนาดยาเพิ่มขึ้นในระยะที่ 3 เทียบกับระยะที่ 2 ($p <0.05$) การมาโรงพยาบาลตามนัดของผู้ป่วยไม่แตกต่างกันในทุกระยะของผู้ป่วยทั้ง 2 กลุ่ม จำนวนครั้งของการมารับการรักษาที่แผนกฉุกเฉินหรือนอนโรงพยาบาล เนื่องจากภาวะแทรกซ้อนจากการใช้ยาวาร์ฟารินในผู้ป่วยกลุ่มที่ 1 เป็น 10, 2 และ 4 ครั้ง ในระยะที่ 1, 2 และ 3 ตามลำดับ ในผู้ป่วยกลุ่มที่ 2 เป็น 2 ครั้ง ทั้งในระยะที่ 2 และ 3*

สรุป: *ผลการศึกษาครั้งนี้แสดงให้เห็นว่าคู่มือประจำตัวผู้ป่วยช่วยให้ผู้ป่วยมีความร่วมมือเพิ่มขึ้นในการวัดระดับ INR ตามคำสั่งของแพทย์ แนวทางการปรับขนาดยาสามารถช่วยให้ผู้ป่วยมีค่า INR อยู่ในช่วง INR เป้าหมายในผู้ป่วยกลุ่มที่ 1 แต่ในผู้ป่วยกลุ่มที่ 2 ไม่มีผลการปรับขนาดยาของแพทย์ตามแนวทางการปรับขนาดยาไม่เป็นไปตามแนวทางที่ตั้งไว้ ยกเว้นในผู้ป่วยกลุ่มที่ 1 เนื่องจากผู้ป่วยกลุ่มนี้บางรายมีการปรับขนาดยามาจากโรงพยาบาลเฉพาะทาง ซึ่งแนะนำให้คงระดับ INR ของผู้ป่วยใกล้เคียงกับแนวทางการปรับขนาดยาของการศึกษานี้ ส่วนผู้ป่วยกลุ่มที่ 2 ส่วนใหญ่เริ่มใช้ยาที่โรงพยาบาลมหาราชนครศรีธรรมราช ซึ่งแพทย์ผู้สั่งมีแนวทางในการปรับขนาดยาต่างกัน การศึกษาต่อไปควรเน้นการจัดทำแนวทางร่วมกันระหว่างเภสัชกรและแพทย์ทุกคนในคลินิกโรคหัวใจ และควรมีการติดตามผู้ป่วยอย่างใกล้ชิดและสม่ำเสมอมากขึ้น*

คำสำคัญ: *คู่มือการใช้ยา, แนวทางการปรับขนาดยา, การรักษาด้วยยาต้านการจับตัวเป็นลิ่มเลือด, วาร์ฟาริน*

Introduction

Oral anticoagulant therapy is routinely used for prevention and treatment of various thrombolic complications. The drug that is most widely used among oral anticoagulants is warfarin[1]. It is a drug of choice for prevention and treatment of thromboembolism in various conditions such as atrial fibrillation (AF), post prosthetic heart valves, deep vein thrombosis (DVT), pulmonary embolism (PE) and valvular heart disease etc.[2]. The limitation of warfarin use is its narrow therapeutic index. When the plasma level is slightly increased or decreased from the therapeutic range, it may cause overdose

reaction or non-control of the diseases due to subtherapeutic dose, respectively. A common complication from warfarin use is bleeding in various parts of the body.[3-10] There are many factors that can potentiate bleeding from warfarin use. The factors include aging[8, 11] and types of co-existing diseases[12], etc. The other complication from warfarin is thromboembolism that results from lower warfarin plasma level leading to lower INR than the target INR. The target INR for each disease or medical condition is different[13-20].

Patients on warfarin should have good knowledge about the diseases they have and the drugs they use and should be monitored for clinical outcome closely. Patients should understand how important it is to comply with therapy. For patients to have good knowledge of drug usage, self-care and optimal outcome of therapy, the health-care team, consisting of physicians, pharmacists and nurses, should be well coordinated to provide continuous education to patients and convince them to have regular clinic visits because long-term care patients might have higher non-compliance[21]. Pharmacists, as members of the health-care team, have responsibilities to provide drug information to patients and health professionals, to identify, resolve and prevent drug-related problems. In Maharaj Nakhon Sri Thammarat Hospital, it was found that many warfarinised patients had INR outside TR. This study was conducted with the aim to help patients who use warfarin comply with clinic visits, have documented INR results and have proper dosage adjustment according to the INR results. Meanwhile, the phar- macist was able to find and resolve other problems relating to drug therapy.

Definition of terms

INR = International Normalized Ratio

= (Observed PT (prothrombin time)/mean normal PT)^{ISI}

ISI = International Sensitivity Index

Materials and methods

1. Setting

Maharaj Nakhon Sri Thammarat Hospital is a 1000-beds regional hospital. The heart clinic is an outpatient department, operating every Wednesday. There are 3 physicians attached to the clinic with 100-150 patients being seen at each week. The patients can be divided into 2 groups: those with hypertension and those with heart diseases. There are about 350 heart-disease patients per month. Forty of them are taking warfarin. Thus, about 10 warfarinised patients visit the heart clinic each week.

2. Study Design

This study was designed to have 3 phases: phase 1, phase 2 and phase 3.

Phase 1: A control phase of 10 months from January 1997 to October 1997. During phase 1, patients received information about warfarin from pharmacist comprising only the information on the package label without INR monitoring. The investigator reviewed patient history from patient charts. The following data were reviewed and recorded; medical history of each patient; demographic data, indications for warfarin use, co-existing diseases, history of warfarin use, INR result, date of appointment and dosage adjustment at each clinic visit. History of emergency room visits and / or hospital admissions that might relate to warfarin use were also reviewed.

Phase 2: A 12-month period of counseling phase from November 1997 to October 1998. In this phase, the patients were educated about warfarin through pharmacist counseling and warfarin leaflet. Patients' data were reviewed in a similar manner to phase 1. All patients from phases 1 who entered the heart clinic during phase 2 were included in the study. In this phase, the pharmacist used patient medication profile and warfarin record form.

Phase 3: An 8-month study period from November 1998 to June 1999. Patients from phase 1 and phase 2 were enrolled in the study. In this phase, the pharmacist recommended the Dosage Adjustment Protocol to physicians in the heart clinic. This protocol was developed from that proposed by Ansell et al, 1997, by the investigator and approved by the physician who was the consultant of the study. All physicians who took care the patients at the heart clinic accepted the protocol at the beginning of the study. The pharmacist reviewed the INR results from OPD cards and the laboratory reports from the laboratory room to monitor the dosage adjustments of the physicians.

The patients' files and records from counseling were reviewed. The patients were divided into 2 groups according to the time of entering the heart clinic at Maharaj Nakhon Sri Thammarat Hospital because the period of warfarin using could lead to the different results of each patient. Group 1 patients were patients who entered the heart clinic before and during phase 1. This group had outcomes to compare for all 3 phases. Group 2 patients were patients who entered the heart clinic during phase 2. This group had outcomes to compare only for phase 2 and phase 3.

The pharmacist interviewed the patient using the patient medication profile and warfarin record form. Via counseling, patients received the Patient Booklet for Warfarin Use. At each visit, the pharmacist interviewed patients for any drug-related problems (DRPs) and recorded his/her INR in the booklet.

Twelve patients were interviewed for satisfaction with the booklet. There were 3 questions: (1) Do you understand the content of this booklet? (2) What do you think about the look of this booklet? (3) Are you satisfied with this booklet?

Target INR

There are two recommended ranges of target INR based on literature review[25] and discussion with the physicians in the heart clinic.

1. INR 2.0-3.0 for patients with atrial fibrillation, cardioembolic stroke, left ventricular dysfunction, following myocardial infarction, valvular heart diseases, bioprosthetic heart valve.

2. INR 2.5-3.5 for patients with the following embolic event in cardioembolic stroke despite anticoagulation, following embolic event in left ventricular dysfunction despite anticoagulation, recurrent myocardial infarction, status post embolic event in mitral valve prolapse despite anticoagulation, status post embolic event in rheumatic valve disease despite anticoagulation, mechanical prosthetic heart valve.

3. Outcome Measures.

3.1 number of INR results/number of clinic visits

3.2 number of INR within therapeutic range (TR)/number of INR results

3.3 number of dosage adjustments following the protocol/number of INR outside TR

3.4 number of clinic visits/number of appointments

3.5 number of emergency room visits and/or hospital admissions associated with warfarin therapy

4. Data Analysis

Descriptive statistics were used for: (1) demographic and medical conditions of patients (2) number of ER visits and/or hospital admissions associated with warfarin therapy in phases 1, 2 and 3 for group 1 patients and in phase 2 and 3 for group 2 patients. Repeated-measure ANOVA was used for comparison among phases 1-3 in group 1 patients for the proportions of: (1) number of INR results/number of clinic visits, (2) number of INR within TR/number of INR results (3) number of dosage adjustments following the protocol/ number of INR outside TR (4) number of clinic visits/ number of appointments. Paired t-test was used for comparison between phase 2 and 3 in group 2 patients for the same measures as those of group 1.

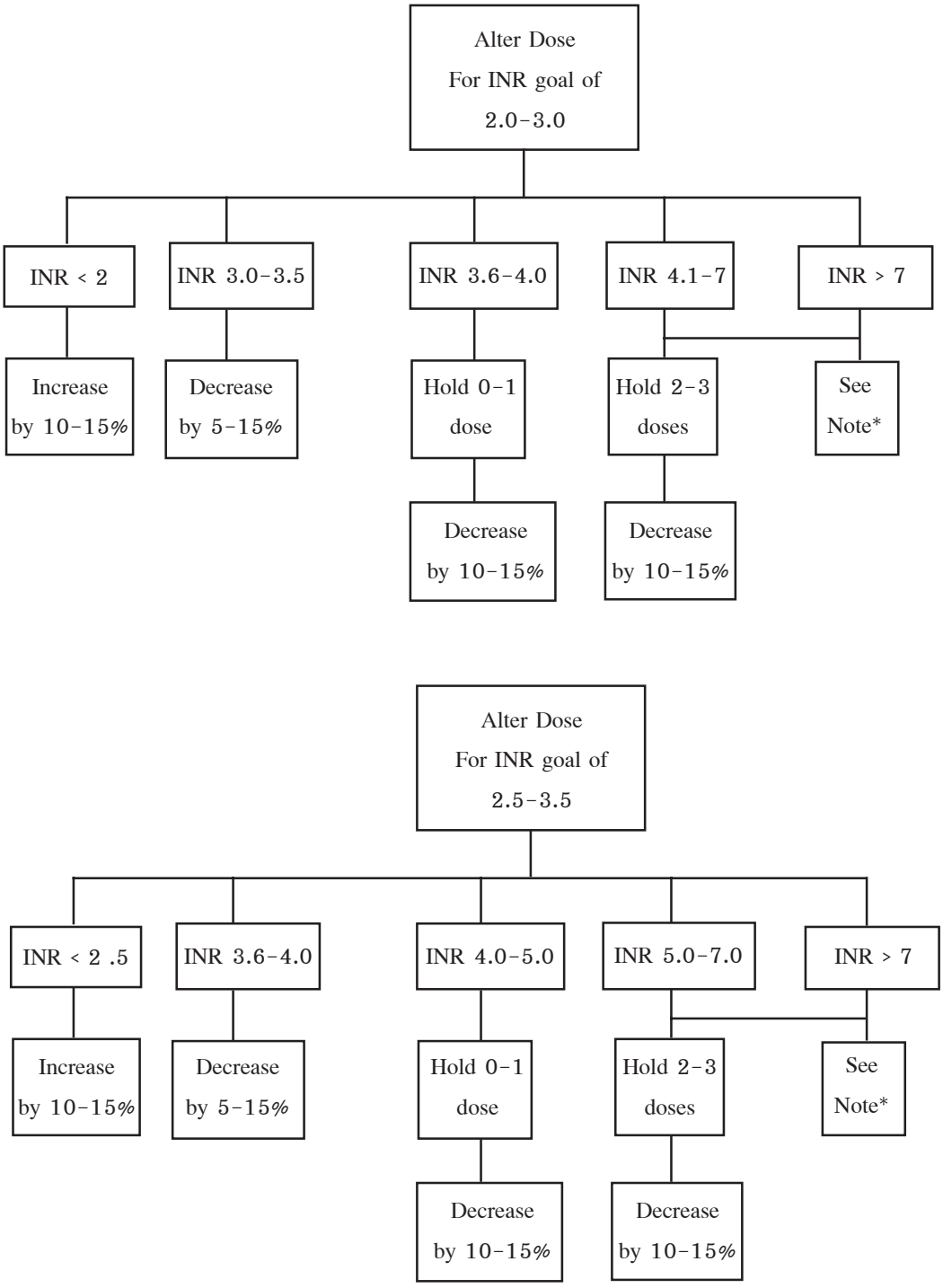
Results

From the study, there were 102 warfarinised patients attending the heart clinic at Maharaj Nakhon Sri Thammarat Hospital in the study phase. Seventeen patients were excluded from the study. Among these, 3 patients were referred to the specialty hospitals in Bangkok, 1 patient died and 13 patients were lost to follow-up without reasons being recorded. Twenty three patients just entered the heart clinic in phase 3, and had no data to compare with the 2 previous phases. Only 62 patients had complete data for analysis of the results; 38 patients in group 1 and 24 patients in group 2.

Twelve patients were interviewed for satisfaction with the booklet: eleven of them (91.7%) were satisfied with the booklet. The another one had his own booklet from an other hospital, but he also had an INR record and was monitored for the outcome of warfarin therapy in this study.

In group 1, twenty seven patients had target INR between 2.5-3.5, while 11 patients had target INR between 2.0-3.0. The average age of patients ± SD in this group was 42.3 ± 11.3 years (range 20-66 years). The majority of the patients had been on warfarin from 1-10 years. Only a few had recently started warfarin. In group 2, 10 patients

had target INR between 2.5-3.5, and 14 patients had target INR between 2.0-3.0. The average age of patients ± SD in this group was 39.3 ± 12.6 years (range 17-73 years). About half of the patients (58.3%) in this group had commenced warfarin during phase 2. The characteristics of patients in both groups are summarized in Table 1.



Note *: Reduction or reversal of warfarin effect for INR > 7

Figure 1 Warfarin dosage adjustment protocol Maharaj Nakhon Sri Thammarat Hospital

Table 1 Demographic data of patients in group 1 and group 2

	Group 1 (n = 38)	Group 2 (n = 24)
Sex		
Female	24 (63.2%)	13 (54.2%)
Male	14 (36.8%)	11 (45.8%)
Average age ± SD (years)	42.3 ± 11.3	39.3 ± 12.6
Goal INR		
2.0 - 3.0	11 (29.0%)	14 (58.3%)
2.5 -3.5	27 (71.1%)	10 (41.7%)
Time since starting warfarin		
during phase 2	-	14 (58.3%)
< 1 year	4 (10.5%)	4 (16.7%)
1-3 years	17 (44.7%)	3 (12.5%)
4-10 years	16 (42.1%)	2 (8.3%)
> 10 years	1 (2.6%)	1 (4.2%)

The number of INR results/number of clinic visits

The proportion of number of INR results/number of clinic visits of group 1 patients significantly increased in phase 3 as compared to phase 1 and phase 2 ($p < 0.001$ and < 0.025 respectively). It also increased in phase 2 as compared to phase 1 ($p < 0.001$) as shown in Table 2. The proportion of number of INR results/number of clinic visits of group 2 patients significantly increased in phase 3 as compared to phase 2 ($p < 0.001$) as shown in Table 3.

The number of INR within therapeutic range (TR)/ number of INR results

The proportion of number of INR within TR/number of INR results of group 1 patients significantly increased in phase 3 as compared to phase 1 and phase 2 ($p = 0.001$ and 0.005 respectively) as shown in Table 2. But in phase 2, the number of INR within TR was not different from phase 1 ($p > 0.05$). The proportion of number of INR within TR/number of INR results of group 2 patients in phase 3 was not different from phase 2 ($p > 0.05$) as shown in Table 3.

Table 2 Outcomes of group 1 patients from phase 1 to phase 3 (n = 38)

Outcomes		Phase 1	Phase 2	Phase 3
Proportion of number of INR results/number of clinic visits	min - max	0.00 - 1.00	0.00 - 1.00	0.40 - 1.00
	mean ± S.D.	.73 ± .26	.87 ± .21	.97 ± .11
Proportion of number of INR within TR/number of INR	min - max	0.00 - 0.60	0.00 - 0.67	0.00 - 0.80
	mean ± S.D.	.16 ± .20	.19 ± .18	.33 ± .25
Proportion of number of results dosage adjustments following the protocol/number of INR outside TR	min - max	0.00 - 1.00	0.00 - 1.00	0.00 - 1.00
	mean ± S.D.	.38 ± .36	.35 ± .28	.54 ± .34
Proportion of number of clinic visits/number of appointments	min - max	0.33 - 1.00	0.50 - 1.00	0.00 - 1.00
	mean ± S.D.	.91 ± .16	.93 ± .12	.93 ± .19

The number of dosage adjustments following the protocol/ number of INR outside TR

The number of dosage adjustment following the protocol/number of INR outside TR of group 1 patients significantly increased in phase 3 as compared to phase 2 ($p < 0.05$), but was not different from phase 1 ($p > 0.05$). Difference between phase 2 and phase 1 was not also found ($p > 0.05$) as shown in Table 2. The proportion of number of dosage adjustment following the protocol/number of INR outside TR of group 2 patient was not different in phase 3 as compared to phase 2 ($p > 0.05$) as shown in Table 3.

Number of clinic visits/number of appointments

The proportion of number of clinic visits/number of appointments of group 1 patients from phase 1 to phase 3 is shown in Table 2. This proportion in phase 3 was not different in comparison to phase 2 and phase 1 ($p > 0.05$). The corresponding figure was not found to differ between phase 2 and phase 1 ($p > 0.05$). The proportion of number of clinic visits/number of appointments of group 2 patients from phase 2 to phase 3 is shown in Table 3. This proportion was not different in phase 3 as compared to phase 2 ($p > 0.05$).

Number of ER visits or hospital admissions

Number of ER visits or hospital admissions together with their causes in group 1 and group 2 patients are shown in Table 4 and Table 5. Five patients in group 1 who experienced ER visits or hospital admissions had used warfarin for more than 5 years. Three patients recently started before phase 1 of this study. Subtherapeutic doses caused 2 patients to admit with cerebral embolism. The others 4 were without evidence of emboli but had exacerbation of their diseases such as atrial fibrillation. In group 2, 4 of 24 patients experienced ER visits and hospital admissions, all of them admitted with overdosage of warfarin. One of the 4 patients had used warfarin for more than 20 years, while the rest just started warfarin before or during phase 2 of this study.

Table 4 Number of ER visits or hospital admissions and their causes of group 1 patients (n = 38)

	Phase 1	Phase 2	Phase 3
Total	10	2	4
Causes			
overdose	4	-	4
subtherapeutic dose	6	1	-
ADR (adverse drug reactions)	-	1	-

Table 3 Outcomes of group 2 patients from phase 2 to phase 3 (n = 24)

Outcomes		Phase 2	Phase 3	P
Proportion of number of INR results/number of clinic visits	min - max	0.33 - 1.00	0.50 - 1.00	.001
	mean ± S.D.	.77 ± .19	.94 ± .14	
Proportion of number of INR within TR number of INR results	min - max	0.00 - 1.00	0.00 - 0.50	568
	mean ± S.D.	.22 ± .28	.20 ± .15	
Proportion of number of dosage adjustments following the protocol/ number of INR outside TR	min - max	0.00 - 1.00	0.00 - 1.00	.073
	mean ± S.D.	.46 ± .39	.63 ± .27	
Proportion of number of clinic visits/number of appointments	min - max	0.67 - 1.00	0.67 - 1.00	.306
	mean ± S.D.	.95 ± .08	.98 ± .08	

Table 5 Number of ER visits or hospital admissions and their causes of group 2 patients (n = 24)

	Phase 2	Phase 3
Total	2	2
Causes - overdose	2	2

Discussion

As the characteristics of patients in the two groups were different, the effect of the intervention in the study cannot be evaluated by combining the results of each group. The two groups had different outcome measures due to the time of entering the heart clinic at Maharaj Nakhon Sri Thammarat Hospital. Group 1 patients had control phase (phase 1), while group 2 patients had no control phase. Thus for group 2 patients, only the results between counseling phase and study phase were compared.

The results showed that pharmacist's counseling in phase 2 and the patient warfarin booklet in phase 3 had induced positive outcome for the number of INR results. Via counseling, patients received the information from the pharmacist about how important it is to have blood tests for INR and in phase 2 the number of INR results increased compared to phase 1 that had lacked counseling from the pharmacist. When patients received booklets from pharmacist in phase 3 the number of INR results also increased compared to phase 2 in both groups of patients. The booklet helped to remind patients to come to the heart clinic on the appointment dates and to have blood tests for INR, thus physicians could adjust the warfarin dose according to their INR results. Most patients (91.7%) were satisfied with the booklet and pharmacist counseling.

For group 1, the number of INR within TR / number of INR results significantly increased in phase 3 as compared to phase 1 and phase 2, but this difference was not found in group 2 patients. The reason might be the difference in patient characteristics of group 1 and group 2. Most patients in group 1 used warfarin for more than one year, while most patients in group 2 started warfarin for less than one year. Some group 1 patients were recommended from specialty hospitals to keep INR similar to the guidelines in this study. Thus, the INRs in group 1 patients were more in TR than those in group 2 patients. It was also found that more group 2 patients had INR above TR than group 1. Usually, warfarinised patients are more likely to experience bleeding complication during the first month of therapy[5]. In this study, the high INR also resulted from dosage adjustment by physicians. From the dosage adjustment protocol of warfarin (Figure 1), if the INR value is lower or higher from the TR, the dose of warfarin should be increased by 5-15% or decreased by 10-15% or the dose withheld. But from this study it was found that sometimes physicians did not follow the dosage adjustment protocol possibly due to the lack of both time and personnel to monitor patients closely. The doses were sometimes outside the TR. According to the dosage adjustment protocol and Hirsh (1991)[1], after adjustment of warfarin dosage, physicians should have patients return to the clinic within 1-2 weeks and then once a month if patients have a stable res- ponse. However, in this study, when the physicians adjusted dosage of warfarin, they always asked the patients to return to the clinic within a month. In some cases, if patients showed a stable response, the schedule for return to the clinic would be within 2-3 months or even 4 months. Some patients had INR level lower than TR for many visits, and this led to admission with thromboembolism in some cases. The reasons for no dosage adjustment despite the lower INR than TR were: (1) physicians did not rely solely on INR laboratory results, as sometimes INR was low, but patients had stable response with no sign and symptoms of thrombolembolism; (2) physicians suspected that patients did not comply with the drug therapy because of experience of bleeding complications; (3) some patients accepted that they did not comply with drug therapy; (4) some patients failed to receive the drug for some reasons such as prescription error, nursing error or economic problems. The patient booklet and the dosage adjustment protocol could not affect the number of INR within TR in group 2 patients. Non-compliance of the patients and variations of the physicians might be an explanation.

The other reason may be the pharmacist's intervention. In phase 3, the pharmacist gave the dosage adjustment protocol to physicians in the heart clinic and also consulted physi-

cians in case of INR being outside the TR. Although physicians did not always follow the dosage adjustment protocol, the overall results of INR values of patients in this phase were within TR.

This problem can be resolved more properly if the pharmacist can adjust the dosage of warfarin directly by using a guideline or dosage adjustment protocol, as is the role of pharmacists in anticoagulant clinics in U.S.A.[22-25]. Another way to resolve the problem is to have the consensus guideline agreed by every physician in the heart clinic and have the health-care team help physicians in monitoring patients. If physicians have not enough time to monitor patients, then they can ask pharmacists to adjust dose following the guideline or ask nurses (or pharmacists) to make the appointment with patients more often to have a blood test until patients have stable INR.

The number of dosage adjustments following the protocol/number of INR outside TR significantly increased in phase 3 as compared to phase 2 in group 1 patients, but was not different in phase 3 as compared to phase 1 or in phase 2 as compared to phase 1. The corresponding figure was also not different in group 2 patients between phase 3 and phase 2. Group 1 patients had more stable INR than group 2 patients; when INR deviated from TR and physicians adjusted the dosage of warfarin, the target INR could be achieved more easily than in group 2 patients. Non-adherence to the protocol and dosage adjustment based on the physician's clinical judgement was evidenced in the study.

The number of clinic visits/number of appointments was not affected by patient booklet or dosage adjustment protocol, but it reflected the behavior of patients. Via counseling, pharmacists could find the reason for loss to follow-up in each clinic visit of patients.

The dosage adjustment protocol and patient booklet did not affect the number of ER visits or hospital admissions. There were many factors that affected these results such as patient characteristics, patient behavior, the severity of their diseases etc.

There were some limitations in this study. First, the dosage adjustment protocol in the study was adapted from the foreign literature which was not Thai-based, thus INR within TR may or may not reflect an effective dose of warfarin received. Second, the study design was a pre-post intervention study, i.e. the outcome of warfarin therapy was determined before and after providing patient booklets and implementing the dosage adjustment protocol. A better study design may be to randomize patients into control group and study group to ensure even distribution of patients' characteristics and diseases. The control and study group should be studied at the same period to avoid the effect from time difference.

Conclusion

The patient booklet in this study showed a positive outcome on patients' INR laboratory result recording. Most patients (91.7%) were satisfied with the booklets. Patient booklets for warfarin use should thus be further provided to patients. For dosage adjustment of warfarin, it is recommended to have the consensus guideline of warfarin therapy based on the standard guideline of the Heart Association of Thailand. It should also be agreed upon by doctors at the heart clinic of the hospital. The frequency of patients' follow up should be within 2 weeks for new cases and every 4-6 weeks for patients with stable response.

References

1. Hirsh J. Oral anticoagulant drugs. Drug Ther 1991; 324: 1865-1875.
2. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1995; 108(4 suppl): 231s-246s.
3. Petitti DB, Strom BL, Melmon KL. Duration of warfarin anticoagulant therapy and the probabilities of recurrent thromboembolism and hemorrhage. Am J Med 1986; 81: 255-259.
4. Jaffin BW, Bliss CM, Lamont JT. Significant of occult gastrointestinal bleeding during anticoagulant therapy. Am J Med 1983; 83: 269-272.
5. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prerdiction by factors known at the start of outpatient therapy. Am J Med 1989; 87: 144-152.

6. Talalak P, Chotmonggol V, Bhakeecheep S, Prachubmoh K, Opartkiattikul N. Long term oral anticoagulant therapy after heart valve prostheses at Siriraj Hospital. J Med Assoc Thai 1989; 72: 250-255.
7. Fihn S.D, McDonell M, Martin D, Henikoff J, Vermes D, Kent D, et al. Risk factors for complications of chronic anticoagulation. Ann Intern Med 1993; 118: 511-520.
8. Meer FJM, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. Arch Intern Med 1993; 153: 1557-1562.
9. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. Chest 1995; 108: 276s-290s.
10. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH, et al. The risk for and severity of bleeding complications in elderly patients treated with warfarin. Ann Intern Med 1996; 124: 970-979.
11. Gurwitz H,Avorn J, Ross-Degnan D, Choodnovskiy G, Ansell J. Aging and anticoagulant response to warfarin therapy. Ann Intern Med 1992; 11: 901-904.
12. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993; 95: 315-328.
13. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323: 147-151.
14. Cannegieter SC, Rosendaal FR, Wintzen AR, Meer FJM, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995; 333: 11-17.
15. Hyers TM, Hull RD, Weg JG. Antithrombolic therapy for venous thromboembolic disease. Chest 1995; 108: 335s-351s.
16. Laupacis A, Albers G, Dalen J, Dunn M, Fienberg W, Jacobson A. Antithrombotic therapy in atrial fibrillation. Chest 1985; 108: 352s-359s.
17. Levine HJ, Pauker SG, Echman MH. Antithrombotic therapy in valvular heart disease. Chest 1995; 108: 360s-370s.
18. Stein PD, Alpert JS, Copeland J, Dalen JE, Goldman S, Turpie AGG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest. 1995; 108: 371s-379s.
19. Kenyon J. Anticoagulant required in patients with prosthetic heart valves. Drugs & Ther Per 1996; 7: 8-10.
20. Vongpatanasin W, Hillis D, Lange RA. Prosthetic heart valves. N Engl J Med 1986; 335: 407-416.
21. Lewis RK, Lasack NL, Lambert BL, Connor SE. Patient counseling - a focus on maintenance therapy. AJHP 1997; 54: 2084-2097.
22. Wilt VM, Gums JG, Ahmed OL, Moore LM. Outcome analysis of a pharmacist - managed anticoagulation service. Pharmacotherapy 1995; 15: 732-739.
23. Lee Y, Schommer JC. Effect of a pharmacist - managed anticoagulation clinic on warfarin - related hospital readmissions. AJHP 1996; 53: 1580-1583.
24. Norton JLW, Gibson DL. Establishing an outpatient anticoagulation clinic in a community hospital. AJHP 1996; 53: 1151-1157.
25. Ansell JE, Buttaro ML, Thomas OV, Knowlton CH. The anticoagulation guidelines task force. Consensus guidelines for coordinated outpatient oral anticoagulation therapy management. Ann Pharmacotherapy 1997; 31: 604-615.
26. The Pharmacy Council of Thailand. Mandatory requirement for professional practice in pharmacy. The Announcement of the Pharmacy Council of Thailand, 1997.