COMPARISON OF THERAPEUTIC OUTCOMES BETWEEN WARFARIN CLINIC VERSUS USUAL CARE

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COMPARISON OF THERAPEUTIC OUTCOMES BETWEEN WARFARIN CLINIC VERSUS USUAL CARE

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ABSTRACT

The study compared the impact on clinical outcomes of warfarin clinic with point-of-care (POC) device versus usual care. This was a randomized, controlled study conducted at the Chest Disease Institute in Nonthaburi province, Thailand from June to September 2008. Patients in the intervention group received warfarin education, INR tests by POC device, and participated in a monitoring program by clinical pharmacists. The study was terminated early due to patients' requests for equal service between the two groups. At the time of termination, 83 patients partially had undergone the study process and were included in the data analysis (39 patients in control group and 44 patients in intervention group). Baseline characteristics such as age, gender, and co-morbidity diseases were comparable between the two groups, except INR in target at baseline. Based on the available data, percent of time in therapeutic range was comparable between intervention and control groups (45.6% vs 54.3%, $p = 0.379$). Major bleeding in the intervention group was slightly lower than in the control group (none vs 29.17 events/100 patient-years, $p = 0.218$). No thromboembolic complications were found. Due to the early termination, data from only 36 patients were available for evaluation of cost. Cost of therapy was higher in the intervention group than the control group (276.49 THB vs 112.40 THB; $p < 0.001$). Patient satisfaction was not systematically assessed due to early termination of the trial. Although clinical outcomes were comparable between the two groups, there was a positive trend toward improvement for time in therapeutic range in the intervention group, while an opposite trend was seen in the control group. Major limitations in the study were 1) the randomization method, which could have been biased and resulted in the difference of INR in target between the two groups at baseline, and 2) the lack of concealment for the intervention. Results of the study should therefore be carefully interpreted.

KEY WORDS: WARFARIN / PHARMACIST / INR / POINT OF CARE ANTICOAGULATION CONTROL

123 pages

การเปรียบเทียบผลลัพธ์ของการรักษาระหว่างคลินิกวาร์ฟารินและการดูแลผู้ป่วยแบบปกติ
COMPARISON OF THERAPEUTIC OUTCOMES BETWEEN WARFARIN CLINIC VERSUS USUAL CARE

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาเปรียบเทียบผลของการดูแลผู้ป่วยในคลินิกวาร์ฟารินร่วมกับการใช้เครื่องเจาะที่ปลายนิ้วกับการรักษาแบบปกติ การศึกษาวิจัยนี้เป็นแบบ randomized control trial ณ สถาบันโรคทรวงอก ระหว่างเดือนมิถุนายน – กันยายน 2551 ผู้ป่วยที่เข้ากลุ่มทดลองจะได้รับคำแนะนำเกี่ยวกับยาวาร์ฟาริน, เจาะเลือดโดยใช้เครื่องเจาะที่ปลายนิ้ว, และได้รับการดูแลโดยเภสัชกร แต่มีการปิดการศึกษานี้ก่อน เนื่องจากผู้ป่วยเรียกร้องที่จะได้รับการรักษาที่เท่าเทียมกันทุกคน หลังปิดการศึกษาจำนวนผู้ป่วยที่วิเคราะห์ได้รวมทั้งสิ้น 83 ราย กลุ่มควบคุม จำนวน 39 ราย และกลุ่มทดลอง จำนวน 44 ราย พบว่าลักษณะพื้นฐานของผู้ป่วยทั้งสองกลุ่มเช่น อายุ เพศ โรคประจำตัว ไม่แตกต่างกัน ยกเว้น จำนวนค่า INR ที่อยู่ในช่วงที่เหมาะสม ณ ครั้งแรกที่เข้าการศึกษา ซึ่งในกลุ่มควบคุมมีค่ามากกว่ากลุ่มทดลองอย่างมีนัยสำคัญ จากการวิเคราะห์ข้อมูลที่มีพบว่าผู้ป่วยกลุ่มทดลองมีระดับ INR อยู่ในเป้าหมายไม่แตกต่างจากกลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 45.6 กับ ร้อยละ 54.3, p = 0.379) อัตราการเกิดเลือดออกในผู้ป่วยกลุ่มศึกษาน้อยกว่ากลุ่มควบคุมเล็กน้อย (ไม่พบเหตุการณ์ เทียบกับ 29.17 เหตุการณ์/100 ผู้ป่วย-ปี ตามลำดับ) ซึ่งไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ (p = 0.218) และไม่พบภาวะลิ่มเลือดอุดตันในผู้ป่วยทั้งสองกลุ่ม เนื่องจากหยุดการศึกษาก่อน จึงสามารถวิเคราะห์ค่าใช้จ่ายในการรักษาได้เฉพาะในผู้ป่วย 36 ราย เท่านั้น และพบว่าค่าใช้จ่ายในกลุ่มทดลองมีค่าสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (276.49 บาท และ 112.40 บาท, p < 0.001) สำหรับความพึงพอใจของผู้ป่วย ไม่มีการศึกษาแบบเก็บข้อมูลเนื่องจากการหยุดการศึกษาล่วงหน้า แม้ว่าผลทางคลินิกของผู้ป่วยทั้งสองกลุ่มไม่มีความแตกต่าง แต่ผลการรักษาในกลุ่มศึกษามีแนวโน้มที่ดีขึ้น ขณะที่กลุ่มทดลองมีแนวโน้มตรงข้ามกัน ข้อจำกัดที่สำคัญของการศึกษานี้ คือ วิธีการสุ่ม ซึ่งอาจมีผลให้เกิดอคติและมีผลให้ค่า INR ที่เหมาะสมของผู้ป่วยสองกลุ่มนั้นมีความแตกต่างกันอย่างมีนัยสำคัญตั้งแต่จุดเริ่มการศึกษาและอีกข้อจำกัดหนึ่ง คือ การไม่มีการปกปิดรูปแบบของการศึกษา ทั้งนี้ การแปลผลการศึกษานี้จึงควรกระทำอย่างระมัดระวัง

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LIST OF ABBREVIATIONS

%	Percent
γ	Gamma
ACCP	American College of Chest Physicians
ADR	Adverse drug reactions
AF	Atrial fibrillation
ALT	Alanine aminotransferase
AVR	Aortic valve replacement
AST	Aspartate aminotransferase
CVA	Cerebrovascular accident
CVC	Central venous catheter
CAM	Complementary and alternative medicine
DI	Drug interaction
DVT	Deep vein thrombosis
F/U	Follow-up
FFP	Fresh frozen plasma
g	Gram
GI	Gastrointestinal
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HN	Hospital number
IE	Infective endocarditis
IM	Intramuscular
INR	International normalized ratio
IRP	International reference preparation
ISI	International sensitivity index
ISTH	International Society on Thrombosis and Haemostasis
Kg	Kilogram
LMWH	Low molecular weight heparin

LIST OF ABBREVIATIONS (cont.)

LFT	Liver function tests
mg	Milligram
MI	Myocardial infarction
ml	Milliliter
mM	milli-molar
MNPT	Mean normal prothrombin time
MVR	Mitral valve replacement
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Oral anticoagulant
OPD	Out patient department
PAF	Platelet-activating factor
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
POC	Point of care
POCT	Point of care testing
PT	Prothrombin time
rFVIIa	Recombinant activated factor VIIa
SC	Subcutaneous
SD	Standard deviation
SPSS	Statistical Package for Social Science
TIA	Transient ischemic attack
VHD	Valvular heart disease
vs	Versus
VTE	Venous thromboembolism
VKA	Vitamin K antagonist

LIST OF ABBREVIATIONS (cont.)

VKOR	Vitamin K epoxide reductase
WHO	World Health Organization

CHAPTER I
INTRODUCTION

Oral anticoagulants are widely used in the treatment and prevention of thromboembolic disease. While benefits of anticoagulants are clear, many patients experienced treatment complications including bleeding or thromboembolic complications. Several strategies were implemented to decrease these adverse events. Among these strategies, the anticoagulation clinic or warfarin clinic has established in many countries including Thailand. The pharmacist in this setting obtain a patient drug history, monitoring adverse reactions, monitoring response to drug therapy, provide drug information to the patient and healthcare providers, and acting as a liaison to the warfarin clinic. Warfarin clinic has been shown to be effective in minimization of bleeding complications, death rates, length of hospital stay and costs of treatment. These results lead to improve quality of life of the patient. In Thailand, further studies evaluating the impact of warfarin clinic were conducted and showed similar results as those conducted in the Western countries. However, limitations of these studies are non-randomized nature of the trials.

INR monitoring is an important step for evaluating outcome of treatment with other clinical outcomes. The traditional laboratory method requires venipuncture for INR measurement. Clinic visit using traditional laboratory leads to a prolonged visit which could eventually lead to non-compliance of patients to hospital follow-ups. Moreover, in developing countries including Thailand, spending protracted period of time in the hospital may result in a significant loss of income of an indigent patient. Point of care testing (POCT) device is an alternative for this solution. This well-tested technology has been implemented in numerous warfarin clinics for INR measurement in developed countries. Incorporating the POCT may be advantageous for patients and physicians in reducing time spent in the hospital and improved patient satisfaction for hospital’s service.

At the Chest Disease Institute, a pilot warfarin clinic has been developed through multidisciplinary approach with pharmacists at the core of such service. The clinic was initially started in July of 2007 with only a small group of 25 patients. The POCT has been adopted into this pilot project also. The informal evaluation of the clinic shows strong potential. In order to show the effectiveness of this clinic, a formal evaluation with a randomized trial is needed. The results could then be regarded with high quality for national and international acceptance.

Consequently, the primary objective of this study is to compare therapeutic outcomes of warfarin clinic versus usual care through the comparison of percent INR in target, rates of complications of warfarin therapy, patient satisfaction and overall cost of therapy. The results generated from this study should be beneficial in justifying the development of warfarin clinic model for other hospitals countrywide.

Objectives

1. To compare the percentage of INR in target between warfarin clinic and usual care.
2. To compare the rate of thromboembolic events and hemorrhagic complications from warfarin between warfarin clinic and usual care.
3. To compare patient's satisfaction between warfarin clinic and usual care.
4. To compare cost of treatment between warfarin clinic and usual care.

Comparison of anticoagulation control between intervention and control groups has been assessed by using Student's t test or Mann-Whitney U test. Percent of time in therapeutic range was calculated to express anticoagulation control in each group. The rate of thromboembolic and hemorrhagic complications were compared between intervention and control group by using Chi-square test or Fisher-Exact's test. Patient's satisfaction and cost of treatment were planned to be assessed by using Student's t test or Mann-Whitney U test.

CHAPTER II
LITERATURE REVIEW

2.1. Pharmacology of warfarin

Warfarin or vitamin K antagonists (VKAs) is an oral anticoagulant which has proved its efficacy for the primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, as an adjunct in the prophylaxis of systemic embolism after myocardial infarction, and for reducing the risk of recurrent myocardial infarction. Warfarin produce their anticoagulant effect by interfering with the activity of vitamin K dependent clotting factors, factor II, VII, IX, and X. These factors are synthesized mainly in the liver and biologically inactive unless 9 to 12 of the amino-terminal glutamic acid residues are carboxylated. The γ-carboxylation requires the reduced form of vitamin K (vitamin KH_2) which serves as the cofactor. Vitamin KH2 is oxidized to vitamin K epoxide (vitamin KO) which plays an important role in the carboxylation of clotting factor. Subsequently, vitamin KO is reversed to vitamin KH_2 for next carboxylation. Vitamin KO is reversed to KH_2 through two reduction steps. The vitamin K dependent coagulation factors II, VII, IX, and X require γ-carboxylation for their procoagulant activity, and treatment with VKAs results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity (1). The VKAs inhibit carboxylation of the regulatory anticoagulant proteins C, S, and Z and thereby have the potential to be procoagulant (2). Because vitamin K epoxide reductase (VKOR), is more sensitive to VKA, whereas vitamin K reductase is less sensitive. Therefore, the anticoagulant effect of the VKAs can be overcome by low doses of vitamin K (phytonadione) (Figure 1). And high dose of vitamin K results in VKA resistant, because accumulated vitamin K in the liver could substitute inactivated vitamin K in vitamin K cycle and acts its ability to activate several types of vitamin K dependent clotting factors (1, 3). Therefore inappropriate high dose of vitamin K can delay time in therapeutic range for

warfarin reversal process. Warfarin or VKAs indirectly block carboxylation Gla proteins likely affects bone density and risk to increase osteoporotic fractures (4-6). Long term warfarin therapy possibly risks for bone material quality impairment, hence bone fracture awareness should be implied for patients taking warfarin in especially geriatric patients.

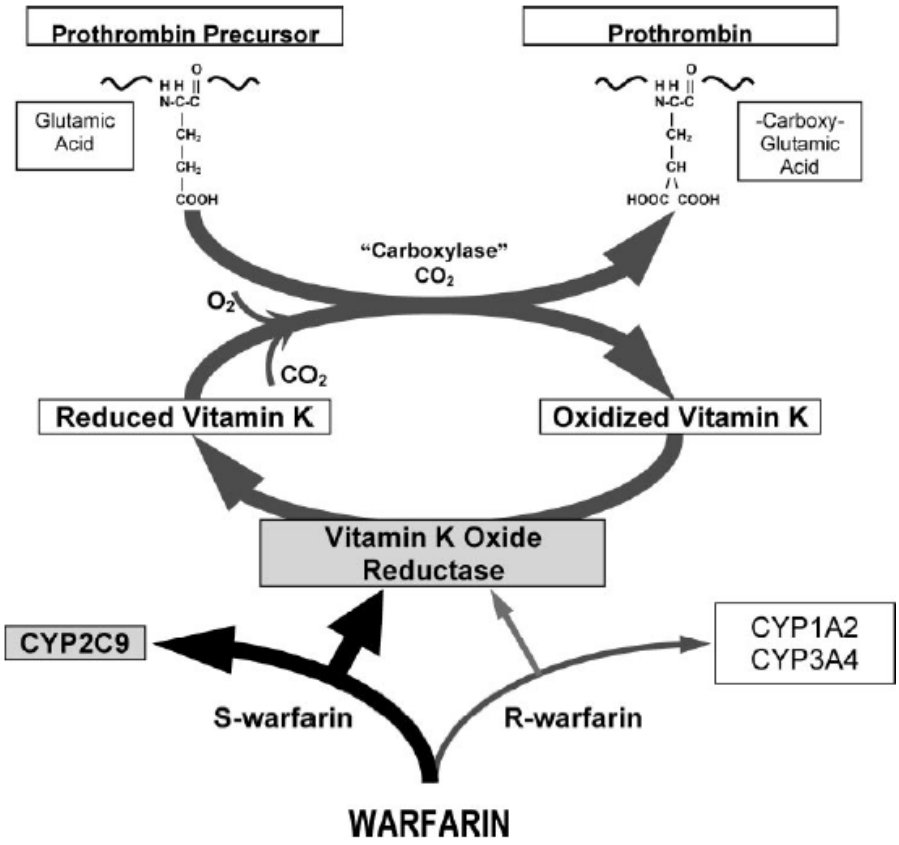


Figure 1. Vitamin K cycle: Vitamin K1 is reduced to vitamin KH2. The major warfarin-sensitive enzyme in this reaction is the vitamin K oxide reductase mainly inhibited by the S enantiomer of warfarin. S-warfarin is metabolized by the p450 cytochrome enzyme, CYP2C9.(1)

Vitamin K dependent coagulant proteins also influence warfarin activity. The biological half-life of factor II is 60 to 123 hr, of factor IX, 17 to 40 hr, and of factor X, 20 to 48 hr, while that of factor VII is only 1.5 to 6 hr. Because of its short half-life, factor VII is the first to disappear under the influence of warfarin, while factor II which is the crucial factor activating fibrin in coagulation cascade. For this reason, it is the principal determinant of the one-stage prothrombin time during the

first few days of treatment. VKA particularly modulates new clotting factor production, while full effect of drug depends on degradation of vitamin K dependent coagulation protein. Hence, anticoagulant effect needs 7 to 10 days for steady state of warfarin activity. Loading dose could not abruptly elevate anticoagulant effect, since incremental dose does not result in faster metabolism of the clotting factors already presented in the plasma (7).

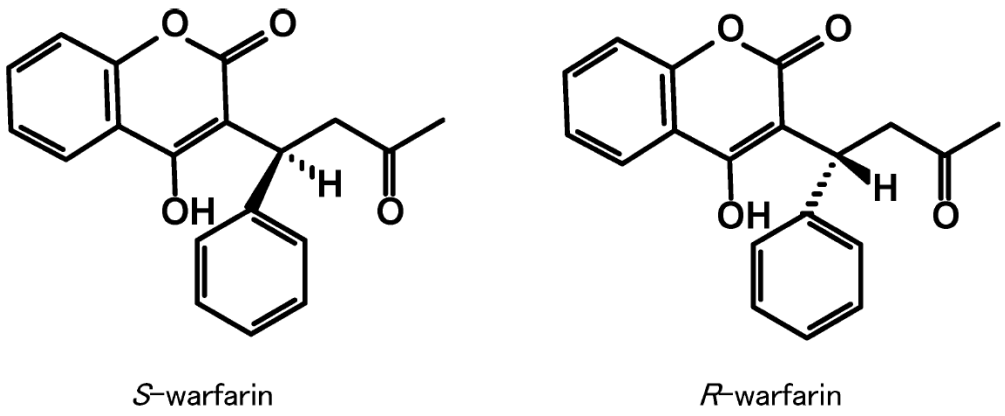


Figure 2. Warfarin enantiomers

Chiral structures of warfarin differentiate anticoagulant activity with stereoselectivity of its metabolism (8). Warfarin is composed of S- and R-enantiomers (Figure 2). Potency of S-warfarin is more than R-warfarin in anticoagulant activity for two to five times. Nevertheless, R-warfarin has longer half-life than S-warfarin (R-warfarin, 45 hours; S-warfarin, 29 hours). Warfarin is well absorbed via oral route owing to its high bioavailability, and bounded to albumin in plasma for 99%. The unbound fraction undergoes biotransformation in the liver by the cytochrome P450 system (CYP). S-warfarin is mainly metabolized by CYP2C9 enzyme, while inferior potent R-warfarin is metabolized primarily by CYP1A2 and CYP3A4 enzyme (1, 9). In addition, the enzymes CYP2C8, CYP2C18, CYP2C19 may also play a role in the metabolism of S-warfarin. And CYP1A1, CYP2C8, CYP2C18, CYP2C19, and CYP3A5 may be involved in the metabolism of R-warfarin (Figure 3) (10). Therefore, dose response of warfarin can be affected by genetic and environmental factors that can influence warfarin absorption, its pharmacokinetics and pharmacodynamics.

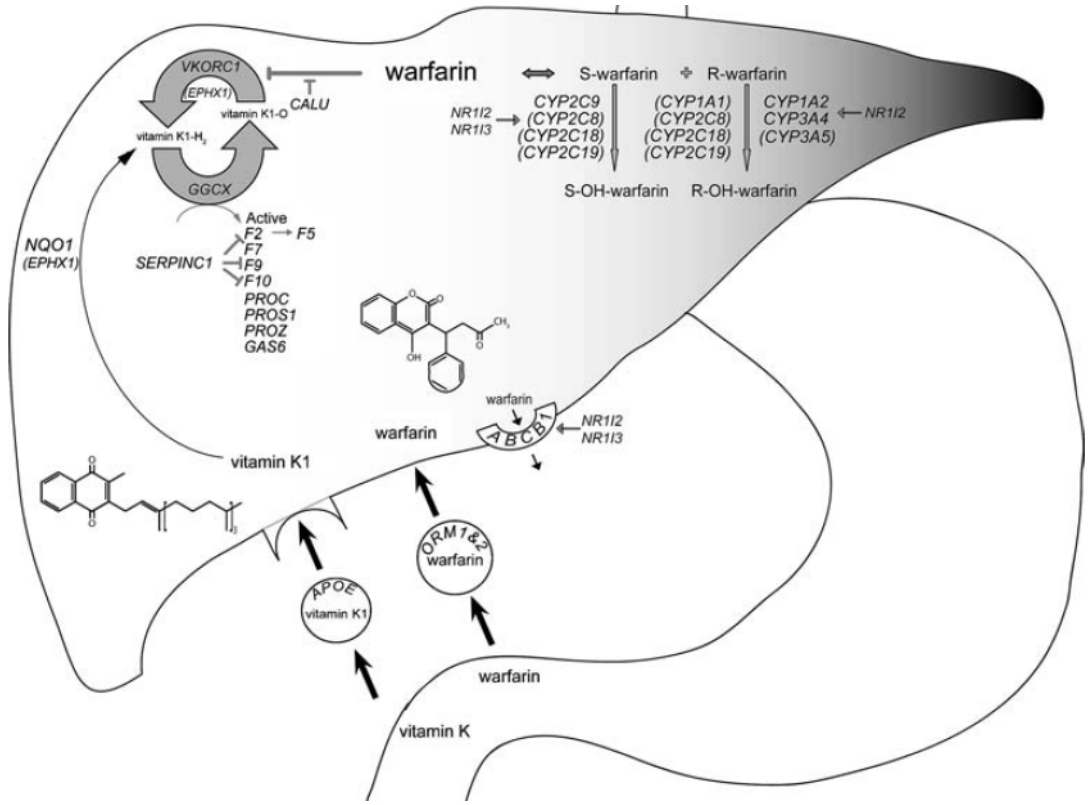


Figure 3. Genetic factors affecting warfarin activity with simplified biotransformation of warfarin and vitamin K (10)

2.1.1. Genetic factors

In the past, warfarin response varied amongst individualized patients. Gene expression is one of numerous factors causing differential anticoagulation activities of warfarin. Patients, who response to warfarin especially low dose, were called warfarin sensitive, while patients who response particularly high dose of warfarin, were called warfarin resistance (11). As warfarin action, vitamin K epoxide reductase (VKOR) plays an important role in vitamin K cycle, and it is the target of warfarin. The encoded gene for the VKOR protein was called vitamin K epoxide reductase complex subunit 1 gene (VKORC1) which located on chromosome 16 (9, 12). Transcription of VKORC1 occurs primarily in the liver; however, smaller amounts of VKORC1 are present in the heart and pancreas (13). Rieder et al identified 10 common noncoding VKORC1 single-nucleotide polymorphisms (SNPs) and inferred 5 major haplotypes in 368 patients (119 white, 96 of African descent, 120 of Asian descent), declaring a low-dose haplotype group (A) and a high-dose haplotype group (B). VKORC1 haplotype groups A and B explained approximately 25 percent of

the variance in dose (14). The VKORC1 mutation had been studied to be related to the pharmacodynamic mechanism of warfarin resistance, hence warfarin dose requirement may be predicted by genetic biomarker (15).

Another gene involved to pharmacokinetic mechanism of warfarin resistance is cytochrome P, especially CYP2C9 gene. Genetic variations of CYP2C9 polymorphism involve to differentiation of warfarin metabolism and sensitivity of drug (1, 9, 16). CYP2C9*1 haplotype is the wild-type allele, whereas CYP2C9*2 and CYP2C9*3 haplotypes are variant alleles. CYP2C9*2 and CYP2C9*3 haplotypes related to warfarin sensitive in patients encoded these non-wild type allele, therefore carriers of CYP2C9*2 and CYP2C9*3 haplotypes had risked hemorrhagic episodes than wild-type (17). These genetic variations had been found in different ethnic groups. Approximately 86% of those of Asian descent and 16% of white people carry the 2C9*1*1 VKORC1AA variant, predisposing them to wide swings in INR throughout drug initiation. An additional 9% of white people and a lesser percentage of those of African descent carry the combination of CYP2C9 and VKORC1 allelic types associated with high sensitivity to warfarin (13). Chern et al had found the relationship between genetic variation and warfarin requirement dose, and they estimated maintenance daily dose of warfarin to be 3.11 ± 1.62 mg in 239 Chinese-Taiwanese patients and the researchers (18). Kuanprasert et al study found that CYP2C9*1/*1 and VKORC1 haplotype AA was the most common among the Northern Thai population, hence warfarin dosing guided by pharmacogenetics and non-pharmacogenetic factors could be beneficial for a more proper starting dose and this could lead to a faster achievement of the best maintenance dose to minimize the patient risk (19). Genetic testing is technically feasible, acceptable to the patient and physician, and likely to improve the clinical management of anticoagulation (20). However genetic factor is not only one of various causative factors related to warfarin response, but also the wide variety of physiological and environmental factors are possibly responsible for anticoagulation control.

2.1.2. Environmental factors

Many factors can affect pharmacokinetic of warfarin which are responsible to diverse drug response for instance environmental factors. Environmental factors

such as drug, diet and any disease states are able to affect anticoagulation control in patients taking warfarin.

2.1.2.1. Drug-drug interaction

Several patients taking warfarin need more than one type of medicine. Prevalence of health utilization behavior amongst Thai people in 1996-2006 showed that 20.9-37.9% of Thai populations preferred self-medication (21). Therefore potential drug interaction can occur and possibly risk to adverse drug events. Many drugs can interact with warfarin by several ways as shown in Table 1, which shows particular level 1 and level 2 of drug interaction level (22). Some medicines potentially interact with warfarin for more than a single mechanism as explanation in followings.

Table 1. Common drug interactions with warfarin

Warfarin effect increased	**Warfarin effect decreased**
Acetaminophen Acetylsalicylic acid Alteplase Amiodarone Antibiotics: • Cephalosporins (Cefazolin,, Cefoperazone, Cefotetan, Cefoxitin, Ceftriaxone) • Chloramphenicol • Cotrimoxazole • Macrolide (Clarithromycin, Erythromycin, Telithromycin) • Metronidazole • Penicillin (Ampicillin, Dicloxacillin, Nafcillin, Oxacillin, Penicillin G, Piperacillin, Ticarcillin) • Quinolones (Ciprofloxacin, Levofloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Trovafloxacin) • Tetracyclines (Doxycycline, Tetracycline)	Azathioprine Barbiturates Bosentan Carbamazepine Cholestyramine Ethchlorvynol Glutethimide Griseofulvin Mercaptopurine Rifampicin Trazodone Vitamin K

Table 1. Common drug interactions with warfarin(cont.)

Warfarin effect increased	**Warfarin effect decreased**
Antifungals: • Fluconazole • Itraconazole • Ketoconazole • Miconazole • Voriconazole Antineoplastics • Bosentan • Capecitabine • Carboplatin • Cyclophosphamide • Etoposide • Fluorouracil • Gemcitabine • Placlitaxel Beta-blockers • Metoprolol • Propanolol Carbamazepine Disulfiram Fibrates • Fenofibrate • Gemfibrozil H2-antagonists • Cimetidine • Ranitidine HMG-CoA reductase inhibitors • Fluvastatin • Lovastatin • Rosuvastatin • Simvastatin Levamisole NSAIDs: • Ibuprofen • Indomethacin • Ketoprofen • Ketorolac • Mefenamic acid • Naproxen • Piroxicam • Sulfinpyrazone • Sulindac • Celecoxib • Valdecoxib	

HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A

NSAIDs = Non-steroidal anti-inflammatory drugs

Table 1. Common drug interactions with warfarin (cont.)

Warfarin effect increased	Warfarin effect decreased
Quinidine Quinine Sulfisoxazole Thyroxine Vitamin E	

NSAIDs = Non-steroidal anti-inflammatory drugs

2.1.2.1.1. Interference with platelet function

Platelet aggregation is a crucial first step in primary hemostasis. Antiplatelet drugs, such as acetylsalicylic acid and clopidogrel, increase the risk of major hemorrhage in patients taking warfarin. The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic vs hemorrhagic risk of the patient (23). Nevertheless American College of Chest Physicians (ACCP) recommended combination of aspirin with warfarin or even triple antithrombotic therapy (warfarin and dual antiplatelet therapy) for prevention of coronary disease in some specific conditions with meticulous monitoring anticoagulant therapy (24).

2.1.2.1.2. Protein binding displacement

Warfarin is highly bound to serum albumin (97-99%). Unbound fraction of warfarin is increased by the displacement of the binding site caused by the coadministration of numerous drugs. Impaired renal or liver function and hypoalbuminemia also change the binding properties of warfarin to plasma proteins. Tatsumie et al found that ethanol, which is used as a pharmaceutical excipient for injections, changes the stereoselective binding properties of warfarin enantiomers. Unbound fractions of both the S- and R-enantiomer were increased by ethanol, therefore both the physicochemical interactions and pharmacokinetic interactions between drugs and pharmaceutical excipients should be considered (25). Conventional non-steroidal anti-inflammatory drugs (NSAIDs) are influence alteration of warfarin pharmacokinetic property with high protein-binding mechanism such as

ibuprofen (26). Hence co-medication of warfarin and NSAIDs can increase risk of bleeding episode.

2.1.2.1.3. Warfarin absorption alteration

Some drugs, such as cholestyramine, may prevent absorption of warfarin when coadministered. The outcome is a reduction in the anticoagulant response. Of concern has also been the possibility that changing formulations could result in changes in warfarin bioavailability, with alterations in therapeutic response (27). Small population of clinical studies found no significant different amongst distinct brands of warfarin. They showed similar regarding target INR achievement and safety profile (28-29). One systematic review and meta-analysis assessed 11 articles studied warfarin (Coumadin). These studies showed generic and brand name warfarin performed similarly with respect to clinical end points such as INR, frequency of adverse events, and number of required dose adjustments unless One of the cohort studies found a small but significant decrease in INR in patients using the generic drug, although it did not translate into differences in morbidity or mortality (30).

2.1.2.1.4. Modulation of warfarin metabolism

Main metabolism path way of warfarin involves to enzyme CYP, especially CYP2C9, with less influence of CYP1A2 and CYP3A4. Therefore drugs metabolized primarily by cytochrome P path way possibly risk to interact with warfarin. For instance, rifampicin can induce activity of cytochrome P 450 isoenzyme 2C9, patients receiving both rifampicin and warfarin probably enhance of thromboembolic complications caused by warfarin activity lowering (31). Statins or HMG-CoA reductase inhibitors possibly interact with CYP2C in various intensities, in particular 2C9, by CYP2C enhancement in endothelial cells. Fluvastatin can enhance the expression of some hepatic CYP enzymes, and is reported to be extensively metabolised by CYP 2C9 in the liver, while 10% of rosuvastatin is metabolized, mainly by CYP2C9 (32-34). Patients taking many drugs with warfarin should aware complications resulting from drug interaction, because several drugs are particularly metabolized via cytochrome P 450 enzyme, in particular CYP3A4 isoenzyme as shown in Figure 4 (35).

CYTOCHROME P-450 DRUG INTERACTIONS *Michalets*

Table 1. Cytochrome 3A4 Isoenzyme: Substrates, Inducers, and Inhibitors[2, 3, 9, 10, 16, 17, 19–117]

Substrates			
Alfentanil	Diazepam (minor)	Ketoconazole	Quinine
Alprazolam	Diltiazem	Lansoprazole (minor)	Rifampin
Amitriptyline (minor)	Disopyramide	Lidocaine	Ritonavir
Amlodipine	Donepezil	Losartan	Saquinavir
Astemizole	Doxorubicin	Lovastatin	Sertraline
Atorvastatin	Dronabinol	Mibefradil	Tacrolimus
Busulfan	Erythromycin	Miconazole	Tamoxifen
Cannabinoids	Estrogens, oral contraceptives	Midazolam	Temazepam
Carbamazepine	Ethosuximide	Navelbine	Terfenadine
Cisapride	Etoposide	Nefazodone	Testosterone
Clindamycin	Felodipine	Nelfinavir	Triazolam
Clomipramine	Fentanyl	Nicardipine	Verapamil
Clonazepam	Fexofenadine	Nifedipine	Vinblastine
Cocaine	Ifosfamide	Nimodipine	Vincristine
Cyclobenzaprine (demethylation)	Imipramine	Nisoldipine	R-warfarin
Cyclophosphamide	Indinavir	Ondansetron	Zileuton
Cyclosporine	Isradipine	Paclitaxel	
Dapsone		Pravastatin	
Dexamethasone		Prednisone	
Dextromethorphan		Quinidine	
Inhibitors		Inducers	
Amiodarone	Metronidazole	Carbamazepine	
Cannabinoids	Mibefradil	Dexamethasone	
Clarithromycin	Miconazole	Ethosuximide	
Erythromycin	Nefazodone	Phenobarbital	
Fluconazole	Nelfinavir	Phenytoin	
Fluoxetine	Norfloxacin	Primidone	
Fluvoxamine	Quinine	Rifabutin	
Grapefruit juice	Ritonavir	Rifampin	
Indinavir	Saquinavir	Troglitazone	
Itraconazole	Sertraline		
Ketoconazole	Troleandomycin		
Omeprazole (slight)	Zafirlukast		

Figure 4. Numerous drugs metabolized through CYP3A4 isoenzyme (35)

2.1.2.1.5. Interruption of the vitamin K cycle

By far the most important drug in this category is acetaminophen. Thijssen et al suggests that this interaction is caused by N-acetyl (p)-benzoquinonimine, the highly reactive metabolite of acetaminophen responsible for hepatic injury following acetaminophen overdose. Therapeutic doses of acetaminophen yield some of this metabolite, which inhibits vitamin K-dependent carboxylase, a key enzyme in the vitamin K cycle. (36). Acetaminophen or paracetamol at 2 grams or 4 grams daily can potentiate the anticoagulant response produced by warfarin. Clinicians should be aware of this clinically significant and underestimated interaction (37-38). Moreover the hypoprothrombinemic response to warfarin is influenced by vitamin K status, which is converted to be vitamin K2 (menaquinone) by intestinal microflora. . Many antibiotics can alter the balance of intestinal microorganisms, therefore effect of anticoagulant is possibly elevated and

hemorrhagic risk could be concerned in this circumstance (39-40). Although interactions of this type are predictable, their expression is highly variable. Holbrook and colleagues have sensibly urged caution when co-medication of any antibiotics with warfarin are needed, but some antibiotics also inhibit the hepatic metabolism of warfarin and therefore merit special consideration (41). As shown in retrospective cohort study of Glasheen et al, among acutely ill outpatients, oral antibiotics (azithromycin, levofloxacin, and TMP/SMX) increase the incidence and degree of overanticoagulation (42).

2.1.2.2. Drug- herb interaction or Drug- food interaction

Complementary and alternative medicine products using amongst warfarin-treated patients are potential dilemma in anticoagulation control. Some patients miss to tell their physicians that they are using such products, and physicians rarely ask. Excessive anticoagulation is associated with a substantial risk of serious bleeding, while inadequate anticoagulation increases the risk of thromboembolic events. Main mechanism of drug-herb interaction associates with P-glycoprotein, a well known drug transporter, and enzyme CYP450. All CYPs are subject to inhibition or induction by a variety of xenobiotics, including drugs and herbal medicines. Expression of CYP3A4 is regulated by the nuclear factor pregnane X receptor (PXR/ NR112), which is activated by a variety of structurally distinct ligands, including certain herbal components such as St. John's wort (43). St John's wort (*Hypericum perforatum*) is effective for mild to moderate depression. St John's wort raises the activity of P-glycoprotein, and increases the elimination of drugs. Probably via these mechanisms, it has been shown to reduce the plasma concentrations of warfarin (44).

Furthermore danshen, a Chinese herb commonly used in mainland China for the treatment of atherosclerosis-related disorders, can increase the bioavailability of both R- and S-warfarin, thus exaggerating the anticoagulant response to warfarin. Not surprisingly, patients receiving warfarin therapy may present with gross overanticoagulation and bleeding complications when they also take danshen. Danshen can affect hemostasis in several ways, including inhibition of platelet aggregation, interference with extrinsic blood coagulation, antithrombin III–like activity, and promotion of fibrinolytic activity, danshen should be avoided in patients

taking warfarin due to the risk of these pharmacokinetic and pharmacodynamics interactions (45).

Coenzyme Q10, is another dietary supplement, possibly aggrandizes procoagulant properties by resulting in a significant increase in the total clearance of both R- and S-warfarin without other mechanisms related to hypoprothrombinemic response reduction, even alteration of protein binding, and absorption and distribution of S- and R-enantiomers. Although coenzyme Q10 interacting warfarin had been reported in few cases with no evidence based of well-designed studies, patients receiving concomitant therapy with warfarin and coenzyme Q10 should be closely monitored (46).

Ginger has been found to be a potent inhibitor of thromboxane synthetase with potential effects on bleeding time. And ginkgolide B, a potent inhibitor of platelet-activating factor, have been suspected to be a causative factor of spontaneous bilateral subdural hematomas (47-48). Although both of ginger and ginkgo ingestion at recommended doses do not significantly affect clotting status, the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects, The significance of herb–drug interactions in elderly patients receiving warfarin or in patients taking higher than recommended doses or combinations of these herbal medicines has yet to be established. (47-49). Awareness of hemorrhage should be suggested for patients taking warfarin with these herbs.

Vitamin K is a fat soluble vitamin which is rich in leafy green vegetables. Dietary vitamin K intake, theoretically, influences warfarin activity by substitute for malfunctioning vitamin K in vitamin K cycle. Increased vitamin K intake was independently associated with undercoagulation and decreased intake with overcoagulation. Franco et al had found that both increases and decreases in vitamin K intake are independently and directly associated with INR instability. The vitamin K–enriched diet had a more rapid effect on INR than the depleted diet, reaching statistical significance on day 4 versus day 7 (50). The variable vitamin K intake in stable patients did not affect their stability of anticoagulation, likely due to their consistently high intake and thus a greater body store of phylloquinones for steady clotting factor activation. Conversely, in unstable patients because of their consistently lower vitamin

K intake body stores of the vitamin could be depleted more rapidly (51). Since warfarin resistance is probably caused by high intake of vitamin K containing diets.

Dietary fat could also affect anticoagulation response to warfarin through its effect on vitamin K absorption. It is estimated that a meal containing over 35 grams of fat maximizes vitamin K oral bioavailability (52). Consistency of dietary vitamin K intake should be maintained for INR stability in particular patients taking warfarin. The patients on warfarin should not alter their vitamin K intake by more than 250-500 mg/day in order to maintain stable and safe anticoagulation regimens (53). Physicians should concern in vitamin K intake of patients with instability INR, especially vegetarians. Patient education is necessary for understanding the problems caused by unintended prolonged high intake of vitamin K, which may thus prevent unnecessary exposure to subtherapeutic INR values and risk of thrombosis.

2.1.2.3. Drug-disease interaction

Hepatic dysfunction potentiates the response to warfarin through the impaired synthesis of coagulation factors. INR measurements could be varied amongst liver impaired patients. Hypermetabolic states produced by fever or hyperthyroidism increase warfarin responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors (1, 54). Especially, thyroid diseases can modify primary and secondary haemostasis and lead to bleeding and thrombosis. The possible pathophysiological mechanisms are thyroid hormone excess or deficiency, autoimmunity or a direct mechanical effect of an enlarged thyroid gland. An influence of overt thyroid dysfunction on oral vitamin K antagonist sensitivity exerts the effect of vitamin K antagonists and be potentiated in thyrotoxicosis and attenuated in hypothyroidism. Hypothyroid patients require higher dosages to obtain the target INR compared to euthyroid anticoagulated patients and, conversely, hyperthyroid patients require a reduced dosage to reach the target INR (55). More frequent INR monitoring is needed for patients taking warfarin with specific disease.

2.2. Optimal monitoring anticoagulation

As complexity of warfarin characteristics, varieties of anticoagulation response challenge healthcare providers to improve therapeutic outcome by many strategies implementation. However, the coagulation time, a crucial indicator assessed blood coagulation status of anticoagulated patients as prothrombin time and international normalized ratio (INR), varies in individualized patients and types of coagulometer. Moreover integrated numerous factors affecting pharmacokinetic or pharmacodynamic properties of warfarin influence to intensify procoagulant or even potentiate anticoagulant effect of warfarin. Meticulous speculation of various effects is possibly able to avoid oscillated INR values and resulting to achieve desirable clinical outcome as followings.

2.2.1. International normalized ratio (INR)

Monitoring anticoagulation therapy is processed by the measured international normalized ratio (INR). Coagulation laboratories are important for dosage adjustment. The prothrombin time (PT) responds to a reduction of three of the four vitamin K-dependent procoagulant clotting factors (such as factor II, VII, X) that are reduced by warfarin at a rate proportional to their respective half-lives. Thus, during the first few days of warfarin therapy, the PT reflects mainly a reduction of factor VII, the half-life of which is approximately 6 hours (1). Most laboratories report prothrombin time (PT) results using INR together with either seconds, and seconds and PT ratio. Reporting of PT results exclusively in INR at 99.9% in 2001 US survey (56).

However, PT monitoring of warfarin treatment is not standardized when expressed in seconds, as a simple ratio of the patient's plasma value to that of plasma from a healthy control subject, or as a percentage of diluted normal plasma. A calibration model (1, 57), which was adopted in 1982, is now used to standardize reporting by converting the PT ratio measured with the local thromboplastin into an INR, calculated as follows:

$$INR = (PT^{patient} / PT^{control})^{ISI}$$

INR are derived from the international sensitivity index (ISI), a quantitative measurement of the responsiveness of individual thromboplastin reagents

and prothrombin time (PT) test systems. This is obtained from the comparison of the local PT results with those of a WHO thromboplastin international reference preparation (IRP). The international sensitivity index (ISI) characterize thromboplastins and it is obtained by comparison of the log PT results of 20 normals and 60 stabilized patients (over 6 weeks on anticoagulant treatment), with the local PT reagent manual PT tests plotted against log PT on the same plasmas using the same species WHO IRP. The lower its ISI implies the greater sensitivity of the local thromboplastin. Although the ISI corrects for major differences in PT results between test systems (reagent or coagulometer combinations), persistent INR disagreement between results with different test systems is frequently observed. (58). Source of thromboplastins might involve bias of INR which could be found slight bias in INR for human compared with rabbit thromboplastins, within acceptable level of clinical relevance. Ongoing stability monitoring of World Health Organization thromboplastin international reference preparations is recommended (59).

2.2.2. Dose management of warfarin

Appropriate intensity of anticoagulant and therapeutic INR control are major factors testifying therapeutic effectiveness. Healthcare providers manage dosage regimens of anticoagulated patients with comprehensive knowledge related to anticoagulation therapy and manipulate multidisciplinary system to ameliorate clinical outcome.

2.2.2.1. Initiation and maintenance dose of warfarin

INR modification after initiation dosage of warfarin occurs in two or three days, meanwhile anticoagulation effect needs several days. Overlapping heparin or low-molecular weight heparin with warfarin therapy should be managed when a rapid anticoagulant effect is demanded, until the INR has been in the therapeutic range for at least 2 days. A loading dose of warfarin is not recommended (1). Low dosage is recommended for warfarin initiation in particular Asians. Owing to genetic differences in drug metabolism across ethnic groups may account for the variable response observed with warfarin (60). As prior study of genetic prevalence, CYP2C9*1/*1 and VKORC1 haplotype AA are the most common among the Northern Thai populations (19). Dosing with low dose of warfarin may lessen the

complication risk and pharmacogenetic factor could account for warfarin dose variability. Furthermore, time to steady state of warfarin varies by genotype; 3-5 days for CYP2C9*1/*1 to 12-15 days for CYP2C9*1/*3. Warfarin dosing guided by pharmacogenetics and non-pharmacogenetic factors could be beneficial for a more proper starting dose and this could lead to a faster achievement of the best maintenance dose to minimize the patient risk (19, 61).

In geriatric patients, dose requirement for patients over 60 years decreases with increasing age, possibly due to a reduction in the clearance and plasma albumin with age (1, 62). Since age increasing correlates with liver volume decreasing, the fall in functional hepatic mass contributes to the increase in target organ sensitivity by demonstrating a significant correlation between liver volume and dosage, in addition to the negative correlation between age and dosage (63). Gender also influences dose, with women requiring less warfarin to maintain a therapeutic INR than men at an equivalent age. Therefore the initial dose of warfarin should not more than 5 mg per day in geriatric patients (64). The correlations between warfarin dose and the variables body surface area, body height, and body weight also affect anticoagulation responsiveness, even the latter influencing a small significant contribution to warfarin dose requirements in the regression model (65). This may be the cause of lower warfarin dose in Asian countries than in European countries.

Furthermore, other contributing factors as drug interaction or disease state should be concerned. Amiodarone is frequently prescribed concurrent with warfarin. Its pharmacokinetic interaction with anticoagulant causes bleeding risk in particular geriatric patients. Patients with CHF could also risk to hemorrhagic episode. Low initiation dose with prudential dose adjustment could reduce thromboembolic and hemorrhagic complications, and more frequent INR testing is needed in the first period of warfarin initiation (1).

In patients beginning anticoagulant therapy, the INR monitoring is recommended to start after the initial two or three doses, meanwhile the patients receiving a stable dose of anticoagulants, are recommended to be monitored INR at an interval of no longer than every 4 weeks (1). Nevertheless, patients in stable condition with a prosthetic heart valve who are monitored at an anticoagulation clinic,

a 6-week interval between INR determinations does not increase the biologic risk of thromboembolic or hemorrhagic events (66).

2.2.2.2. Management in Non-therapeutic INR

INR value is a principle indicator for evaluating anticoagulation response. High INR value shows over-anticoagulation with hemorrhagic risk, while low INR value means under-anticoagulation with potential thromboembolism. Dose adjustment is required for manage these non-therapeutic INR with cautious consideration of other contribution factors. It ranges in 5 to 20 percent dosage adjustment of previous dose. Patient adherence could be a major cause of the variation of INR value, adherence assessment should be done before dose adjustment is considered. Moreover, INR value should be proved that it is the actual value for the individualized patient, because more work load of healthcare providers could accidentally cause the wrong INR value.

For patients INR above therapeutic range more than 5, dosage management depends on severity of symptom and INR values as described in Table 2 (1).

Table 2. Recommendations for managing elevated INRs or bleeding in patients receiving vitamin K antagonists (1).

Condition	Management
INR more than therapeutic range but <5; no significant bleeding	• Lower the dose or omit dose, monitor more frequently, and resume at the lower dose when INR therapeutic range; If only minimally above therapeutic range, no dose reduction may be required **(Grade 1C).**
INR ≥5 but <9; no significant bleeding	• Omit next one or two dose, monitor more frequently and resume at appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K1 (1-2.5 mg po), particularly if at increased risk of bleeding **(Grade 1C)**. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (≤ 5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K1 (1 to 2 mg) can be given **(Grade 2C).**

Table 2. Recommendations for managing elevated INRs or bleeding in patients receiving vitamin K antagonists (1) (continued).

Condition	Management
INR ≥ 9; no significant bleeding	• Hold warfarin therapy and give higher dose of vitamin K (2.5-5 mg po) with the expectation that the INR will be reduced substantially in 24-48 h **(Grade 1B).** Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic **(Grade 2C).**
Serious bleeding at any elevation of INR	• Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with fresh frozen plasma or prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation; vitamin K can be repeated q 12 h. **(Grade 1C).**
Life-threatening bleeding	• Hold warfarin therapy and give fresh frozen plasma, prothrombin complex concentrate or recombinant factor VIIa, supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR **(Grade 1C**).
Administration of vitamin K	• In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously **(Grade 1A)**.
INR more than therapeutic range but <5; no significant bleeding	• Lower the dose or omit dose, monitor more frequently, and resume at the lower dose when INR therapeutic range; If only minimally above therapeutic range, no dose reduction may be required **(Grade 1C).**

2.2.3. Factors contributing uncontrolled anticoagulation effect

Many documents described oscillation effects of INR and attempted to find the risk factors for the best clinical outcome with less complication risk. Comprehensive knowledge of all constituents influencing anticoagulant responsiveness is required for effective anticoagulation control. There are many factors affecting warfarin activity and complication risk as follows.

2.2.3.1. Patient characteristics

Older age, female sex and small body size result in low dose warfarin and low target INR as described in numerous studies. Stroke can occur in elderly patients, warfarin dosing should be considered between risk and benefit (67). Genetic mutations involve in target INR determination and dosage regimen. The ACCP (American College of Chest Physicians) had recommended initial warfarin dose in specialized status that the patients who are debilitated, malnourished, have CHF, have liver disease, have had recent major surgery, or are taking medications known to increase the sensitivity to warfarin (eg, amiodarone), the initiation dose are recommended to be less than 5 mg with subsequent dosing based on the INR response (1). However, the patients receiving hemodialysis and those with target INRs less than 3.0 were at higher risk for falsely elevated results Because blood for these INR measurements was frequently drawn prior to hemodialysis via a central venous catheter (CVC), whereas the therapeutic repeat samples were drawn via a peripheral vein. CVCs are prone to complications, including thrombosis, necessitating the need for periodic instillation of heparin into the lumen of the line. It has been hypothesized that heparin contamination of blood samples collected from CVCs may compromise INR reliability. Adjustment of warfarin dosing based on falsely elevated INR values increases the risk of treatment failure or thrombosis (68).

2.2.3.2. Target INR

Target INR of warfarin management varies amongst patients taking warfarin. It depends on indication of warfarin, genetic factor, disease state, especially anticoagulation responsiveness. Most of patients need target INR in 2 to 3 for control thromboembolic disease. For Thai patients, low target INR is probably suitable, because of the small body size compared with Americans and potential risk of bleeding by ethnicity and genetics. Many studies showed that Asians could be managed with low target INR to avoid hemorrhagic risk and manipulating INR in therapeutic range (69-71). Nevertheless, Target INR determination should base on warfarin response in individualized patients with considering other contributing factors and it could be adjusted when coagulation status of patient is changed by any situations such as advanced age, drug interaction, varied amount of vitamin K intake, malfunction of hepatic caused by alcohol consumption or even by viral infection.

2.2.3.3. Frequent INR testing

Frequency of monitoring also may have a major effect on the outcome of warfarin therapy, decrease fluctuations in anticoagulation status, and this action leads to increase the therapeutic benefit and decrease the potential for adverse events (72). More frequency of INR testing make more chance to detect deviated INR values and the physicians can solve it before complication could occur. In the present, INR monitoring is frequent in the first few days or every three days until it reaches therapeutic INR level. For stable INR, 4-week interval is recommended in ACCP guideline, however 6-week interval could be implemented for patients in multidisciplinary approached clinic (1, 66). Nevertheless, Appointment of patients taking warfarin in countries with shortage of healthcare providers, rarely follows this guide. Distance of their houses and the hospital, long time for waiting their physician, high work load of physicians are considerable obstacles for proper interval-INR monitoring.

2.2.3.4. Drug interaction

Pharmacokinetic and pharmacodynamic properties of warfarin are complicated, these characteristic properties can cause unpredicted anticoagulation response. Drug interaction can also alter pharmacokinetic of warfarin, resulting in INR result deviation and anticoagulation response alteration. As prior mention, drug interaction is enumerated to be various types such as drug-drug, drug-food, drug-disease, drug-herb, drug-dietary supplement interaction. Many patients, who take many medicines or have many diseases, may undergo thromboembolic or even hemorrhagic risk through these drug interactions.

Moreover, alcohol is another factor which is able to interact with warfarin. Prevalence of alcohol drinkers was higher in male than female for six times. The national survey of Thai populations drinking alcohol in 2007, had found 28.4% of all populations experiencing alcohol consumption in one year ago and 22.7% of current drinkers; people had recently drunk alcohol in 30 days ago. From this survey, 14.5% of populations had a binge drinking such as more than 6 cans or 3 large bottles of beer, or more than 5 glasses of spirits, or drank wine for more than 5 glasses or a half of bottle at once (73). This report reflects high risk of developing alcohol-induced liver disease, which could lead to insufficient clotting factor productions with

potential hemorrhagic risk in particular patients taking warfarin. Although women had lower rate of pattern alcohol drinking than men, but women had a higher relative risk of development of alcohol-induced liver disease by increasing alcohol intake than men (74).

Furthermore, long-term alcohol consumption has a similar potential to increase the clearance of warfarin, but ingestion of even relatively large amounts of wine had little influence on the PT in normal volunteers who were given warfarin. The increased antithrombotic effect of warfarin involved protein binding interactions and decreased warfarin metabolism through the cytochrome P450 (CYP) enzyme system. With regard to the CYP enzymes, alcohol is predominantly metabolized through CYP2E1, but it is also broken down by CYP3A4 and CYP1A2. With small amounts of alcohol, the CYP2E1 pathway is not a predominant route of metabolism, but with heavy consumption CYP2E1 activity is increased almost 10-fold. CYP3A4 and CYP1A2 also contribute to alcohol metabolism and are important enzymes involved in drug metabolism. CYP2E1 activity varies among individuals. In people with low CYP2E1 activity, alcohol is less dependent on CYP2E1 for metabolism, and the potential for alcohol-drug interactions increases because of the shift to the other CYP enzymes for metabolism (75). The low concentration of alcohol, at as low as 0.1 vol% (17 mM), can allosterically inhibit S-warfarin metabolism resulting in structural changes in the binding site of CYP2C9, with partially serum albumin binding. Alcohol in medical preparations could potentially interact with warfarin (76). Deliberation of all factors influencing anticoagulation response will help to detect problems resulting in appropriate management.

2.2.3.5. Patient adherence

Warfarin therapy needs long term to treatment, and some patients have to take anticoagulant for life-long. Unintentional omit dose could occur during therapy. Poor adherence of patients taking warfarin would be the causative factor of instability anticoagulation control and variation of INR. Kimmel et al found that nonadherence was associated with underanticoagulation and out-of-range INRs but not overanticoagulation, meanwhile a significant association had been found between underadherence and underanticoagulation. Two-fold increase in the odds of underanticoagulation could be caused by one or two missed doses in each week. And

patients, who took warfarin over than 10% of days, were potential risk to be overanticoagulation (77). Many strategies had implemented to encourage adherence such as warfarin clinic. Patient education is an important role of healthcare providers to acknowledge patients for increasing adherence, lowering potential drug interaction with alcohol or even other drugs and herbal medicines, and decline of self-medication (78-79).

2.2.3.6. Vitamin K intake

Vitamin K is an essential element in coagulation cascade. It is derived from food and from the microflora of the gut. For consideration of source of vitamin K, green leafy vegetables are high, fruit and cereals low, and meats and dairy products intermediate in concentration. In fact, the intestinal absorption of vitamin K from plant sources ranges from 30% to 70% of the actual content determined by extraction. Dietary vitamin K is absorbed in the small bowel, is incorporated into chylomicrons, and appears in the lymph. Since patients, with biliary obstruction or taking broad spectrum antibiotic drug, potentially face to bleeding episode resulting from vitamin K deficiency (80). The changes in vitamin K intake play a major, independent role in INR fluctuations in patients taking oral anticoagulants. Stability of anticoagulation control could vulnerably change in patients with constantly low vitamin K consumption. Thus, stable vitamin K intake is an essential aspect of anticoagulation therapy that must be actively pursued by clinicians, nurses, dietitians, and pharmacists. However, gaps in knowledge about warfarin–vitamin K interactions were identified among health care providers who counsel patients taking anticoagulants (50-51).

2.2.4. Anticoagulation management

The health care system is important in anticoagulation management. In the past, many studies expressed the advantages of the multidisciplinary team in the collaborative anticoagulation management for the patient care. Several strategies are implemented in anticoagulation clinic or called warfarin clinic. In this system, the pharmacist acts major role to improve patient education, warfarin-therapy problem resolution, complication risk reduction for better clinical outcome. The outcomes of many studies found that pharmacist-managed anticoagulation service decreased

bleeding complications, death rates, length of hospital stay, costs of treatment even who starting warfarin for the first time (81-83). Another benefit is an improvement of compliance showed in a case-control study at a large teaching general hospital in Massachusetts (84). However many studies in Asian countries presented the outcomes as same as in the European countries.

Chan FWH et al performed a prospective randomized clinical study at the anticoagulation clinic of a teaching hospital in Hong Kong (85). One hundred and thirty-seven patients were recruited and completed the study. Patients in the pharmacist-managed group (n=64) were in the target INR 64% of patient time and 59% in the physician-managed group (n=69) ($P < 0.001$). The incidence of major thromboembolic events or bleeding was not significant different in two groups. The cost per patient per month in the pharmacist-managed group (US$ 76 ± 95) was lower than the physician-managed group (US$ 98 ± 158) ($P < 0.001$). The patient satisfaction was detected by the satisfaction questionnaire (PSQ)-18, which assessed general satisfaction, technical quality, interpersonal manner, communication, financial aspects, time spent with clinician and accessibility and convenience. The PSQ-18 score of the pharmacist-managed group was higher than that of the physician-managed group (3.6 ± 0.3) ($P < 0.001$). Benefits of multidisciplinary approach in warfarin clinic are well described for many years. However, the evolution of patient care system has been advanced, in foreign countries, the self-management is recently implemented for therapeutic outcome improvement with quality of life in anticoagulated patients. This novel strategy needs meticulous training of device instruction with dosage adjustment regimen and multidisciplinary team for consultation. The self-management is limited for well-trained patients.

2.2.5. Point-of-care testing

Warfarin is an effective medicine for the prevention of thromboembolic diseases. Because warfarin is widely used and considered a narrow therapeutic index drug with various pharmacokinetic and pharmacodynamic properties, several strategies of patient care have been suggested to manage the work load increasing. Although the pharmacist-managed anticoagulation clinic experienced better anticoagulation control, less variation in INR test values and less adverse events than

the traditional group, bleeding episodes had been found among patients managed by pharmacist-run anticoagulation clinic (83, 86-88). Frequency of monitoring also may have a major effect on the outcome of warfarin therapy, decrease fluctuations in anticoagulation status, and this action leads to increase the therapeutic benefit and decrease the potential for adverse events (72). One solution is the point of care testing (POCT) devices with concerning about accuracy, precision and reliability. There are many studies conducted to prove these properties. Comparison between point of care devices and laboratory resulted in acceptable correlation, they give the accurate and precise outcomes of INR measurements (89-92).

There is a study conducted in Thailand about the comparison of INR measurements with the portable monitor and laboratory methods and processed by Sirithunyanont et al in the heart clinic of Bangkok Heart Institute, Bangkok Hospital. This study demonstrated that the CoaguCheck has the potential to improve the management of patients receiving long term warfarin by decreasing patient inconvenience related to laboratory-based INR measurement, increasing patient compliance with INR monitoring and facilitating to perform more frequent INR testing (93). However some limitations of POCT devices were discovered that the accuracy and precision of INR measurement decreased when INR increased (89-90, 93-94). There is one study revealed lack of accuracy of POC device and suggest to restrict its use for monitoring oral anticoagulant therapy (95). Dorfman DM et al found that INR values generated by POC monitors exhibit positive bias for INR values at the high end of the anticoagulation range (89). Potential explanations for deviation of INR measurement are the possibility of problems with POC devices or procedure such as inaccuracy of the measurement system related to variation between different individual POC monitors, the calibration of the test strip lot by the manufacturer, deterioration in the individual test strips employed, or by inappropriately handled QC samples, or other unmeasured patient variables such as nutritional status and diet. Antiphospholipid antibodies of hypercoagulable patient have been also demonstrated to reduce the accuracy of POC devices (96-97). Even though some deviated INR measurements unable to change the patient management, INR will be retested if correlation between INR result and clinical appearance does not occur or INR value seems to deviate unexpectedly from prior patterns (94).

When anticoagulation testing is performed by the patient in the home setting, two strategies can be applied: patient self-testing, when patients test their own PT-INR and call in results to the physician's office or anticoagulation service for warfarin dose adjustment, and patient self-management, when patients are trained and allowed to manage their own warfarin therapy based on their own self-test results (98-99). The value of patient self-testing has been documented. Gardiner C et al conducted a prospective study to determine the accuracy and reliability of POC test INR results measured by patients. They found excellent correlation between the INR results from the CoaguCheck S and laboratory method ($r = 0.95$), with 85% of CoaguCheck S with the result they obtained and 77% preferred self-testing (100). One way to assess the quality of the oral anticoagulation therapy is time within therapeutic range. The evaluation of time within therapeutic INR target range was shown no significant different or superior results in POC device-used group compared to control group. Although, time within therapeutic range is a surrogate endpoint, the result of time within therapeutic INR target range is highly dependent of the therapeutic INR target range and the frequency of testing. These make comparison between studies difficult (101-103). Coagulation assessment utilizing POC technology is an effective, useful and efficient tool and can be advocated in appropriate clinical settings. It has improved result the result turnaround time in outpatient anticoagulation clinics which require immediate results reporting. The patients with poor venous access or have limited accessibility for clinic follow-up also benefit through capillary fingerstick POC assessment or home POC use (104). Because of the POC device's advantages, POC device is widely used in many countries and useful in self-monitoring patients. The National Academy of Clinical Biochemistry recommended that the use of point-of-care devices be considered a safe and effective alternative to laboratory prothrombin time (PT) testing for oral anticoagulation monitoring and management in a clinic setting (Strength B, Levels II and III), hemostasis monitoring in the hospital setting (Strength B, Levels I and II) by patient self-testers for appropriately trained and capable individuals (Strength B, Levels I, II and III) (105). For the best outcome of oral anticoagulation therapy monitoring, the patients suitable for using POC device should be trained before use the device.

CHAPTER III
METHODOLOGY

Materials

1. Data collection form for patient's profile and INR records (Appendix A)
2. Warfarin Booklet (Appendix B)
3. Questionnaire for patient's satisfaction evaluation-Intervention group (Appendix C)
4. Questionnaire for patient's satisfaction evaluation-Control group (Appendix D)
5. Warfarin calendar (Appendix E)
6. Consort statement (Appendix F)

Methods

3.1. Definition of terms

The term used throughout the study are defined as following:

Warfarin Clinic Service was established in June 2007 according to the Hospital policy. This service is defined as the collaboration between physician, nurse and pharmacist to optimize warfarin therapy using multidisciplinary approach. The aim is to improve anticoagulation control and decrease adverse drug events. INR measurement of patients participating in warfarin clinic will be performed by CoaguChek. All patients will be evaluated by clinical pharmacists before being seen by the participating physicians. The clinical pharmacists evaluate potential risks of undesired outcomes of anticoagulation therapy, such as patient's status or disease state effecting pharmacokinetic or pharmacodynamic of warfarin, drug-drug interaction, drug-food interaction, non-adherence, thromboembolic event and hemorrhagic complications, then report to the doctor with suggestions of appropriate solution. The clinical pharmacist facilitates adherence of patients by providing education of patients

about warfarin and the importance of self-care behavior leading to appropriate outcomes of therapy. Moreover, clinical pharmacists suggest dose adjustment through OPD card. The doctors review drug related problems information and make decision on dose adjustment, drug selection, complication management and follow-up time. All cases, which have received interventions, will be followed-up in the next visit. The service time of warfarin clinic is according to the Cardiology and Cardiovascular and Thoracic Clinic service, which include Tuesday and Thursday morning. Four specialist physicians of the Cardiology and Cardiovascular and Thoracic Surgery will participate in this service.

Major bleeding event is defined as the event involving fatal bleeding, and/ or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/ or bleeding causing a fall in hemoglobin level of 20 g / L (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells. This definition is based on a discussion held at the meeting of the subcommittee of Control of Anticoagulation at the 50th Scientific and Standardization Committee Meeting of the ISTH in Venice (106).

Thromboembolic events are defined as obstruction of blood vessel with thromboembolic material carried by the blood stream from the site of origin to plug another vessel associated with either one of the following situations.

- **Cerebrovascular accident (CVA)** or stroke is defined as a sudden neurological deficit that persists for more than 24 hours with a computerized tomographic brain scan that is negative for primary intracranial hemorrhage (69, 107).
- **Transient ischemic attack (TIA)** is defined as a sudden neurological deficit that persists for less than or equal to 24 hours (69).
- **Valve thrombosis** is defined as impairment of the valve by the deposition of thrombus on the valve, documented by two-dimensional echocardiography or surgery and resulting in hemodynamic dysfunction (107-108).
- **Peripheral or systemic embolism** is defined as the occurrence of acute ischemic caused by an arterial embolism, documented by angiography or surgery (87, 107).

Warfarin therapy problem is defined as drug interaction, non-compliance and medication error in accordance to findings from studies conducted by Sapoo and Liabthawee (109-110).

- **Drug interaction** is defined as the unexpected/ adverse event caused potentially by the substance/ situation effect with the activity of warfarin. These factors affect to mechanism of warfarin or outcome of anticoagulation therapy. In this study the interactions of interest are drug interaction in 3 categories including drug-drug interaction, drug-complementary and alternative medicine (CAM)/food interaction, and drug-disease interaction. Drug-CAM/ food interaction will be the situation in which a complementary and alternative medicine or food affects the activity of anticoagulation therapy resulting in decrease or increase therapeutic effect of anticoagulant or altered health status of the patient. Literatures and database of warfarin drug interactions were reviewed and used a source for evaluating drug interactions for this study. The occurrence of drug interactions will be collected and reported to the patient's care provider.

- **Non-compliance** is defined as the patient's inability or unwillingness to take a drug regimen that the practitioner has clinically judged to be appropriately indicated, adequately efficacious, and able to produce the desired outcomes without any harmful effects (111). The patient's care provider will be notified when non-compliance is detected by patient self-report using Warfarin calendar and patient interview by clinical pharmacist. Clinical pharmacists will provide education and other assisting devices such as warfarin calendar, pill splitter and other methods of reminder as appropriate.

- **Medication error** is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patients, or caregivers. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling; packaging; and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use (112). This term has been classified into four categories; prescribing errors, transcribing / interpretation errors, dispensing errors, and

administration errors (113). In this study, we will collect only events caused by prescribing errors and transcribing errors. According to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), the categorization of these errors based on the severity or outcome of an error will be arranged into nine categories as following (114).

Categories of Medication error :

A = Circumstances or events that have the capacity to cause error

B = An error occurred, but the medication did not reach to patient

C = An error occurred that reached the patient , but did not cause the patient harm

D = An error occurred that resulted in the need for increased patient monitoring, but cause no patient harm

E = An error occurred that resulted in the need for treatment or intervention and caused temporary patient harm

F = An error occurred that resulted in initial or prolonged hospitalization and caused temporary patient harm

G = An error occurred that resulted in permanent patient harm

H = An error occurred that resulted in a near-death event (eg. Cardiac arrest)

I = An error occurred that resulted in patient death

- **Point of care testing (POCT)** is defined as clinical laboratory testing conducted close to the site of patient care, typically by clinical personnel whose primary training is not in the clinical laboratory sciences or by patients (self-testing) (105). In this study, the POCT device used is CoaguChek (Roche Diagnostic Co, Ltd.)

3.2. Study design

This study is a randomized, controlled trial aiming to compare patient outcomes between warfarin clinic versus usual care. For INR measurement, POCT

was used in warfarin clinic while conventional laboratory was used in the usual care group.

3.3. Ethical Approval

This protocol was reviewed and approved by the Ethic Committee of the Chest Disease Institute.

3.4. Population

Patients receiving warfarin therapy under the care of the Cardiology and Cardiovascular Thoracic Surgery Departments in Chest Disease Institute served as our pool population. Patients who met the following inclusion criteria in the absence of exclusion criteria were enrolled into the study.

3.4.1. Inclusion criteria

3.4.1.1 Patients who are older than 15 years old.

3.4.1.2 Patients receiving warfarin therapy with the planned duration of treatment of no less than 6 weeks during the study period and participating in the study at least two visits.

3.4.1.3 Patients whose indications including atrial fibrillation/ atrial flutter (AF), valvular heart disease (VHD), or mechanical heart valve (aortic valve replacement, tricuspid valve replacement, mitral valve replacement, double valve replacement).

3.4.2. Exclusion Criteria

3.4.2.1 Patients with planned duration of warfarin therapy of less than 6 weeks and participating in the study less than two visits.

3.4.2.2 Patients who refuse to participate in this research or unwilling to sign the consent form.

3.4.3. Sampling Methods

Patients who met the inclusion criteria with voluntary enrollment were randomized into 2 groups using stratified random sampling technique. The researcher collected the name lists of patients and categorized them in according to the target INR. And the patients were rearranged by random allocation into two groups; target INR range 1.5-2.5 and 2-3. For the procedure of random allocation, the patients were numbered sequentially in each group of indication at the first visit. For instance, the patient with target INR 1.5-2.5, walking in the clinic for the first one, was the first one in the group of target INR range 1.5-2.5 and the latter was ranked by the sequence of clinical visit. The patients ordered in the odd numbers were allocated to control group, while those getting even number participated in the intervention group. Sampling method was demonstrated in figure 5 as following:

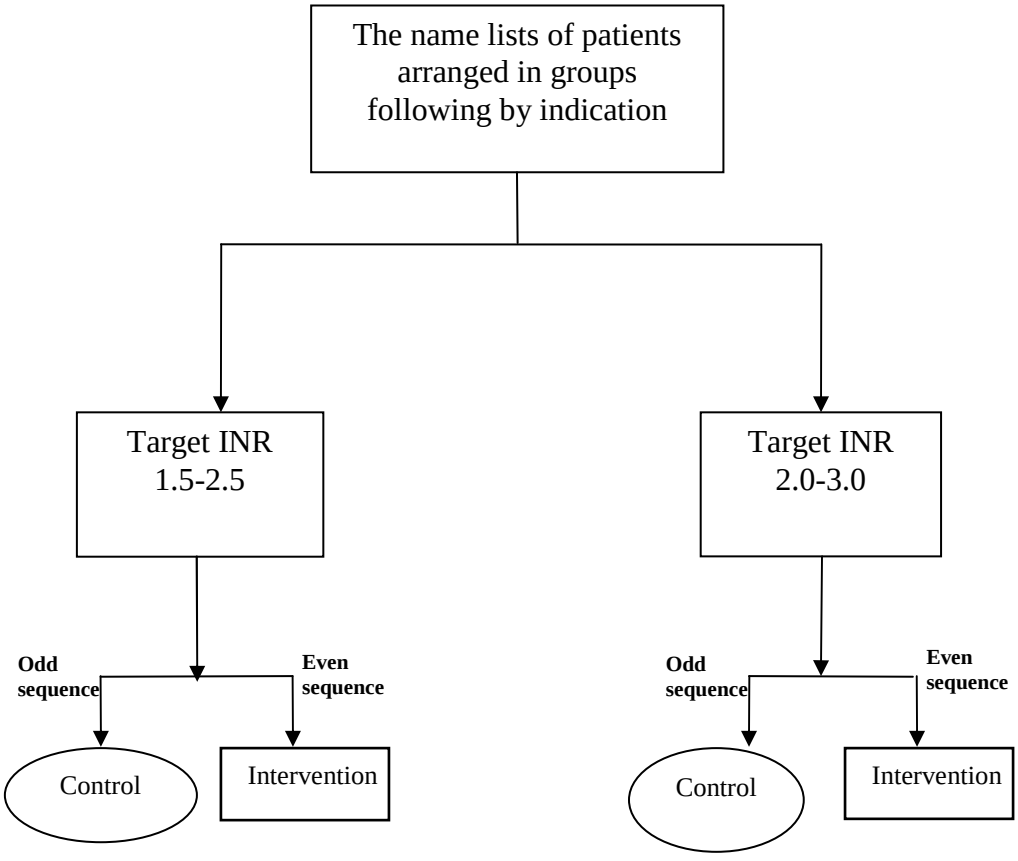


Figure 5. Sampling method

3.4.4. Sample size

The proportion of therapeutic INR was used for sample size calculation, since it has been the widely accepted surrogate markers for clinical outcomes for anticoagulation therapy. This proportion is a dichotomous variable. The comparison of such outcome was made between two independent groups. Therefore, sample size was estimated using the following formula (115).

$$2N = \frac{2\{ Z\alpha \sqrt{2\,\bar{p}\,(1-\bar{p})} + Z\beta \sqrt{p_c\,(1-p_c) + p_I\,(1-p_I)}\,\}^2}{(p_c - p_I)^2}$$

Where

2N = total sample size (N= participants/group)

Zα = the critical value that corresponds to the significance level α

Zβ = the value of the standard normal value not exceeded with probability β

$\bar{p} = (p_c + p_I)/2$

p_I = the event rate in intervention group

p_c = the event rate in control group

Based on the preliminary study conducted at the Cardiovascular Thoracic Surgery clinic, the INR values in the pre-implementation period were within the therapeutic range for approximately 40% of the time. We estimated that the enrollment into the Warfarin Clinic Service would lead to a 50% improvement in the rate of anticoagulation control compared to the control group. Thus the investigator set p_c = 0.40, p_I = 0.60 and therefore, $\bar{p}$ = (0.40+0.60)/2 = 0.5. The study was designed as two-sided with a 5% significance level and 80% power. From statistic table, two-sided 0.05 critical value is 1.96 for Zα and 0.84 for Zβ. Substituting these values into the sample size formula yields 2N to be:

$$2N = \frac{2\{ 1.96 \sqrt{2 \text{ X } 0.5 \text{ X } 0.5} + 0.84 \sqrt{0.4\,(1-0.4) + 0.6\,(1-0.6)}\,\}^2}{(p_c - p_I)^2}$$

2N = 194.05 patients

Therefore the calculated total sample size was 195, or 98 in each group. We expected a dropout rate of 10 %. Therefore, the lowest number of patients needed in the analysis to show a 50 % difference in the anticoagulation control between intervention and control group were 108 in each group.

3.5. Period of study

The study period started from June 2008 to October 2008. Data collection period starts from May 27, 2008 until 220 patients are enrolled into the study. After the screening visit, the numbers of visit for both groups were 3 visits in clinic with 6 weeks interval.

3.6. Outcomes measures

3.6.1 Percentage of INR in target:

Comparison of percentage of time in therapeutic range between the two groups was compared using Student's t test or Mann Whitney U test. Time in therapeutic range was calculated in accordance with Rosendaal method (116). This method assumes the INR changes in a linear fashion between each INR measurement (117). Based on this linear change, each day between two INR measures can be classified as either in, above or below the therapeutic range and a true estimate of the time in range can be calculated. The time in therapeutic range had been calculated by counting the days of INR in target range, and then it was calculated to be the percentage of time in therapeutic range by comparing total days in target range with total days of treatment.

In example, the patient has INR reading of 2.0 on October 1st, then reading of 5.8 on October 16th. Assuming the patient gradually moves towards a reading of 5.8 throughout the 15-day period between June 1st and June 16th, then we can estimate that the patient was within their INR therapeutic range [1.5 – 2.5] for a minority of that time period. To calculate the value as followings

1. To calculate amount of the total shift (2.0 to 5.8 = 3.8 increase) that is within the therapeutic range (0.5 of shift is within range, [2.5 - 2.0 = 0.5])

2. To calculate percent of total shift within therapeutic range (0.5/3.8 = 13.16%)

3. To estimate number of days since last visit that were within range (13.16% x 15 days since last visit = 0.1316 x 15 = 1.97 days within range, and approximately 13 days out of range). Percentage for that time period is 13.16% in range, and 1.97 total days in range.

4. To calculate overall % in range, add total days in range for each time period, and divide by total therapeutic days

Table 3. Example of time-in-therapeutic range calculation using Rosendaal method

Visit date	Type	INR	INR Different	Percent in target	Days in therapeutic range
1/6/2008	Screening visit	2.0			
16/6/2008	Visit 1	5.8	3.8	13.16%	1.97
3/7/2008	Visit 2	1.8	4	17.5%	2.98
20/7/2008	Visit 3	2.0	0.2	100%	17
					Total = 21.95

A total day of treatment was 49 days which was the day starting at June 1, 2008 and ending at July 20, 2008. Since time in therapeutic range for this patient was calculated as followings;

$$\%\text{Time in therapeutic range} = \frac{\text{Days in therapeutic range}}{\text{Total days of treatment}} \times 100$$

$$= \frac{21.95}{49} \times 100$$

$$= 44.80\%$$

In fact, the time in therapeutic range can be calculated with three methods; the fraction of INR's in range, Cross-section-of-the files and the Rosendaal method (118). The first one is simple to calculate and requires only one INR value per patient.

This method becomes more precise as the number of patients increases. However this method should underestimate time in therapeutic range for a group if unstable patients are tested more frequently. For our study, the fraction of INR's in range method was not suitable, because the study had been controlled with follow-up period not more than 6-week interval. The second method is the cross-section-of-the-files methodology, which is also simple to perform, and provides a snap shot of how individual patients are managed at a particular point in time. Hence a single result does not suggest how well patients are managed over time. Neither of these two methods can be used to calculate incidence rates at different INR values, which can be done with the Rosendaal method. Nevertheless, the Rosendaal method is a more complicated calculation. It also makes assumptions that may not be true, and extreme values of out-of-range INRs may have an overall impact on the time in therapeutic range for the entire group. Even this method could reflect to actual days in target range, but some information could be lost in patients with frequent uncontrolled INR measurements. Furthermore, the prior studies which had long follow up-period could not use the Rosendaal method for time in therapeutic range assessment as these reasons. The translation of time in therapeutic range should be done with awareness of bias.

3.6.2 Thromboembolic and major bleeding events:

Diagnosis of these complications was performed by participating physicians. The researcher counted the numbers of thromboembolic events (CVA, TIA, Valve thrombosis, Peripheral or Systemic emboli) and major haemorrhagic events. The comparison in thromboembolic and major bleeding events between the two groups will be done by using Chi-square test or Fisher's Exact test and expressed as event/ 100 patient-year. Such data will be collected and calculated as number of events per 100 patient-year as follow.

$$\text{events per 100 patient-year} = \frac{\text{(number of events)} \times 100 \times 12 \text{ months}}{\text{(total number of patient)} \times \text{(mean follow-up period in months)}}$$

3.6.3. Patient satisfaction

Patients who were enrolled in the control group and intervention group answered the questionnaires using Likert scale at the last visit (Appendix C and D). For the purpose of patient satisfaction measurement, mean of satisfaction score will be calculated in each issue and the conversion of Likert scale data will be performed by using the conversion formula in Cummins' study (119). Therefore the Likert scale data will be converted to the percentage of satisfaction as:

$$\% \text{ patient satisfaction} = \frac{(\text{satisfaction score} - 1)}{\text{Maximum score} - 1} \times 100$$

$$\text{Or} \quad \% \text{ patient satisfaction} = \frac{(\text{satisfaction score} - 1)}{5 - 1} \times 100$$

The percentage of patient satisfaction will be calculated and summarized for comparison between two groups. It will be compared by statistic method using Student's t test or Mann-Whitney U test.

3.6.4. Cost analysis

Overall cost of care will be analyzed including cost as following:

- Patient's income (baht/ hour)
- Time used to care for each patient (hour)
- Cost of therapy (baht)
- INR testing cost (baht)
- Cost of human resources used to care for a patient including income of physicians, pharmacists, nurses (baht/ hour)

All of the cost above were assembled and summarized in total service cost of two groups and compared by Student's t-test. The calculation of total service cost had been estimated by the following formula:

$$\text{Total service cost (baht)} = \{(\text{patient's income} + \text{cost of human resources}) \times \text{time}\} + \text{cost of therapy} + \text{INR testing cost}$$

Where as;

Cost of human resources = Income of healthcare providers (physicians, pharmacist, nurse) caring patient (baht/ hour)

Time = Time used to care for each patient (hour)

INR testing cost = Cost of INR testing for venopuncture with patients in control group or cost of the test strip for patients in intervention group

Cost of therapy = Cost of hospital service and facilities

3.7. Criteria for termination

The patient was terminated from the study according to the following criteria

- Death during the follow-up period from causes other than thromboembolic events or hemorrhagic complications of warfarin.
- Lost to follow-up
- Desire to withdraw from the study for any reasons.

3.8. Study procedures

Step I. Preparation of Warfarin Clinic Team

1. Pharmacist training

Three clinical pharmacists had participated in the clinic. Pharmacist team was composed of 1 senior and 1 junior clinical pharmacist of Chest Disease Institute and a clinical pharmacist researcher of this study. The senior clinical pharmacist trained junior clinical pharmacist and the researcher with a structured didactic teaching along with practice sessions with case studies for a period of approximately 2 months. The training program included the following areas; basic physiology of hemostasis and coagulation, pharmacology of warfarin, pharmacokinetics of warfarin, pharmacotherapy of related disorders such as atrial fibrillation, stroke, deep vein thrombosis, pulmonary

embolism and valvular heart diseases. Related practice guidelines especially the latest guideline of anticoagulant used from the ACCP had been incorporated to familiarize trained pharmacists with evidence of anticoagulation therapy in various disease states.

2. Health-care team agreement

The investigator made an agreement with the physicians, nurses, medical record librarians in details about the steps of procedure in this study, time of an appointment or follow up, role of clinical pharmacists, cooperation among health professionals, patient management plan and schedule of this research.

Step II. Patient screening and randomization

1. Collecting the name lists of patients who had an appointment with cardiology or cardiovascular and thoracic clinic in Chest Disease Institute.

2. Clinical pharmacists had found the patients who are potential candidates to participate in this research according to the inclusion and exclusion criteria and mark the sign, “Warfarin Clinic”, on the cover of the OPD card. Baseline data of these patients were collected using patient monitoring sheets as a preparation before the first visit.

- Demographic data: sex, age
- Clinical data:
  - indication of warfarin
  - duration of warfarin therapy
  - underlying disease/ illness
  - concurrence drugs
  - medical history
  - history of warfarin dose adjustment and INR values since beginning warfarin therapy.
  - history of thromboembolic events and hemorrhagic complications
  - history of admission or emergency room causes from complication of warfarin including data as following:
    - Final diagnosis
    - Types of complications
    - Lab: INR, Hct, Hb, BUN, Cr, SGOT, SGPT

- Management: dosage of vitamin K, units of blood, or blood products transfusion.
- Home medications

- Patient's income

At the first visit, potential subjects were interviewed and recruited into the study based on inclusion and exclusion criteria. Patients willing to participate in the study must sign the informed consent. The patients were randomized in two groups by stratified randomization method. Random allocation was based on sequence of the consent form and target INR. All patients participated in this study for four visits (visit 0, 1, 2, and 3) with a 6-week interval between each visit.

Step III. Process of the study

Intervention group

1. INR testing

Baseline INR measurement of patients participating in warfarin clinic was performed by conventional laboratory at the first visit. Subsequent INR measurement for patients in the warfarin clinic was performed by the trained nurses using POCT at the second, third, and fourth visit. Visit interval was 6 weeks (week 0, 6, 12 and 18 weeks). During this 6-week period, extra appointments were made if it is deemed necessary for patient safety by the investigator.

2. Patient education

Clinical pharmacists had educated patients enrolling in this study. The details of information involved indication of warfarin, importance of compliance, follow-up visits, and INR monitoring, sign/symptoms of bleeding and thromboembolic complications, steps need to take when complications of warfarin occurs, potential drug interactions, pregnancy issues with warfarin, and general advices on how to live with warfarin. The patients were given the warfarin booklet to remind about warfarin information and record INR value.

3. Warfarin management

- Clinical pharmacist evaluated INR in each case and screen warfarin therapy problems that might affect warfarin therapy such as bleeding or thromboembolism complications, non-compliance, drug interaction, and medication

error. These data were reported to physician by documentation in OPD card and be recorded in patient record. In case where drug interaction was identified, safer drug or appropriate warfarin dosage adjustment was suggested to the physician. For INR over target with or without clinical bleeding, a recommendation to decrease or omit dose of warfarin along with other appropriate measures were provided to the physician. If a patient had presented with a low INR, a recommendation to increase the dose of warfarin was provided. For a potential thromboembolic event, patients were sent for physician's evaluation. Moreover, the medication errors were recorded in warfarin complication record and be reported to their physicians with appropriate solution by clinical pharmacists. The clinical pharmacist evaluated the compliance of patients by patient interview and record of patient self-reported in warfarin calendar (Appendix E). The patients were asked to record the time of taking warfarin everyday on the warfarin calendar.

- Physicians reviewed drug related problems and their solutions provided by clinical pharmacist. An independent decision was made by physician as one's deemed appropriate.

- All patients in intervention group were made an appointment for no longer than 6 weeks. However, extra appointments could be made if it is deemed necessary for patient safety by the investigator.

- Clinical pharmacist reviewed medical chart, record the patient information on the patient collection form (Appendix A), summarized and planed for patient management in the next visit. If a patient had experienced adverse event, the data was filled in the record form (Appendix A) and the adverse event was assessed for prevention plan.

Responsibilities of Healthcare professionals

- Nurses:

  - Measure and record vital sign of patients and INR value with POCT device.

  - Provide information to the patients in details of appropriate behavior/ lifestyle for patients taking warfarin at the first visit.

o Ask for bleeding episodes or other illness and inform the complication that may occur to clinical pharmacist and physician through OPD card record.

o Record all information in OPD card for the clinical pharmacist to evaluate drug therapy problems and find suitable solution.

o Explain the way to use warfarin calendar (Appendix E) and convince the patient to record time of taking warfarin on it.

- Clinical Pharmacists:

o Obtain a patient drug history through patient interview and patient chart review, monitoring adverse reactions, monitoring response to drug therapy, and acting as a liaison to the warfarin clinic.

o Provide patient education in details related to warfarin therapy, their disease states, and appropriate medication use, and concentrate to perform intervention when encountering adverse event, treatment goals and importance of drug adherence.

o Evaluate INR with health status of patients, identify adverse drug event/warfarin-related symptoms and their potential causes, report the information to physicians with proper recommendation for individual patients.

o Provide drug information or medication consultation to patients and healthcare providers.

o Summarize patient information, warfarin therapy problems, complication management, outcome of management, including intervention plan for the next visit and record all of these documents on the data collecting form (Appendix A).

- Physicians:

o Examine clinical status of patients, evaluate patient's health status/ disease state.

o Review drug therapy problems and their solutions provided by clinical pharmacists.

o Manage drug therapy problems of the patients and make decision for appropriate therapy based on recommendation from clinical pharmacists

- Record all of patient intervention and management on the OPD card.

Control group

1. INR testing

INR measurement of patients, randomized in control group, was tested by venopuncture using the conventional laboratory. INR result was reported to the physicians based on normal clinic procedure.

2. Physician examination and management

The physician evaluated patient status from the INR result, physical examination and patient interview. All patients in the control group were made an appointment for no longer than 6 weeks. However, extra appointments were made if it is deemed necessary for patient safety by the investigator.

Responsibilities of Healthcare professionals

- Nurses:
  - Measure and record vital signs of a patient
  - Ask for bleeding episodes, other illnesses and inform these data to the physician through OPD card record.
  - Provide information to the patients in details of appropriate behavior/ lifestyle for patients taking warfarin.
  - Record all information in OPD card for the physician
- Clinical Pharmacists:
  - Obtain a patient drug history, monitoring adverse reactions, monitoring response to drug therapy through patient chart review.
  - Summarize patient information, warfarin therapy problems, complication management, outcome of management, and record these entire document on the data collecting form (Appendix A).
- Physicians:
  - Examine clinical status of patients, evaluate patient's health status/ disease state, and monitor response to drug therapy.
  - Review drug therapy problems, monitoring adverse reactions, and find the potential causes of them.

- Manage drug therapy problems of the patients and make decision for appropriate therapy.

Workflow of the research is demonstrated in Figure 6.

3.9. Data collections

The data were collected and recorded in the data collection form as follows:

3.9.1. Demographic data (Appendix A):

Patient's name, age, gender, hospital number (HN), weight, height, date of follow-up, length of stay, history of warfarin usage, social history, allergy , and co-morbidity disease.

3.9.2. Laboratory data (Appendix A):

Vital signs, blood chemistry, complete blood count, urinalysis, and coagulation test.

3.9.3. Medication data (Appendix A):

Medication history, concomitant medications during admission and at discharge.

3.9.4. Warfarin therapy data (Appendix A):

Indication, dosage regimen including the day of taking warfarin, co-medication, INR value, drug interaction, dose adjustment, adverse drug events, including patient's behavior affecting warfarin therapy

3.10. Data Analysis

All data was analyzed concurrent with consort statement as shown in Appendix F (120).

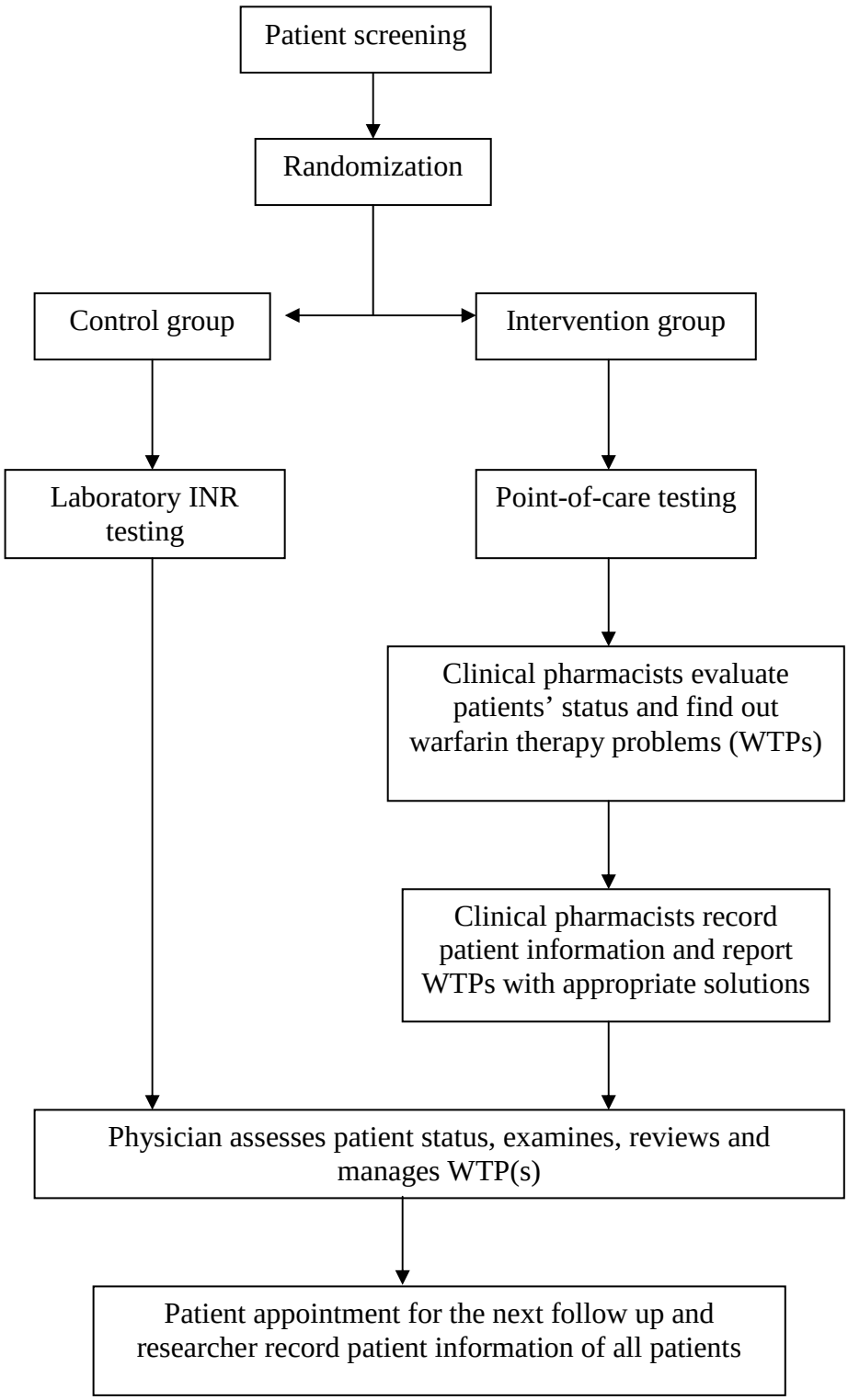


Figure 6. Workflow of intervention group and control group

(WTP(s) = warfarin therapy problem(s), OPD = outpatient department)

3.10.1 Patients' characteristics

Patients' characteristics in the both groups will be analyzed by descriptive statistics as following:

- Interval or ratio scale with normal distribution of data will be compared using unpaired t-test such as mean of age.
- Interval or ratio scale with non-normal distribution of data will be compared using Mann Whitney U test such as follow-up time.
- Nominal scale will be compared using chi-square test or Fisher's Exact test such as sex, indication of warfarin therapy, risk of bleeding, risk of stroke, duration of warfarin therapy and the INR target range.

3.10.2 The clinical and economic outcome of anticoagulation control

3.10.2.1 Percent of INR in target range

Time of INR in target range will be presented as percent of time in therapeutic range and compared between intervention and control groups using Mann Whitney U test. The time in therapeutic range was calculated by Rosendaal method. This method was the way to calculate the amount of time between visits by counting the days of INR in therapeutic range, and calculate in percent of total days of treatment in the study.

3.10.2.2 Major bleeding or Thromboembolism event rates were reported by numbers of event per 100 patient-year and compared between groups using Chi-square test or Fisher's Exact test.

3.10.2.3 Patient satisfaction

The score of questionnaires would be summarized and calculated as percentage of satisfaction. The figures of both groups would be compared with Student's t test or Mann-Whitney U test.

3.10.2.4 Cost analysis

The direct and indirect cost of treatment was calculated to the total cost and compared with Student's t-test or Mann-Whitney U test.

CHAPTER IV
RESULTS

I. Population characteristics

A total of 109 patients enrolled in this study were randomized into two groups. There were 55 and 54 patients in the intervention and control groups, respectively. Four patients in the control group were excluded from the study, because all of them did not participate in the study after the screening visit. One patient was lost to follow up after the screening visit, and three patients had asked to stop participating in the study. For the patients in the intervention group, three patients were excluded from the study, because they did not participate in the study after the screening visit. One patient was lost to follow up after the screening visit. There were 2 patients who were admitted secondary to warfarin overdose and heart failure, respectively. Consequently, 52 patients of intervention group and 50 patients of control group were included into the study.

However, this study had to be terminated before the process had been completed. The reason for termination was the demand from patients in the control group to receive the same service as the intervention group. With this demand, the termination was discussed and agreed by the warfarin clinic team. At the beginning, the number of patient visits was planned to be four times. At the point of study termination, there were 11 and 8 patients in control and intervention groups who passed only one visit (screening visit). As a result, these patients were not included in the data analysis.

Consequently, the data of 39 patients in the control group and 44 patients in intervention group were summarized and analyzed. There were 10 patients in the intervention group passed through all planned visits, while none in the control group had participated through all planned visits. There were 13 patients of the intervention

group and 25 patients of the control group who visited the warfarin clinic for 3 times. There were 21 and 14 patients in the intervention and control groups who visited the clinic for 2 times. In total, the data of all participating 83 patients were analyzed.

Demographic data of both groups were similar in gender, age, education level, occupation, duration of warfarin therapy (before the patients participated in this study), indication of warfarin, target INR, history of major bleeding, history of stroke, and patient income. Before the patients participating in the study, the mean follow-up times of the patients in the intervention group were almost equal to those in the control group (34.05 ± 47.51 months in the intervention group vs 29.72 ± 24.82 months in the control group). Based on this follow-up time, there were a total of 2.95 ± 4.05 vs 2.48 ± 2.07 patient-years of follow-up in the intervention and control groups, respectively. The average (mean ± SD) age in both groups was approximately 51 years old, and slightly more than a half of patients were female.

The most common indications for warfarin therapy were aortic valve replacement, mitral valve replacement, double valve replacement and mitral valve replacement with atrial fibrillation. For target INR, approximately half of the patients in both groups required INR target range of 1.5-2.5 and 2.0-3.0. For duration of therapy, more than half of the patients in both groups had been receiving warfarin therapy for less than 2 years (53.8% in the control group and 59.1% in the intervention group; $p = 0.151$). At the screening visit, the INR (mean ± SD) values was slightly higher in the intervention group than in the control group (2.02 ± 1.75 vs 1.82 ± 0.49, respectively; $p = 0.225$). The percent INR in therapeutic range was found significantly higher in control group than in intervention group (61.5 and 38.6, respectively; $p= 0.037$). Furthermore, the rate of under-anticogulation (INR value less than 1.5) was slightly higher in intervention group than in control group (31.8% and 17.9%, respectively; $p = 0.147$), and the rate of over-anticogulation (INR value more than 1.5) was slightly higher in intervention group than in control group (4.5% and 0%, respectively; $p = 0.496$). Two-third of patients in both groups was graduated in primary school level or less than this level (66.6% in the control group and 68.2% in the intervention group). For the occupation, the most of patients in both groups had no job or were housekeepers (38.5% in the control group and 47.7% in the intervention group; $p = 0.952$). For comparison of income between patients in the control group

and the intervention group, there were not statistic significantly different (322.54 ± 463.11 vs 268.72 ± 373.11, respectively; p = 0.727), but most of them had no income. Most patients in both groups used healthcare services of universal coverage scheme (66.7% in the control group and 68.2% in the intervention group; p = 0.888). The demographic characteristics, underlying diseases, and co-medicine were presented in Table 4-8.

Table 4. Characteristic of the patients

Characteristics	UC (%)	Intervention (%)	p value
Patients (N)	39	44	
Age (years)			
Mean ± SD	51.13 ± 12.31	51.64 ± 10.57	0.840 [a]
Range	29-87	22-75	
Gender			
Male	17 (43.6)	19 (43.2)	0.970 [c]
Female	22 (56.4)	25 (56.8)	
Follow up time (before participating in the study; patient years)	2.48 ± 2.07	2.95 ± 4.05	0.642 [b]
Mean of follow up time(before participating in the study; months)	29.72 ± 24.82	34.05 ± 47.51	0.559 [b]

a= Student-T Test ; b= Mann-Whitney U Test ; c= Chi-square Test

Table 4. Characteristic of the patients (Continued)

Characteristics	UC (%)	Intervention (%)	p value
Indication of warfarin			
1. One indication	**25 (64.1)**	**33 (75.0)**	**0.531** [f]
- AVR	16 (41.0)	18 (40.9)	
- MVR	5 (12.8)	7 (15.9)	
- DVR	3 (7.7)	7 (15.9)	
- AF	1 (2.6)	1 (2.3)	
2. Two indications	**12 (30.8)**	**10 (22.7)**	
- MVR+AF	9 (23.1)	6 (13.6)	
- DVR+AF	3 (7.7)	2 (4.5)	
- VHD+AF	0 (0)	1 (2.3)	
- AF + Tissue valve	0 (0)	1 (2.3)	
3. Three indications	**2 (5.1)**	**1 (2.3)**	
- MVR+AF+CVA	2 (5.1)	0 (0)	
- DVR+AF+CVA	0 (0)	1 (2.3)	
Duration of warfarin therapy (month)			
< 24	21 (53.8)	26 (59.1)	0.151 [f]
24-48	9 (23.1)	12 (27.3)	
49-60	4 (10.3)	1 (2.3)	
61-120	5 (12.8)	2 (4.5)	
> 120	0 (0)	3 (6.8)	

f = Fisher's Exact test

Table 4. Characteristic of the patients (Continued)

Characteristics	UC (%)	Intervention (%)	p value
Target INR range			
1.5-2.5	20 (51.3)	21 (47.7)	0.746 [c]
2.0-3.0	19 (48.7)	23 (52.3)	
Mean of number of INR value @ V0 /pt	1.82 ± 0.49	2.02 ± 1.75	0.225 [b]
Numbers of INR in target @ V0	24 (61.5)	17 (38.6)	0.037 [c]
Number of low INR value @ V0 (INR<1.5)	7 (17.9)	14 (31.8)	0.147 [c]
Number of high INR value @ V0 (INR>5)	0 (0)	2 (4.5)	0.496 [f]
Education level			
Primary school	26 (66.6)	30 (68.2)	0.800 [f]
Secondary school	5 (12.8)	6 (13.6)	
High school	4 (10.3)	2 (4.6)	
Bachelor degree	4 (10.3)	6 (13.6)	

b = Mann-Whitney U Test

c = Chi-square Test

f = Fisher's Exact test

Table 4. Characteristic of the patients (Continued)

Characteristics	UC (%)	Intervention (%)	p value
Occupation			
Government officer	4 (10.3)	5 (11.4)	0.952 [f]
Company officer	2 (5.1)	2 (4.5)	
Saler/ merchant	7 (17.9)	7 (15.9)	
Housekeeper	15 (38.5)	21 (47.7)	
Monk/ priest/ nun	1 (2.6)	0 (0)	
Farmer	3 (7.7)	4 (9.1)	
Freelance	7 (17.9)	5 (11.4)	
Income (bath/pt/day)			
Mean ± SD	322.54 ± 463.11	268.72 ± 373.11	0.727 [b]
Range	0-1750	0-1750	
Median	200.00	137.50	
Type of healthcare and medical payment			
Government or State enterprise officer	8 (20.5)	10 (22.7)	0.888 [f]
Universal coverage scheme (UCS)	26 (66.7)	30 (68.2)	
Social Security Scheme (SSS)	5 (12.8)	4 (9.1)	

b = Mann-Whitney U Test

f = Fisher's Exact Test

Table 5. Numbers of underlying disease per patient at baseline

Numbers of underlying diseases	UC (%)	Intervention (%)	p value
None	7 (17.9)	10 (22.7)	0.910 [f]
One disease	9 (23.1)	10 (22.7)	
Two diseases	14 (35.9)	11 (25.2)	
Three diseases	4 (10.3)	7 (15.9)	
Four diseases	4 (10.3)	5 (11.4)	
Five diseases	1 (2.5)	1 (2.3)	

C= Chi-square Test

Table 6. Types of underlying disease at baseline

Type of underlying disease	UC (N=39)	Intervention (N=44)
Anemia	14	15
Asthma	1	0
Cancer	1	0
Chronic Obstructive Pulmonary Disease	0	1
Diabetes Mellitus	1	4
Dyslipidemia	7	10
Dyspepsia/ GERD	1	2
Euthyroid	1	0
Heart failure	6	9
Hemoglobin H disease	1	0
Hx of TIA or Old CVA	3	1
Hypertension	21	20
Hyperuricemia	3	2
Ischemic heart disease	1	0
Marfan's Syndrome	2	1
Myoma	0	1
Osteoarthritis	0	1
Osteoporosis	1	1

Table 6. Types of underlying disease at baseline (continued)

Type of underlying disease	UC (N=39)	Intervention (N=44)
Pulmonary hypertension	0	1
Post myocardial infarction (MI) or Old MI	0	1
Renal calculi	1	0
Renal insufficiency	5	3
Seizure	0	1
Pterygium	0	1
Cataract	0	1
Valvular dysfunction (even after surgical valvular replacement)	0	1
Viral hepatitis	0	1
Total	70	78

Some patients have more than one underlying disease.

Table 7. Co-medications at baseline

Medicines	UC (N=39)	Intervention (N=44)
Aspirin gr I/ V	2	1
Amiodarone	5	0
Atorvastatin	2	2
Ciprofloxacin	0	1
Digoxin	0	1
Metoprolol	6	1
Omeprazole	4	4
Phenytoin	0	1
Propanolol	0	1
Ranitidine	1	1
Rosuvastatin	0	1
Simvastatin	2	4
Total	22	18

Assessment on risk of major bleeding at baseline was conducted to compare such risk of the two populations. There was no difference between the two groups

regarding the thromboembolic events and major bleeding events. Thromboembolic events at baseline were 1.35 and 1.60 events per 100-patient year for patients in the control and intervention groups, respectively (p = 0.722). For major bleeding events at baseline, the rates were 3.11 and 2.40 per 100-patient year in the control and intervention groups, respectively. (Table8)

Table 8. Thromboembolic and major bleeding events at baseline

Complications	UC (N=39)	Intervention (N=44)	p value*
Thromboembolic events (events per 100-patient year)	1 (1.35)	2 (1.60)	0.722
Major bleeding events (events per 100-patient year)	3 (3.11)	3 (2.40)	1.000

* p value <0.05 statistically significant

: Fisher's Exact test used to compare mean between groups

Because timing of treatment could be one of the crucial factors influencing clinical outcome of patients, the analysis of patients particularly participating at least three visits corresponding the study protocol had been processed. This subgroup analysis did not show in different results of the characteristics of prior analysis. All characteristics of patients were not different between two groups, except the number of INR in target. The number of INR in target at the screening visit was found significantly more in the control group than in the intervention group (Table 9), even underlying diseases did not show significant different between two groups (Table 10-11). The demographic characteristics, underlying diseases, and co-medicine were presented in Table 9-12.

Furthermore, risk of complications at baseline conducted to compare such risk of the two populations revealed insignificantly different. Thromboembolic event at baseline was not found for patients in both groups. But the patients in the control group experienced major bleeding events, for two events or 3.20 events per 100-patient year and the patients in another group were found only one event or 2.53 events per 100-patient year (p = 1.000; Fisher's Exact Test). Even though, the complications at baseline

was slightly different from prior, there were not significant different between populations in control and intervention group as prior assessment.

Table 9. Characteristics of patients participating at least three visits in the study

Characteristics	UC (%)	Intervention (%)	p value
Patients (N)	25	23	
Age (years)			
Mean ± SD	48.84 ± 10.73	49.17 ± 11.42	0.917 [a]
Range	32-73	22-66	
Gender			
Male	10 (40.0)	12 (52.2)	0.398 [c]
Female	15 (60.0)	11 (47.8)	
Follow up time (before participating in the study; patient years)	2.50 ± 1.59	1.72 ± 1.22	0.083 [b]
Mean of follow up time(before participating in the study; months)	30.00 ± 19.03	20.65 ± 14.70	0.083 [b]
Indication of warfarin			
1. One indication	**14 (56.0)**	**18 (78.3)**	0.102 [c]
- AVR	10 (40.0)	10 (43.5)	
- MVR	2 (8.0)	4 (17.4)	
- DVR	2 (8.0)	4 (17.4)	
2. Two indications	**11 (44.0)**	**5 (21.7)**	
- MVR+AF	8 (32.0)	3 (13.0)	
- DVR+AF	3 (12.0)	2 (8.7)	

a= Student-T Test, b= Mann-Whitney U Test, c= Chi-square Test**,** f= Fisher's Exact test

Table 9. Characteristics of patients participating at least three visits in the study (Continued)

Characteristics	UC (%)	Intervention (%)	p value
Duration of warfarin therapy (month)			
< 24	12 (48.0)	15 (65.2)	0.427 [f]
24-48	8 (32.0)	7 (30.4)	
49-60	3 (12.0)	1 (4.4)	
61-120	2 (8.0)	0 (0)	
Education level			
Primary school	15 (60.0)	16 (69.6)	1.000 [f]
Secondary school	4 (16.0)	3 (13.0)	
High school	3 (12.0)	2 (8.7)	
Bachelor degree	3 (12.0)	2 (8.7)	
Target INR range			
1.5-2.5	13 (52.0)	11 (47.8)	0.773 [c]
2.0-3.0	12 (48.0)	12 (52.2)	
Mean of number of INR value @ V0 /pt	1.84 ± 0.39	2.28 ± 2.37	0.189 [b]
Number of low INR value @ V0 (INR<1.5)	4 (16.0)	9 (39.1)	0.072 [c]
Number of high INR value @ V0 (INR>5)	0 (0)	2 (8.7)	0.224 [f]
Number of INR in target @ V0	17 (68.0%)	7 (30.4%)	0.009 [c]

b= Mann-Whitney U Test

c= Chi-square Test

f= Fisher's Exact Test

Table 9. Characteristic of the patients participating at least three visits in the study (Continued)

Characteristics	UC (%)	Intervention (%)	p value
Occupation			
Government officer	3 (12.0)	3 (13.1)	0.964 [f]
Company officer	1 (4.0)	1 (4.3)	
Saler/ merchant	5 (20.0)	5 (21.7)	
Housekeeper	9 (36.0)	10 (43.5)	
Farmer	3 (12.0)	1 (4.3)	
Freelance	4 (16.0)	3 (13.0)	
Income (bath/pt/day)			
Mean ± SD	347.00 ± 460.08	304.50 ± 418.46	0.782 [b]
Range	0-1500	0-1750	
Median	200	200	
Type of healthcare and medical payment			
Government or State enterprise officer	6 (24.0)	7 (30.4)	0.347 [f]
Universal coverage scheme (UCS)	16 (64.0)	16 (69.6)	
Social Security Scheme (SSS)	3 (12.0)	0 (0)	

b= Mann-Whitney U Test

c= Chi-square Test

f= Fisher's Exact test used to compare mean between groups

Table 10. Numbers of underlying disease per patient at baseline (for the patients participating at least three visits in the study)

Numbers of underlying diseases	UC (%)	Intervention (%)	p value
None	6 (24.0)	10 (43.5)	0.539 [f]
One disease	8 (32.0)	7 (30.4)	
Two diseases	6 (24.0)	2 (8.7)	
Three diseases	3 (12.0)	2 (8.7)	
Four diseases	2 (8.0)	2 (8.7)	

f= Fisher's Exact test used to compare mean between groups

Table 11. Types of underlying disease at baseline (for the patients participating at least three visits in the study)

Type of underlying disease	UC (N=25)	Intervention (N=23)
Anemia	7	6
Diabetes Mellitus	1	1
Dyslipidemia	4	3
Dyspepsia/ GERD	1	0
Euthyroid	1	0
Heart failure	0	1
Hemoglobin H disease	1	0
Hx of TIA or Old CVA	1	0
Hypertension	14	7
Hyperuricemia	1	1
Marfan's Syndrome	2	0
Osteoporosis	1	1
Pulmonary hypertension	0	1
Renal Insufficiency	1	1
Seizure	0	1
Cataract	0	1
Viral hepatitis	0	1
Total	37	25

Some patients have more than one underlying disease.

Table 12. Co-medications at baseline (for the patients participating at least three visits in the study)

Medicines	UC (N=25)	Intervention (N=23)
Aspirin gr I/ V	2	1
Amiodarone	2	0
Atorvastatin	2	1
Metoprolol	4	0
Omeprazole	4	1
Phenytoin	0	1
Ranitidine	1	0
Rosuvastatin	0	1
Simvastatin	1	0
Total	17	5

Furthermore, risk of complications at baseline conducted to compare such risk of the two populations was similar. All patients of this subgroup never experienced thromboembolic event prior to study participation. For major bleeding, the rates were 3.26 and 2.53 events per 100-patient year in the control and intervention groups, respectively ($p = 0.580$).

II. Anticoagulation control

The anticoagulation control was evaluated in the percentage of INR in target. At baseline, 39 and 44 INR values in the control and study groups were analyzed, respectively. In the both groups, the average (mean ±SD) INR values of screening visit were 1.82 ± 0.49 and 2.02 ± 1.75 in the control and study group, respectively. These figures were not significantly different. As previously seen during the preliminary study, percentage of INR in target at the Chest Disease Institute was approximately 40%. At baseline, the percent INR in target of participating patients in both groups were approximately 50.05% (61.5% in the control group and 38.6% in the study group; $p = 0.037$). There were statistically significant differences in the percent of INR in target between two groups.

In post-intervention period, a total of 141 INR values were measured including 64 and 77 values in the control and study groups, respectively. The average (mean ±SD) INR values of screening visit were 1.82 ± 0.49 and 2.02 ± 1.75 in the control and study group, respectively (Table 4). These numbers were not significantly different, whereas the average INR values in post study period of the control group were significantly less than those of the intervention group. Average INR value of control group was 1.79 ± 0.39, while as average INR of the intervention group was 1.95 ± 0.81 (Table 13). Corresponding to these results, the rate of under anticoagulation was found higher insignificantly in control group than in intervention group (17.19% vs 14.29%, respectively; p = 0.680). In addition, over anticoagulation of intervention group was three INR values (3.9%) and no one was found in control group, nevertheless these difference was not statistically significant (Table 13).

After the early termination of the study, most of patients in the control group, were asked to participate in the warfarin clinic based on the voluntariness. For the patients in the intervention group, they were still in the same group but the period of the appointment was changed to be longer than the protocol of the study and it depended on individual patients. Consequently, numbers of patients, who could be counted in the protocol of the study, in the third visit (Visit 2) were decreased and none of patients in the control group had participated to correspond with the study protocol at the last visit (Visit 3).

Overall of time-in-therapeutic range was calculated in corresponding with Rosendaal method. The percent of time in therapeutic range during post-intervention period were not different between the study group and the control group (45.06 ± 39.63% vs 54.30 ± 42.74%, respectively; p = 0.379).

In addition, INR values were compared the rates of under- (INR less than 1.5) and over-anticoagulation (INR more than 5) between the two groups. At baseline, the rates of under- and over-anticoagulation were not different in between two groups. At screening visit (V0), there were 7 INR values for under-anticoagulation or 17.9% in the control group and 14 values or 31.8% in the study group (Chi-square test; p = 0.147). Whereas, the over-anticoagulation INR values were found 2 values or 4.5% in the study group, but it was not found in the control group, this was not statistical different between two groups (Fisher's Exact test; p = 0.496). After the study termination, the patients who

had ever participated in the control group, were changed a caring system, and the rate of under- and over-anticoagulation were not different between control and intervention groups. There were 11 INR values for under-anticoagulation or 17.19% in the control group and 11 values or 14.29% in the study group (Fisher's Exact test; p = 0.680). Whereas, the over-anticoagulation INR values were found 3 values or 3.9% in the study group, but it was not found in the control group, this was not statistical different between two groups (Fisher's Exact test; p = 0.244).

Table 13. Results of anticoagulation control

Results	UC (N=39)	Intervention (N=44)	p value*
Numbers of INR value	64	77	
Mean INR value	1.79 ± 0.39	1.95 ± 0.81	0.028
Total follow up days	72.13 ± 23.72	75.50 ± 32.72	0.691
Days of INR in therapeutic range	38.89 ± 33.99	35.57 ± 35.18	0.667
Percent time in therapeutic range	54.30 ± 42.74	45.60 ± 39.63	0.379

* p value <0.05 statistically significant

: Mann-Whitney U test used to compare mean between groups

Table 14. Under- and over-anticoagulation

Type	UC (N=39)		Intervention (N=44)		p-value*
	No. of INR (%)	No. of INR testing	No. of INR (%)	No. of INR testing	
Under	11 (17.19)	64	11 (14.29)	77	0.680
Over	0 (0)	64	3 (3.9)	77	0.244

* p value <0.05 statistically significant

: Fisher's Exact test used to compare mean between groups

Figure 7. INR values of patients in the control group

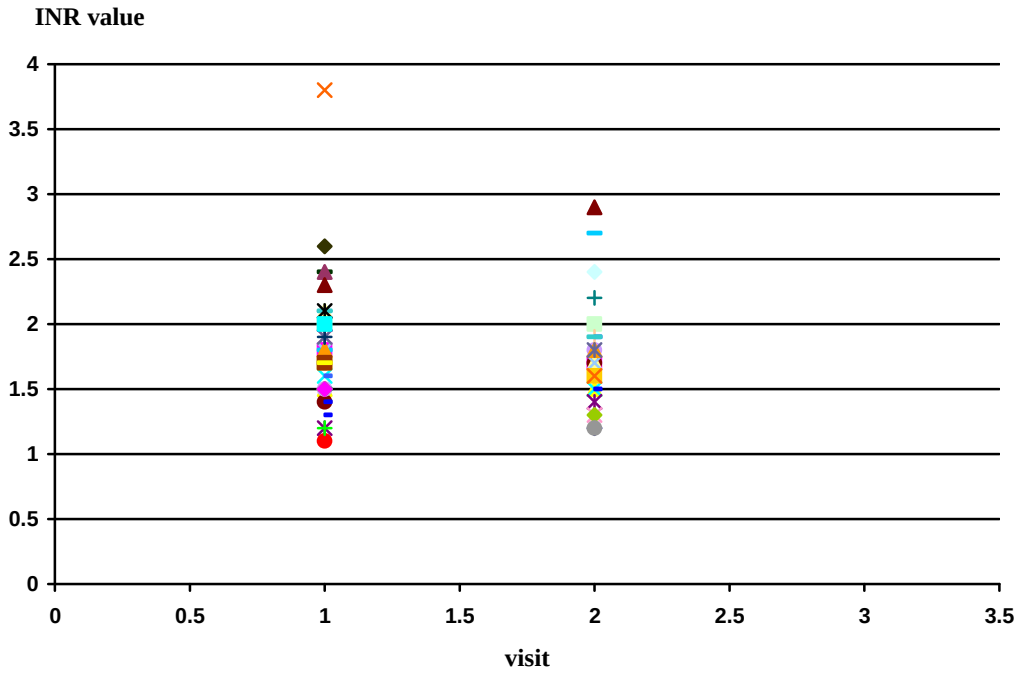
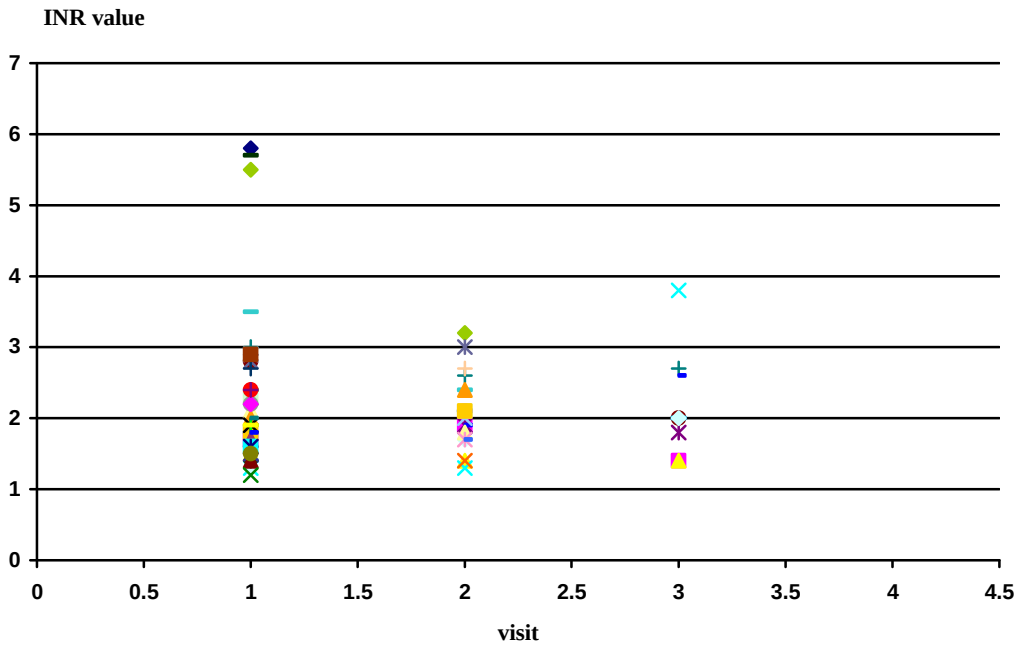


Figure 8. INR values of patients in the intervention group



The results of patients passing through at least three visits in the study were analyzed in the followings. For the intention-to-treat populations participating at least three visits in the study, percent of time in therapeutic range was 53.92 ± 42.26 for control group and 45.32 ± 34.16 for intervention group (Table 15). Even though the

analysis considered in particular patients participating in the study at least three visits, the percent of time in therapeutic range was not different between two groups and almost be the same figure as prior analysis. Furthermore, the rate of under and over-anticoagulation control were not statistically different between the control group and the intervention group (Table 16).

Table 15. Results of anticoagulation control (for the patients participating at least three visits in the study)

Results	UC (N=25)	Intervention (N=23)	p value*
Numbers of INR value	50	56	
Mean INR value	1.78 ± 0.36	2.21 ± 0.67	0.007
Total follow up days	88.44 ± 10.74	102.04 ± 23.05	0.094
Days of INR in therapeutic range	47.30 ± 37.65	48.41 ± 40.55	0.959
Percent time in therapeutic range	53.92 ± 42.26	45.32 ± 34.16	0.497

* p value <0.05 statistically significant

: Mann-Whitney U test used to compare mean between groups

Table 16. Under- and over-anticoagulation (for the patients participating at least three visits in the study)

Type	UC (N=25)		Intervention (N=23)		p-value*
	No. of INR (%)	No. of INR testing	No. of INR (%)	No. of INR testing	
Under	8 (16.00)	50	8 (14.29)	56	0.790
Over	0 (0)	50	2 (3.57)	56	0.224

* p value <0.05 statistically significant

: Fisher's Exact test used to compare mean between groups

The scattered INR values stayed in therapeutic range for more visits in both groups (Figure 9-10). However, the numbers of visit might be too few in the study and the bias could occur in small size of populations. Moreover selection bias could exist in

this study, the patients participating in the control group might be better than the patients in the intervention group in trend of therapeutic control at the start of the study.

Figure 9. INR values of patients in the control group (for the patients participating at least three visits in the study)

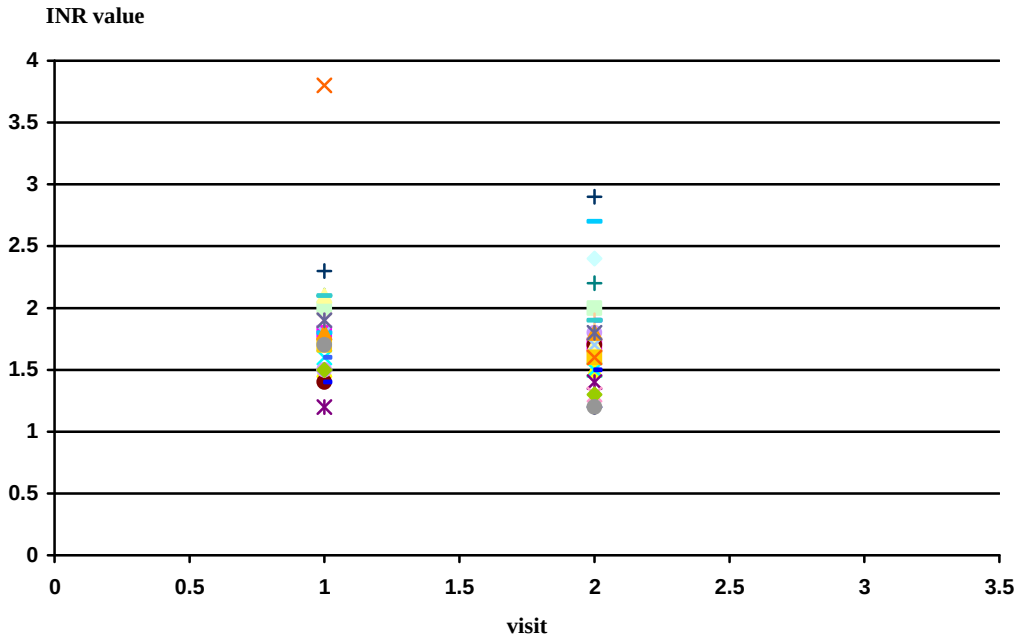
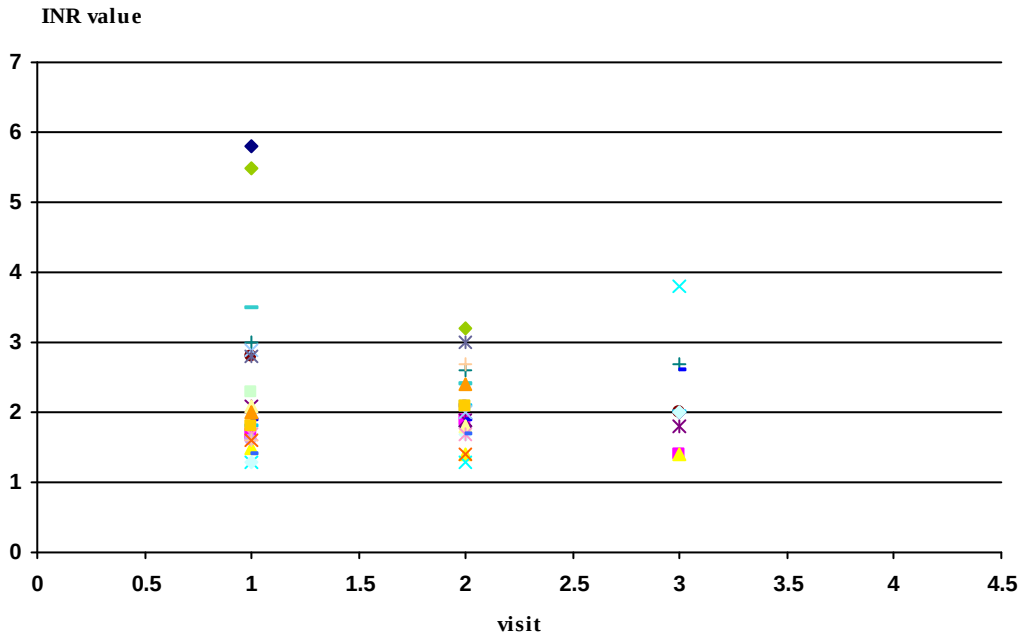


Figure 10. INR values of patients in the intervention group (for the patients participating at least three visits in the study)



III. Thromboembolic and major bleeding events

According to the study protocol, none of patients in the control group and the intervention group had experienced thromboembolic event after they participated in the study. However major bleeding event had existed only two events of patients in control group or 29.17 events per 100-patient year and it did not exist in the intervention group (Table 17). Furthermore, there was no statistically significant different in major bleeding event between two groups (Table 18). Although, an over-anticoagulation trend at baseline was found more events in the intervention group than in the control group, but major bleeding could not been found in patients of intervention group during the study. The over-anticoagulation rate of the patients participating in the study tended to be less in intervention group than in control group.

Table 17. Rate of major bleeding

Major bleeding events	No. of events	
	UC	Intervention
No. of event/follow up period	2	0
Events/ 100-pateint year	29.17	0

Table 18. Major bleeding

Major bleeding events	No. of events		p-value*
	UC	Intervention	
Yes	2	0	0.218
No	62	77	

* p value <0.05 statistically significant

: Fisher's Exact test used to compare mean between groups

The patient experiencing major bleeding was 60 years old male treated with warfarin for mitral valve replacement and atrial fibrillation. His INR value was 2.7 (Target INR was 2-3). Even it was in therapeutic range, but his electrocardiogram showed left-ventricular hypertrophy, atrial fibrillation with rapid ventricular rate, and the chest X-ray showed cardiomegaly. Moreover, while the physician was waiting for laboratory INR result, he ordered to try INR measurement by POCT device. The INR

results were 3.7 and 3.9 with different methods. The recommendation method was resulted INR value to be 3.9, while another method was to drip blood from the syringe filled with the blood drawn from the patient's arm on the strip and INR result was 3.7. The physician decided to hold two doses of warfarin and reduced warfarin dose by 14%. Then the patient returned to see the physician two days later with upper gastrointestinal bleeding with black stools. The physician ordered him to be admitted in Chest Disease Institute and did not measure INR value in the admission day. After four days ago, the patient was discharged with INR 1.7 and had no blood stool. This event was occurred before the premature study termination. After the patient was discharged, he came to be treated in warfarin clinic for the first time in the next one month and had been found that he had taken the wrong dose of warfarin from 14 milligrams per week to 12 milligrams per week. However, the dose of warfarin was adjusted to be 12 milligrams per week as the same due to existence of atrial fibrillation, even INR resulted to be 3.4. And then his dosage regimen was in range of 8 to 9.5 milligrams per week for control INR in therapeutic range without complication.

Another patient was a 34 years old female treated with warfarin for mitral valve and aortic valve replacement. She had taken warfarin for one year before participating in the study. Her INR values were in target range (target INR was 2-3) with elevated trend. Even though she had been controlled with 17.5 mg per week of warfarin, her warfarin dosage was adjusted to be 1.5 milligrams/day (10.5 milligrams per week), which had been lowered from 2 milligrams/day (14 milligrams per week), because her INR was 3.0 at that moment without bleeding complication. This adjustment of warfarin dosage regimen had occurred for six days before she decided to participate in the study. At the screening visit, her INR was 2.0 which could be lessened by dose adjustment. And the next visit, her INR was 2.3 without any complication. The last visit, her INR value was 2.9 and it was elevated from 2.3 within 6 weeks without any record involving in complication risk of warfarin. She took 10.5 milligrams per week of warfarin in that moment. Even though we planned to adjust dose in next visit with drug related problem investigation, nevertheless she had died in a hospital with intracranial hemorrhage after the last visit one month ago.

Table 19. Rate of major bleeding (for the patients participating at least three visits in the study)

Major bleeding events	No. of events	
	UC	Intervention
No. of event/follow up period	2	0
Events/ 100-pateint year	37.35	0

Table 20. Major bleeding (for the patients participating at least three visits in the study)

Major bleeding events	No. of events		p-value*
	UC	Intervention	
Yes	2	0	0.490
No	48	56	

* p value <0.05 statistically significant

: Fisher's Exact test used to compare mean between groups

For patients passing through the study at least three visits, none in the control and intervention groups experienced thromboembolic event during the study period. However major bleeding event had happened only two events of patients in control group or 37.35 events per 100-patient year and it did not exist in the intervention group (Table 19). There was no statistically significant in difference of major bleeding event between two groups (Table 20). Complications showed no statistical difference in both thromboembolic event and major bleeding.

However, the mortality rate had been found in this study for two patients. One was in the control group, and another was in the intervention group. The first patient participated in the study for three visits and then she had died in the other hospital after the last visit one month ago. This case has been described in details of patients experiencing major bleeding event.

The second patient participating in the intervention group was 33 years old female. Before she consented to participate in the study, she had been replaced aortic heart valve for two times and admitted with paravalvular leakage for two times. She had allergy with penicillin since she was young. Moreover, she experienced infective

endocarditis, therefore she had taken ciprofloxacin for prophylaxis of infective endocarditis. Her target INR was 1.5-2.5 with indication of AVR. Even though potential drug interaction possibly existed in this patient, INR values of this patient had been in target even in the study period. She had never experienced thromboembolic and hemorrhagic complications during the study period, which had only two visits. The last visit in this study was the second visit and the patient took 17.5 milligrams per week of warfarin dosage regimen with INR in target (her INR was 2.0) without dyspnea. However, the patient had been planned to redo aortic valve replacement by the surgeon. Her last echo-cardiogram showed 40-50% of ejection fraction. Nevertheless, she had died in the other hospital with respiratory failure from cause other than complication of warfarin, after her last follow up in approximately six weeks.

IV. Patient satisfaction

The evaluation of patients' satisfaction was not performed due to the early termination of the study.

V. Cost analysis

After study termination, only 36 patients who were presented at least three visits were measured time spending in clinic and it was calculated to be total service cost. There were 20 and 16 patients in control and intervention group, respectively (Table 21). Mean of total service cost in control group was less than cost in intervention group (112.40 ± 59.20 and 276.49 ± 194.97 baths, respectively; $p < 0.001$). For consideration at time spending in clinic, the patients in intervention group spent time longer than patients in control group (Table 22), nevertheless period of time spending to see the doctor was not significantly different. The result was contradictory shown in time spending for INR testing, the patients in control groups spent more time than patients in intervention groups (Table 22). Total time and cost of service in intervention group were more than in control group, otherwise, amounts of sample size might be too small to be represented of all populations.

Table 21. Total service cost

Service cost (baths)	UC (N=20)	Intervention (N=16)	p-value
Mean ±SD	112.40 ± 59.20	276.49 ± 194.97	< 0.001
Min	89.47	172.64	
Max	332.55	982.83	

p value <0.05 statistically significant

: Mann-Whitney U test used to compare mean between groups

Table 22. Time spent in clinic

Time	UC (N=20)	Intervention (N=16)	p-value
Doctor room (hours)	0.06 ± 0.02	0.19 ± 0.38	0.051
Pharmacist room (hours)	0	0.30 ± 0.16	NA
INR testing (minutes)	14.8 ± 35.98	2.25 ± 1.13	< 0.001
Total time* (hours)	0.52 ± 0.98	0.82 ± 0.56	< 0.001

p value <0.05 statistically significant

: Mann-Whitney U test used to compare mean between groups

Total time* = Time for spending in clinic (start at vital sign measurement and stop after finish at the appointment counter)

CHAPTER V
DISCUSSION

Warfarin is an effective medicine for prevention and treatment of thromboembolic diseases, the important problem in public health of foreign countries, even in Thailand (121-123) . Amongst many strategies implemented in the healthcare system for anticoagulated patient management, the warfarin clinic is one of the effective models. The warfarin clinic setting is a multidisciplinary care team model which has been proved in many studies for its advantage (82, 124-125). Nowadays, the evolution of patient care system of warfarin clinic has not involved only healthcare providers, but it has also included a tool such as point of care testing (POCT), which can minimize elapsed time (126). In foreign countries, the patients in warfarin clinic were trained to use POCT devices by themselves for monitoring INR values. This model or patient self-testing model has been shown its effectiveness in cost and clinical outcome; moreover it may be useful in patients inconvenient travelling to a hospital (127-129). By the way, clinical studies in Thailand related to warfarin clinic with using point-of-care testing device had not been existed.

At the Chest Disease Institute, there was settled warfarin clinic managed by multidisciplinary team with pharmacists at the core of such service. The clinic was initially started in July of 2007 with only a small group of 25 patients. The POCT has been adopted into the pilot project also. The greater amount of clinical evidence in anticoagulation clinic study with POCT device was developed in this study, and planned to be a substantiated study in benefits of multidisciplinary team managed anticoagulation clinic with POCT device. In healthcare team, important role of pharmacist was to educate the patients, screen drug therapy problems, and find out the suitable solution for individual patients.

At the baseline, the characteristics of patients were approximately 51 year-old, equally both sexes, and aortic valve replacement was the most common indication in both groups. More than half of patients in both groups had experienced of taking

warfarin less than 2 years. For target INR, numbers of patients was almost equal in both groups of low (INR 1.5-2.5) and high (INR 2-3) target INR. Social background of patients in both groups was similar. Most of patients had primary school level and being housekeepers caused by need less activities, thus some of them had no income. Universal coverage scheme was the most of patients' healthcare medical payment. Majority of patients in both groups had two underlying diseases, which were hypertension and anemia.

The study design was randomized controlled for lessening the bias of patient selection. By the way, the intra-variation of patients may be a flaw of the study. However the populations were similar in age, gender, indication, timing of warfarin therapy, target INR, mean of INR at screening visit (V0), number of underlying disease in each patient, and complications related to major bleeding or thromboembolism at baseline. The difference was shown in percentage of INR in target at baseline, even randomized method had been performed. As the results, these patients were supposed to resemble in characteristics in both control and intervention group at baseline except the percentage of INR in target. The randomization method of this study can be another crucial factor producing selection bias. Because the investigator and warfarin clinic team had known that the patients, who consented to participate in the study with odd sequence, was going to participate in the control group and the patients, who decided to participate with even sequence, was going to join in the intervention group. The sequence organization could possibly arranged the patients who had uncontrolled INR values to the intervention group.

The study had to be terminated early before the targeted sample size could be achieved. Nevertheless, all of data was accumulated and analyzed for the results. With the lack of satisfaction evaluation, we could not find the solution in this topic. Even though the study was early terminated, all information was investigated in two methods, during study period prior to termination and subgroup analysis of patients participating in the study at least three visits.

I. Anticoagulation control

After the study termination, total follow up days, days in therapeutic range and percentage of INR in target was not significantly different between control and intervention group, nevertheless mean INR value of control group was less than intervention group in statistically significant difference. Consequently, rate of over-anticoagulation in intervention group was slightly more than in control group and rate of under-anticoagulation of control group slightly more than in intervention group. These results had shown the same trend at the screening visit, it might be caused by short time of follow up period. After study termination, percent of time in therapeutic range was not statistically significant different between two groups, but it trended towards better for more visits in the intervention group. As the results, the percent of time in therapeutic range of intervention group was elevated from 38.6% to 45.6% and it revealed the opposite trend in control group after participating in warfarin clinic (61.5% to 54.3%), however these results were not different in comparison between patients in control group and intervention group.

For subgroup analysis, percent of time in therapeutic range was almost as same as prior analysis. It showed significantly more in control group than in intervention group (30.4% in intervention group and 68.0% in control group; $p = 0.009$), while the result in study period was not different in statistical significance (45.32 % in intervention group and 53.92% in control group; $p = 0.497$). Even though this analysis selected only patients passed through at least three visits, the result in anticoagulation control was still the same as previous analysis.

After the study termination, the percent of time in therapeutic range was calculated to assess percent INR in target of all intention-to-treat populations. These data did not showed statistical difference of percent INR in target between two groups. However, the trend of alteration in numbers of INR in target was observed in scattered plot of INR value. Even though the percent INR in target of patients in control group had trended toward to subside for more visits, on the other hand patients in intervention group had percent time in therapeutic range elevated for more visits. Furthermore mean percent time in therapeutic range after intervention was slightly more than another one at screening visit. It revealed better trend of clinical outcome in

the intervention group. These results supposed to be better trend in outcome improvement from multidisciplinary team with new device.

In Thailand, many studies in clinical outcome of warfarin clinic had been implemented in hospitals and the largest one was conducted by Sapoo at the Maharat Nakornratchasima Hospital (109). It was designed to be prospective study comparing between usual care group and physicians-pharmacists collaborative care group. More than four-hundred patients were conveniently sampling into two groups. Mean age of patients was 47 years old and most of them took warfarin for more than 2 years, which was different from our study. All of 1,547 INR values were measured and analyzed. Percentage of INR in target was seen more value in patients enrolled in warfarin clinic than the usual care group (45.3% vs 34.1%; $p < 0.001$). The improvement of anticoagulation control in intervention group was shown 33% from baseline. However, the important limitation of this study is the non-systematic randomization method. For our study, we designed as prospective comparative study between control and intervention group, it was designed similar as this study. But our study was randomized controlled trial. Unfortunately, our study could not be processed until the numbers of participated patients had reached the target, and the study could not result the statistical significant difference between two groups. Percent INR in target of our study was shown 53.09% in control group and 43.01% in intervention group, which were similar as subgroup analysis and had not been significant different between two group ($p = 0.310$). Nevertheless percent INR in target at baseline had significantly differed between two groups (60.52 % vs 35.71% in the control and intervention group, respectively; $p = 0.027$), this can be another cause of insignificant difference in anticoagulation control.

Another study conducted by Liabthawee was designed as a quasi-experiment, pre- and post-intervention (110). This is another large population study in the Department of Surgery, Siriraj Hospital. There were 284 patients with mechanical heart valve replacement, which was as same as indication of most patients in our study. When the study had approximately ended at 11.6 months of both follow-up periods, the proportion of patients having INR in therapeutic range was statistical significant superior in the post-intervention period (51.8% vs 46.7% in the post- and pre-intervention periods, respectively: $p = 0.016$). Nevertheless a lack of control

group was a limitation of this study. This study was designed in the different way of our study, but the result of percent INR in target in intervention group of our study trended to be the same. However, the number of populations in our study was too less to achieve a statistical significance and selection bias could occur during randomization.

Moreover, Khamkongkhun and Tongsrisomboon determined therapeutic outcome compared between control and pharmacist intervention group with inpatients. Khamkongkhun conducted a quasi-experimental study with 114 patients at the Cardiovascular and Thoracic surgical ward, Siriraj hospital (130). This study purposed to determine the impact of warfarin-monitoring service by clinical pharmacists. The percent of patients with therapeutic INR (2.0 to 3.0) in the intervention group at discharge and at 30 days after initiation of warfarin therapy was significantly higher than in the control group (77.19% vs 59.65%, $p = 0.044$ and 57.89% vs 31.58%, $p = 0.005$, respectively). Most common of drug therapy problem was inappropriate dosage regimen and medication error was an omission. The physicians accepted pharmacist's intervention for problem resolutions more than 90%.

Another study was a quasi-experimental study at Ramathibodi hospital comparing the proportions of patient with therapeutic INR (2.0-3.0) at discharge and at first outpatient visit between historical control and pharmacist service groups conducted by Tongsrisomboon (131). After data of 160 patients were analysed, percent INR in the target was found significantly higher in the intervention group (62.5% vs 30.0%, $p < 0.001$) compared to the control group after follow-up. Most common problems were major drug interactions and inappropriate dosage which were solved by physicians with more than 80% recommendation from pharmacist. Both of these studies were implemented for in-patients, hence the achievement of anticoagulation control might not be interrupted by non-compliance of patients. Percent INR in target of intervention group in these studies was high (60-70%). Even our study could not achieve this figure (45.60% in intervention group), but the trend of intervention group seemed to elevated INR in target. If the intervention period could be postponed, percent INR in target might achieve more than this result.

Previous studies showed superior clinical outcome of warfarin clinic managed by pharmacist. But no one had ever conducted randomized controlled trial determining anticoagulation clinic with point-of-care devices in Thailand, while some studies involving warfarin clinic in foreign countries included self-testing or self-management. In foreign countries, the evolution of warfarin clinic has developed for many years. Nowadays anticoagulated patients in some countries can monitor and test INR value by themselves and adjust dose of warfarin as recommendation by training program or healthcare providers. This was called self-management.

According to previous studies in foreign countries, warfarin clinic implemented with point-of-care devices could improve clinical outcome and patient perceptions, compared with warfarin clinic without those devices. Thompson AM et al investigated percent INR in target range, rate of emergency department visits and hospitalization related to major/ minor bleed or thromboembolism, and patient satisfaction survey for using point-of-care devices (127). The study was designed to be 6 months pre- and post-period of point-of-care device implementation in warfarin clinic. All of 145 patients participated in the study were evaluated their data which showed most of them was female (65%) and average age was 65 year-old. The percentage of time within therapeutic range in period of point-of-care device implementation was not statistical different from pre-implementation period of point-of-care device (47.9% vs 45.7% in pre- and post-device implementation periods, respectively; $p = 0.887$). This study could not prove the better outcome of POCT device in warfarin clinic, but period of device implementation was only six months which might be another factor influencing clinical outcome. As our study, the sample size was too small and period of treatment might be too short caused by early termination. Nonetheless, trend of INR in target seemed to be better for more visits in multidisciplinary-managed warfarin clinic with POCT device.

Even some studies did not show superior benefit of point-of-care device implementation resulting in INR within therapeutic range, a systematic review and meta-analysis of self-management compared with standard monitoring analyzed by Heneghan C et al, discovered that all of 11 studies showed improvement of INR within target range in self-monitoring group, and only six studies were significant (132). As another systematic review and meta-analysis comparing between self-

management of oral anticoagulant therapy and conventional management, evaluated by Christensen TD et al, revealed that self-management increased time within therapeutic INR in statistical significant level for 8 low quality trials, but two high quality trials was not statistical different (133). However, both meta-analysis studies included usual care system, patient education by nurse-led system, and pharmacist-managed care system and their patient selection for capability of self-management with a presumed high level of compliance, thereby the result of these meta-analysis studies should be considered with cautions.

II. Complications

2.1 Thromboembolic complications

After study termination, the researcher found that the rate of under- and over-anticoagulation were not statistically different. The rate of under-anticoagulation (INR less than 1.5) was found comparable between patients in control group and intervention group. And neither transient ischemic attack (TIA) nor stroke was found in our study. The study design might not be able to discard the selection bias of populations, and amount of populations had not enough for statistical significant data resulting from early termination of the study. Although thromboembolic event had not been found in our study, the result need to be cautiously interpreted with low population numbers. The incomplete data of complications in control group could possibly occurred, thus rate of thromboembolic event in control group might be under detectable caused by the lack of closed investigation. The bias of populations could occur in a small population size, because inadequate sample size could continue to influence the quality and accuracy of the study (134). INR in target at baseline showed the patients in control group superior over intervention group which could be another reason of insignificant difference of thromboembolic complication between two groups. This might be caused by selection bias which could be produced during randomization method with unblinded investigator and warfarin clinic team.

Prior studies were conducted in patients at Siriraj hospital by Liabthawee and Khamkonkhun. Two studies were designed in different kind of study and patient populations. Liabthawee studied pre- and post-intervention period of pharmacist-managed anticoagulation clinic (110). This study design was different from our study which was randomized controlled trial, but the thromboembolic complication resulted in the same trend. Lower rate of thromboembolic events was found in the post-intervention period without statistical significant difference (5.5 and 2.9 events/100-patient year in pre- and post- intervention periods, respectively; $p = 0.20$). Another study with different design was conducted by Khamkongkhun to determine impact of pharmacist in warfarin-monitoring service at the Cardiovascular and Thoracic surgical ward (130). This prospective study compared patient's outcome between control and intervention groups with 57 patients in each group. Thromboembolic events were found slightly more in the intervention group than in the control group without statistical significant difference (0.006 events/ 100-pateint day and none, respectively; $p = 1.000$).

Thromboembolic event had obviously been found insignificantly different between control and intervention group in these comparative studies. Our study showed no event of thromboembolic complication while Liabthawee study had found an insignificant lower rate in post-intervention period compared to pre-intervention period. The lower populations and short time of follow up could be the factors of our study flaws. Khamkongkhun study found thromboembolic complication only in intervention group, while no thromboembolic event had existed in control group. It might be caused by the characteristic type of inpatient care. Inpatients were carefully treated by physicians, hence thromboembolic complication should be rarely existed.

In foreign countries, the evolution of anticoagulation clinic progressed to be self-management, which trained patients to test INR value by themselves with point-of-care devices. Kortke H et al study compared clinical outcome between self-management patients and conventional management (135). This large randomized trial included data of 295 patients in conventional group and 305 patients in self-management group. Drop out rate significantly showed in control group with 45 patients (4.7%), meanwhile twenty-nine (2.9%) patients in self-management group asked to withdraw from the study ($p = 0.042$). INR within stipulated range was found

more in self-management group than in conventional group ($p \leq 0.001$). Furthermore, thromboembolic events in self-management group was found less than conventional group without statistical significant difference (1.2% and 2.1%, respectively). Even thromboembolic complication was not significant different, but this study can express benefit of capillary coagulometer and self-management. Our study design did not implement self-management for patients in intervention group, but outcome result trended to be as same as this study. This would be resulting from patient education strategy and intensive care for intervention group by healthcare providers. And the patient education will avoid non-compliance of patients and encourage the appropriate behavior resulting in better therapeutic outcome and safety from complications.

With different study design, Gadisseur et al conducted randomized study in receiving long term oral anticoagulant patients divided into 4 groups: a weekly INR self-testing patients with dosing performed by anticoagulation clinic physician, a weekly self-management patients, a group of patients educated by healthcare-providers, and a routine care group (136). The result did not reveal significant different in INR within therapeutic range between groups, which expressed more than 58% with lack of thromboembolic complication. This study protocol was determined to test INR value weekly for two groups of patients, while INR testing rate of another two groups depended on individualized patients. If we consider for number of INR testing and weeks of follow up, we will find that the least in rate of INR testing, which was shown in a group of patients educated by healthcare-providers and a routine group, was 0.39 INR testing per week or in approximately one INR testing for three weeks. On the other hand, rate of INR testing in our study was in approximately one testing for six weeks. Frequent INR testing allow physicians to aware complications resulting from warfarin therapy. This might be the reason why thromboembolic complication had not been found and a rate of INR in therapeutic range was high in this study (78-79).

Mene´ndez-Ja´ndula et al conducted a randomized trial to compare the clinical outome of anticoagulation management in self-managed patients and conventional therapy (137). For intention-to-treat analysis, data of 369 patients in conventional group and 368 patients in self-management group was analyzed their clinical outcome. Patients with self-management got more INR in target range than

patients in conventional group (58.6% and 55.6% , respectively) and thromboembolic complications were found more in conventional group than in self-management group (5.4% and 1.1% , respectively). This result may be caused by the patient education program, which enhanced superior adherence in resulting from self-awareness of health status when patients need to be responsible for warfarin dosage adjustment themselves. Our study design was similar as Mene´ndez-Ja´ndula study. Eventhough our study could not include large numbers of patients and therapeutic outcome did not show statistically sinificant difference, but trend of clinical outcome seemed to be better for more visits in warfarin clinic with POCT device. The short period of study could be one of reasons why thromboembolic complication could not been found in our study. Furthermore, the patients participating in our study had to see the physician every 6 weeks, which could be another factor effecting clinical outcome. Thus the patients who can be tested INR at least 6-week interval between INR measurements, would be safe from thromboembolic and major bleeding complications (66). However, frequent appointment was hardly to exist in developing countries due to shortage of healthcare providers. Moreover the patients living in distant area would undergo trouble with high travel cost and time.

2.2 Hemorrhagic complications

Major bleeding events were found in two patients participating in the control group and none of hemorrhagic complication was found in intervention group, even the over-anticoagulation INR values (INR value more than 5) were existed slightly more in intervention group than in control group (3 values (3.9%) and none, respectively; $p = 0.244$). One of patients in the control group was found gastrointestinal hemorrhage with normal laboratory INR. Another one had died in the other hospital caused by intracraneal hemorrhage with INR in target during the study period. For subgroup analysis, major bleeding had been found in the same rate of events as prior analysis. None of patients carried out-target laboratory INR had experienced with major hemorrhagic events. The patient education might be lessen the major bleeding events, because the patient would pay attention in avoidance of hemorrhagic risk factors.

In according to prior studies, a trend of hemorrhagic complications was decreased after patient participation in anticoagulation clinic. Different style of studies at Siriraj hospital conducted by Liabthawee and Khamkongkhun expressed in slightly different results (110, 130). Liabthawee study demonstrated slightly smaller hemorrhagic complications in the post-intervention period than in pre-intervention period (14.9 and 15.6 events/ 100 patient-year, respectively; $p = 0.81$), while it had not been found in Khamkongkhun study. These results explained superior efficiency of multidisciplinary approach. Although inpatients had probably risked to confront the complications, healthcare providers could avoid dilemma by collaboration of healthcare team. Hemorrhagic event in our study had existed in the similar trend of these studies.

Another enormous poppulation prospective study comparing between usual care and pharmacist-managed anticoagulation clinic was conducted by Sapoo (109). Total of 218 patient in intervention group and 216 patients in control group with 50 year-old in mean of age, showed greater percent INR in target in intervention group. Even though high variability of INR value was shown more in control group than in intervention group (84.3% and 72.9%, respectively; $p = 0.004$), there was not significant difference in rate of major bleeding (4.5 events/ 100 patient-year in the intervention group and 4.6 events/ 100 patient-year in the control group). However no studies in Thailand was designed to determine the impact of pharmacist-managed anticoagulation clinic with capillary coagulometer.

One randomized study in Spain conducted by Mene´ndez-Ja´ndula et al which is similar design as our study, except the clinical staffs in this study were trained nurses and it compared clinical outcome of patients between self-management group and conventional group, meanwhile our study was collaborated with physicians, pharmacists, nurse, and occasionally nutritionists and we compared the outcome of patients between intervention and control group (137). This study included data of all 368 patients in self-management group and 369 patients in conventional management group with follow-up period in approximately 11.8 months. The self-management group was proved to be better in percent INR in target. Severe hemorrhagic outcome trended to be less for patient participated in self-management group than in conventional group (1.1% and 1.9%, respectively). However a responsibility of

patients for making decision by themseleves resulting in improvement on self-awareness of health status would be a reason of better clinical outcome which never existed in our study, because patients in our study had never adjust dosage regimen by themselves. For minimization of complications, patient education enhancement was a key process in our study for adherence resulting to produce better clinical outcome and complication risk minimization.

However, two patients had died during the study period in the other hospital. Both of them were female and had INR values in target during the study period. One patient participated in the control group with INR 2.9 at the last visit without beeding and thromboembolic complications, but it was in target range (target INR 2-3). She had participated in the study for three visits and died after one month ago in the other hospital due to intracranial hemorrhage. The brain hemorrhage could occur in patients taking warfarin and sometimes, it could suddenly emerge by triggers with lack of sign as this patient. The patient education, in awareness of sign and symptom related to brain hemorrhage, may prevent this occurrence.

Another patient had participated in the intervention group. She visited in warfarin clinic for two times without sign or symptoms of hemorrhagic and thromboembolic complications. But she had to be replaced aortic valve for two time and recently treated with infective endicarditis. After she had participated in the study approximately six weeks, she died in the other hospital with respiratory failure from cause other than complication of warfarin. Both patients were in the middle age and had no sign or symptom related to hemorrhagic and thromboembolic complications before death. However, they might endanger by other life-threatening triggers or their own disease state.

III. Cost-analysis

Determination of financial outcome, the pharmacist-managed anticogulation clinic has been evaluated in cost-effectiveness for many studies. In our study, cost analysis evaluated in perspective of total service cost, which was partially calculated based on healthcare provider cost related with elapsed time spending in warfarin clinic and conventional clinic. Our study was terminated by warfarin clinic

team resolution for best clinical outcome of every patients, consequently 36 patients were analysed their total service cost (20 patients of control group and 16 patients of intervention group). The result revealed more total service cost in intervention group than in control group (276.49 and 112.40 baths, respectively; $p < 0.001$). These outcome reflected to more budget of treatment for anticoagulated patients in warfarin clinic with point-of-care testing than in conventional clinic, therefore total service cost is an important factor of warfarin clinic establishment for developing country in adminitrative perspective. But this total cost was calculated for only one visit in each patient and it was not included cost of any complication. Thus cost-effectiveness of warfarin clinic with POCT device could not apparently prove in this study.

Furthermore, this study had been scheduled in the specialized period of time in Chest disease institute, because study design was different from routine clinic especially in frequency of follow up, which was longer than this study. In the routine clinic, the patients had an appointment for three months or sometimes five months with crowded patients in the clinic, and sometimes there was more than 50 patients in the clinic. While numbers of patients visiting in control or intervention group were not more than twenty patients for one visit, in the reason of controlled trial. The waiting time in every periods in the study could not reflect to real time in routine clinic of hospital with numerous patients, but it can reflect to some specialized clinic. Time of INR testing was apparently fast in the study, because we were not interrupted by other clinics in the Chest disesase institute. The interpretation of this result should be done with awareness.

However, if we had focused on time spent in doctor or pharmacist room, we could realise that patients in intervention group spent time longer than patients in control group. This presumed that patients in intervention group could be more attentively treated and meticulously cared by healthcare providers. Moreover, elapsed time for INR testing was faster in intervention group than in control group (2.25 and 14.80 minutes, respectively; $p < 0.001$), it was resulted from different types of coagulometer in each group.

Prior studies of cost-analysis in pharmacist-managed anticoagulation clinic had proved in greater benefit of economic outcome (85, 138). A study of concern in anticogulation control, patient outcomes, and expenditures of hospitalization and

emergency department visits comparing usual medical care with anticoagulation clinic, included in-patient and out-patient with a total of 318 newly anticoagulated patients was conducted by Chiquette et al (138). Better INR control, lower rate of major to fatal bleeding and thromboembolic events had found greater outcomes in anticogulation clinic than in conventional service. Moreover, financial outcome evaluation based on cost of hospitalization and emergency department visit, showed saving 162,058 dollars annually for every 100 patients enrolled in anticogulation clinic because of fewer hospitalizations and emergency department visits. Major difference between this study and ours was the study design which non-randomized and cost evaluation perspective. Cost reduction of complication avoidance was not estimated in our study, which should be an evidence obviously emerged to prove in cost-effectiveness of pharmacist-managed anticoagulation clinic.

Another study in Hong Kong had a similar style of our study, except the pharmacist role in anticoagulation clinic which allowed a pharmacist to manage patients as the physician in accordance with the management protocol. Chan FW et al conducted a two-year randomized clinical trial for comparison the therapeutic outcome between a clinical pharmacist-managed anticoagulation service and a physician-managed service, recruited with 68 patients (85). To justify the clinical outcome, this study measured patient time spent within the target INR range and found superior result of pharmacist-managed anticoagulation service over physician- managed service (64% and 59%, respectively; $p < 0.001$). But major bleeding and thromboembolic complication was not significant difference. A cost per patient per month represented total direct medical cost to this study and be estimated from the perspective of a public health organization in Hong Kong. Mean cost of pharmacist-managed group was lower than physician-managed group (76 ± 95 and 98 ± 158 US dollars, respectively; $p<0.01$). Patients in pharmacist-managed group were provided intensive education and cared by trained clinical pharmacist as the primary care provider and be adjusted warfarin dosage in accordance with dosage adjustment protocol and occasionally physician consultation, moreover they were tested INR value by point-of-care device. Meanwhile, the patients in physician-managed group were drawn venous blood for hospital laboratory INR testing, be monitored sign and symptoms by hematologists, and be adjusted warfarin dosage using the same dosage adjustment protocol as the

pharmacist-managed group. Eventhough a part of cost per patient per month in pharmacist-managed group was calculated including labour cost of clinical pharmacist of both the clinical management and phone call follow-ups with cost of physician time for occasional consultations, but these cost was not computed by actual time spent in clinic visit and estimated pharmacist cost was approximately a half of the average salary of the two haematologists. These limitations could result in miscalculation of total medical cost, which did not exist in our study, because we calculated healthcare cost based on real salary of healthcare providers and actual time spent in clinic visit. This different study process may be the reason of different result from our study. Furthermore, a lack of concern in medical expenditure for hospitalization and hospital emergency visit was a limitation in our study, hence total service cost of our study in pharmacist-managed group charged more than in conventional group. Nevertheless, our study had limited populations as the same flaw in this study. The numerous populations in randomized controlled trial studied clinical outcome, economic outcome and humanistic outcome in pharmacist-managed anticogualtion clinic compared with conventional clinic could solved these flaws.

IV. Patient satisfaction

Because of the early termination of the study, patient satisfaction was not evaluated. Even the patient satisfaction was not assessed by questionnaires in the study, some patients in control group asked the healthcare providers to let them participating in the intervention group, because they had talked with the patients participating in the intervention group and they wanted to be cared by multidisciplinary team. This can refer to satsfaction of patients over multidisciplinary approach in warfarin clinic without evidence. And it was one of reasons why the study had to be early terminated. Moreover, faster time with convenience of INR testing and more effective in clinical outcome could influence to promote patient satisfaction in pharmacist-managed service with point-of-care device. Long time spent with physicians or pharmacists was another factor encouraged satisfaction and patient adherence resulting in better clinical outcome.

As previous studies, Wilson et al and Thompson et al conducted studies comparing between anticogulation clinic and conventional service in different designs. Wilson SJ et al evaluated quality of oral anticoagulation management by comparison between anticoagulation clinic with family physician- managed clinic (125). This randomized study enrolled 221 patients which 112 patients allocated in anticoagulation clinic and 109 patients participated in conventional service. Therapeutic INR values of patients managed by anticoagulation clinic were found more than in conventional care with insignificant difference of major bleeding and thromboembolic events between two groups. Patient satisfaction assessed with questionaires were filled up by 170 patients (77%) and expressed great satisfaction over anticoagulation clinic (96%), meanwhile only 84% of patients in family physician group satisfied their service. Obviously difference in satisfaction report was seen in topic of time spent with staff (93% in anticoagulation clinic and 76% in conventional service). Others superior topics of satisfaction over anticoagulation clinic were more satisfied with teaching, helpfulness of staff, availability of staff in emergency compared with conventional service.

In our study, patient satisfaction might suppose to be more over pharmacist-managed anticoagulation clinic, because patients spent time in pharmacist-managed anticoagulation clinic longer than in control group and they were educated and be encouraged to maximize adherence. Consequently, the obstracles between physicians and patients could be eliminated by communication collaborated with multidisciplinary team in anticoagulation clinic, eventhough these process need to spend more time. However study of Wilson SJ et al compared only two groups of patients with the same venous puncture INR testing, while our study had compared two groups with different type of INR testing. Therefore, we hoped that our patients in intervention group would satisfy with shortening elapsed time of fingerprick INR testing.

Pre- and post-intervention study analyzed humanistic and clinical outcomes of pharmacist-managed anticoagulation clinic using point-of-care testing device versus venipuncture within warfarin clinic by Thompson AM et al (127). Even though percentage of INR in target range, emergency department visits and hospitalization due to major/ minor hemorrhage or thromboembolism, were not statistical different,

patient satisfaction was detected 95% of patients filling satisfaction survey. The shortening of elapsed time for INR testing was the most impressive reason of point-of-care device. However this study design aimed to compare between pharmacist-managed warfarin clinic with cappillary versus venous puncture INR determination, which was different from our study.

Chan FW et al run a prospective randomized trial comparing clinical pharmacist-managed anticoagulation service with physician-managed service in Hong Kong (85). Time in therapeutic INR range of patients in the pharmacist-managed group was significant greater than physician-managed group, even no significant difference in major bleeding and thromboembolic events existed. Furthermore, patient satisfaction was evaluated by patient questionnaire (PSQ)-18. Time spent within clinic, accessibility, interpersonal manner, communication, and technical quality were significant higher in pharmacist-managed group. However general satisfaction and financial aspect were not significant difference between two groups. As these results, patients in our study might be satisfied in pharmacist-managed service, because time spent for INR testing in anticoagulation clinic was faster than in conventional clinic (2.25 and 14.8 minutes, respectively; $p < 0.001$) and patients spent longer time with physician and pharmacist in anticoagulation clinic.

IV. Limitations of the study

There were several limitations to our study. Major limitation in our study was incomplete study protocol, due to early termination. Patient satisfaction could not be evaluated and humanistic outcome could not prove to be an evidence of effectiveness in pharmacist-managed anticoagulation clinic. The randomization method in our study could be another flaw. Our team and the investigator knew that the odd sequence of patients related to control group participation, while the even sequence of patients indicated intervention group participation. This unblinded method could result in selection bias. Moreover incapacity to reach aimed numbers of study populations, our study could not empower clinical outcome as prior studies. Sample size can influence the detection of significant differences, relationships, or interactions, therefore small population might be a majority flaw (134).

The significant difference of INR in target at screening visit was another flaw. Percent of therapeutic INR value was not obviously superior in anticoagulation clinic and thromboembolic and major hemorrhagic events were not significantly minimized by intervention of multidisciplinary team. Even randomization was implemented in this study, but the bias of percent INR in target possibly existed. Owing to significant difference of therapeutic INR at the screening visit between patients in anticoagulation clinic and control group, the difference of therapeutic INR percentage between two groups may occur even if numbers of anticoagulation clinic visits will be advanced.

Inconsistence of therapeutic regimen could occur amongst individual physicians, since the lack of therapeutic management protocol. Decision in treatment including warfarin dosage adjustment depended on individual patients and physician's experience. However the precisely treatment regimen of warfarin was hard to find and the resolutions were frequently ambiguous, due to complexity of pharmacokinetic and pharmacodynamic properties in individualized patients.

The incomplete chart review was possibly unintended occurrence in control group, therefore a lack of patient interview in conventional clinic could be a flaw of our study leading to miss some incidences of complications. Physician's learning effect was another flaw in this study, because physicians in our study participated in both intervention and control group. Clinical outcome of patients in control group was partially resulted from learning effect of physicians.

For cost analysis, it partially based on period of time. The study was scheduled in the specialized time which could not be interrupted by other clinics in the Chest disease institute. And number of patients visiting in the clinic was less than routine usual care. The period of time in the study was similar specialized clinic, but it can not reflect to usual care in routine. Furthermore, the evaluation of cost analysis purposed only service cost which included healthcare cost in real time without cost of minimized complication. The cost of human resources depended on individuals, hence economic outcome in our study could be considered with cautions. These limitations could be reasons of insignificant superior benefits over clinical and economic outcomes.

V. Recommendation

The pharmacist-managed anticoagulation clinic and point-of-care device had been proved for benefits in clinical, economic, and humanistic outcome in foreign countries, but no scientific evidence was shown in Thai patients. Our study had failed to prove in these benefits due to early termination. The randomization method could be a major reason of different in INR in target at the screening visit or even in the insignificant different between control and intervention group. The further study should evaluate patient perceptions in pharmacist-managed anticoagulation clinic with point-of-care device for humanistic outcome detection with proper randomization method. The block of four or computerized sampling technique could be helpful in this solution. The patients in different group of study should be cared by different physicians for lessening probability of learning bias. Many studies had proved superior clinical efficacy of patients treated in anticoagulation clinic, even in clinic with point-of-care. Cost-effectiveness is another factor which had not been evidenced in randomized controlled trial study of pharmacist-managed anticoagulation clinic with fingerprick coagulometer, which could be helpful in convenience and availability of INR testing.

CHAPTER VI
CONCLUSIONS

Oral anticoagulant was an effective drug for treatment and prevention of thromboembolic diseases, nonetheless its complicated pharmacokinetic and pharmacodynamic attribute resulting in narrow therapeutic property caused several adverse effects. Maximization of patient intensive education resulting in patient adherence was an important factor for advanced in greater therapeutic outcome. Specialized anticoagulation clinic service collaborated with multidisciplinary team had been proved in many studies for its efficiency. The evolution of anticoagulation clinic model has developed for better therapeutic outcome achievement. As previous studies in foreign countries, Anticoagulation clinic serviced with healthcare providers could increase effectiveness and patient perception by point-of-care device implementation. The point-of-care testing device or finger prick coagulometer benefits for lessening elapsed time for INR testing with less pain, hence it may proper for patients living in urban area or disability.

Our study purposed to compare therapeutic, economic and humanistic outcomes between anticoagulation clinic service using point-of-care device collaborated with multidisciplinary team and conventional service. Unfortunately, the study was to be early terminated with warfarin clinic team agreement before the population size had been achieved. Results revealed no significant different of clinical and economic outcome. For humanistic outcome, it could not be assessed because study termination agreement had been submitted before the end of the study. However, all results had been summarized with intention-to-treat analysis.

Result of anticoagulation control did not show statistical statistic difference between patients in control and intervention group. Rate of under-and over-anticoagulation was not different in statistical significant, nevertheless they were found more times in intervention group. But anticoagulation control of patients in intervention group trended towards greater outcome in more visits of anticoagulation

clinic, while anticoagulation control in control group showed the opposite direction. Likewise, thromboembolic and major hemorrhagic complications were not different in statistical significant as therapeutic INR result, however only one major bleeding event had been found in control group. Inadequate population size and short-time of follow up possibly caused the insignificant different between two groups.

Unfortunately, questionnaires of patient satisfaction had not been answered in our study owing to early termination. Nonetheless, elapsed time minimization of INR testing and more time to see the healthcare provider would likely result in satisfaction of patients in warfarin clinic with POCT device. For cost analysis, the cost therapy of anticoagulation clinic with POCT device was more than cost of control group. INR testing of intervention group cost more than control group ninety baths per time and time spent in clinic was more in intervention group than in control group. These could be the reasons of more cost in anticoagulation clinic with point-of-care testing.

Overall, anticoagulation clinic did not show statistical significant different from usual care in our study, except cost therapy. Notwithstanding, population size and time of follow up were inadequate to assess accuracy results of anticoagulation control. Longer time of follow up and sufficient population size in randomized controlled study can possibly achieve impact of multidisciplinary approach in warfarin clinic with point-of-care testing. Many studies proved the effectiveness of warfarin clinic, but none of them had proved effectiveness of improvement in warfarin clinic with point-of-care testing with clinical, economic and humanistic outcome. Point-of-care device was useful in warfarin clinic for minimization of time spent in clinic, accessibility of INR testing in clinic which was shortage of laboratory INR testing and satisfy patients by less painful of needle puncture with small amount of bleed. Warfarin clinic with point-of-care testing probably maximize advantage of anticoagulation therapy.

Recommendations for further study

In order to implement a warfarin-monitoring service, recommendations for future research are as follows:

1. To lessen the selection bias during randomization, further studies should use proper random sampling method.
2. To prove the effectiveness of anticoagulation clinic, further studies should be conducted as a prospective randomized control with multi-center setting.
3. For learning bias avoidance, further studies should implement in the clinic with different physicians for control and intervention group.
4. Further studies should evaluate the possible relationship between patients' knowledge of warfarin therapy with anticoagulation control.
5. In addition, further studies should also report drug therapy problems with other medications and medication errors occurring in the period of study.
6. Further study should analyze cost-effectiveness with cost of complication.

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APPENDICES

APPENDIX A

PATIENT' S PROFILE DATA SHEET

Patient Database Form
(Warfarin Clinic)

1. Demographic Information			**HN :**	Code Wc	Initial date :
Name :	Age :	Gender : ☐ F ☐ M	Occupation :	Education Level :	
Address :			Tel No :	Reimbursement☐ No☐ Yes.....	
Valve position:	No. of valve:	Valve type:	Duration of warfarin therapy		
2. Illness					
Past Illness :	**Acute and Current Illness :**		**Operative Status :**		
1.	1.		Operation	Date	Surgeon
2.	2.		1.		
3.	3.		2.		
4.	4.		3.		
Medication History			Economic data	Patient's Income (Bath/ hour)	
				Travel cost of patient (Bath/visit)	
4. Family/Social/Economic History :				การตั้งครรภ์ ☐ การคุมกำเนิด☐	
5. Allergies/Intolerance		6. Social Drug Use :		7. Herbal/Health food Product:	
☐No know drug allergy		☐ Alcohol			
Medication :		☐ Caffeine			
		☐ Tobacco			
Reaction :					
8. Indication of warfarin					
9. Target INR (INR range) :					
10. Diet : ☐ Low salt ☐Low Fat ☐Diabetic ☐ other.....				11. Routine Exericise :	
12. Baseline Warfarin Compliance : ☐ Very good(100%☐ Good (-95%) ☐ Poor(<95%)☐ Very poor (<80%)					

PATIENT' S PROFILE DATA SHEET (cont.)

13. Baseline Physical Assessment / Laboratory D								Height_____cm			
Data											
- Weight (kg)											
- BP											
- Pulse											
BMI											
Electrolyte											
- Na^+											
- K^+											
- Cl^-											
- HCO_3^{2-}											
Hematology											
Hb											
Hct											
plt											
MCV											
Chemistry											
- FBS											
- BUN											
- Cr.											
- AST											
- ALT											
- Total Bil.											
Direct Bil.											
- Alb											
Lipid profile											
T. chol											
LDL											
HDL											
TG											
- TSH											
- T3											
- T4											
- HBsAg											
- HBA1e											

PATIENT' S PROFILE DATA SHEET (cont.)

Patient Monitoring Form

Name :						Age :		Garder : □ F □M		
Date	Dose Taken	INR	Changed Dose	Physician	F/U	Medication	Regimen	Start Date	Stop Date	Note

PATIENT' S PROFILE DATA SHEET (cont.)

ชื่อ-นามสกุล..... อายุ.....ปี HN..... Target INR.....

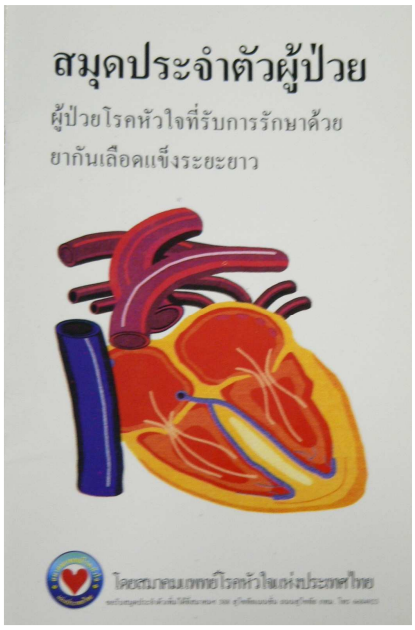
Pharmacist's Care Plan (warfarin Clinic)

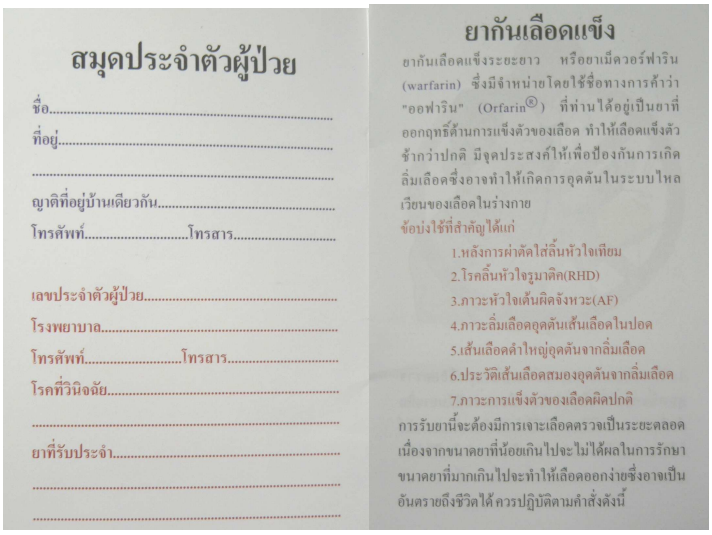
Date	DTPs	Detail	Intervention	Future Plan	ผลที่เกิดขึ้น

Drug therapy problems (DTPs):
1. Unnecessary drug therapy 2. Needs additional drug therapy 3. Ineffective drug 4. Dosage too low 5. Adverse drug reactions 6. Dosage too high 7. Noncompl
8.Major bleeding (Fatal bleeding and/or Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraartic
pericardial, or intramuscular with compartment syndrome, and/or Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to
transfusion of two or more units of whole blood or red cells. 9. Thromboembolic events (CVA, TIA, Valve thrombosis, Peripheral or systemic emboli)
10. Miscellaneous

APPENDIX B

WARFARIN BOOKLET





สมุดประจำตัวผู้ป่วย

ชื่อ.....

ที่อยู่.....

.....

ญาติที่อยู่บ้านเดียวกัน.....

โทรศัพท์.....โทรสาร.....

เลขประจำตัวผู้ป่วย.....

โรงพยาบาล.....

โทรศัพท์.....โทรสาร.....

โรคที่วินิจฉัย.....

.....

ยาที่รับประจำ.....

.....

.....

ยากันเลือดแข็ง

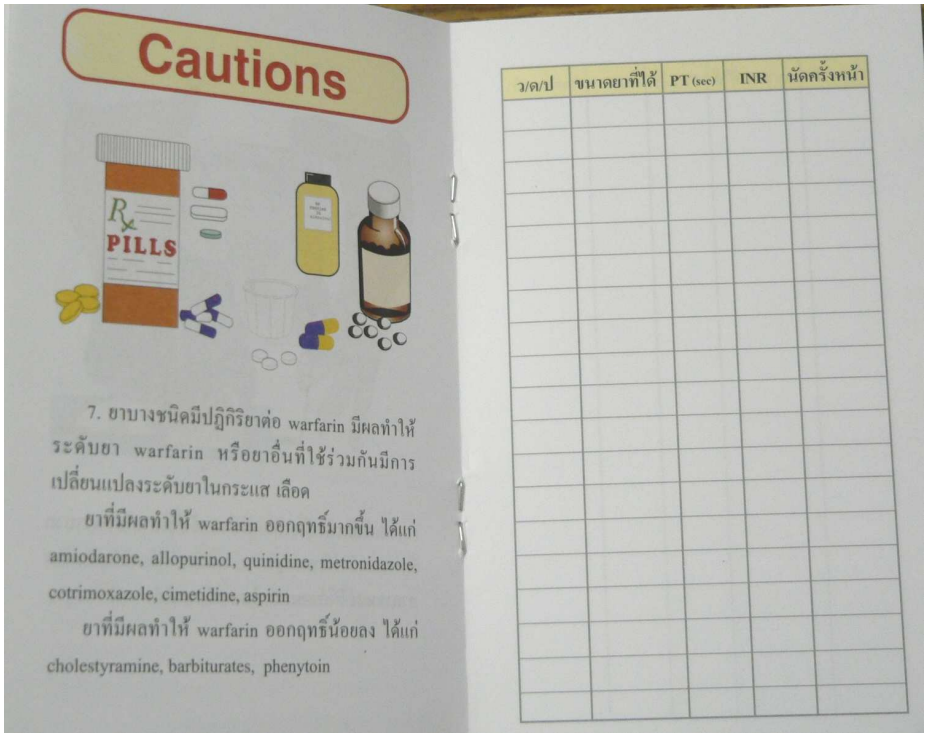
ยากันเลือดแข็งระยะยาว หรือยาเม็ดวอร์ฟาริน (warfarin) ซึ่งมีจำหน่ายโดยใช้ชื่อทางการค้าว่า "ออฟาริน" (Orfarin®) ที่ท่านได้อยู่เป็นยาที่ออกฤทธิ์ต้านการแข็งตัวของเลือด ทำให้เลือดแข็งตัวช้ากว่าปกติ มีจุดประสงค์ให้เพื่อป้องกันการเกิดลิ่มเลือดซึ่งอาจทำให้เกิดการอุดตันในระบบไหลเวียนของเลือดในร่างกาย

ข้อบ่งใช้ที่สำคัญได้แก่

1.หลังการผ่าตัดใส่ลิ้นหัวใจเทียม
2.โรคลิ้นหัวใจรูมาติก(RHD)
3.ภาวะหัวใจเต้นผิดจังหวะ(AF)
4.ภาวะลิ่มเลือดอุดตันเส้นเลือดในปอด
5.เส้นเลือดดำใหญ่อุดตันจากลิ่มเลือด
6.ประวัติเส้นเลือดสมองอุดตันจากลิ่มเลือด
7.ภาวะการแข็งตัวของเลือดผิดปกติ

การรับยานี้จะต้องมีการเจาะเลือดตรวจเป็นระยะตลอด เนื่องจากขนาดยาที่น้อยเกินไปจะไม่ได้ผลในการรักษา ขนาดยาที่มากเกินไปจะทำให้เลือดออกง่ายซึ่งอาจเป็นอันตรายถึงชีวิตได้ ควรปฏิบัติตามคำสั่งดังนี้

WARFARIN BOOKLET (cont.)



APPENDIX C

แบบสอบถามความพึงพอใจของผู้ป่วย

(Patient Satisfaction Evaluation)

โปรดให้ระดับความพึงพอใจกับบริการที่ท่านได้รับขณะร่วมการวิจัยนี้ และเปรียบเทียบกับระบบการให้บริการแบบเดิมก่อนเข้าร่วมการวิจัยนี้ โดยให้คะแนนในคำถามแต่ละข้อดังต่อไปนี้

5 พอใจมากที่สุด 4 พอใจ 3 ปานกลาง 2 แย่กว่าระบบเดิม 1 แย่กว่าระบบเดิมมาก

1. ระยะเวลาในการรอพบแพทย์	5	4	3	2	1
2. ความถี่ในการพบแพทย์	5	4	3	2	1
3. ระยะเวลาในการเจาะเลือด	5	4	3	2	1
4. ความสะดวกและง่ายในการเจาะเลือดจากปลายนิ้ว	5	4	3	2	1
5. ความสะดวกและง่ายในการหยดเลือดลงบนแผ่นทดสอบ	5	4	3	2	1
6. คุณภาพของบริการที่ได้รับจากแพทย์	5	4	3	2	1
7. คุณภาพของบริการที่ได้รับจากเภสัชกร	5	4	3	2	1
8. คุณภาพของบริการที่ได้รับจากพยาบาล	5	4	3	2	1
9. คุณภาพของบริการที่ได้รับจากบุคลากรโดยรวม	5	4	3	2	1
10. เวลาที่ใช้ในการให้บริการในแต่ละครั้ง (ใช้เวลามากไป น้อยไป มีโอกาสซักถามเพียงพอหรือไม่)	5	4	3	2	1
11. คุณภาพของคำอธิบาย/ความรู้เรื่องโรคและเรื่องการใช้ยาที่ได้รับ	5	4	3	2	1
12. การได้รับความรู้/ความเข้าใจเกี่ยวกับโรคและการดูแลตัวเอง	5	4	3	2	1
13. การได้รับความรู้/ความเข้าใจเกี่ยวกับการใช้ยาอย่างถูกต้อง	5	4	3	2	1
14. ความรู้สึกมีส่วนร่วมในการดูแลสุขภาพของตนเอง	5	4	3	2	1
15. ความสามารถในการเข้าถึงบริการหรือขอคำแนะนำนอกเวลานัด	5	4	3	2	1
16. ความช่วยเหลือที่ได้รับเมื่อเกิดปัญหาจากการใช้ยา ปัญหาจากโรค หรือปัญหาจากการตรวจเลือด	5	4	3	2	1

แบบสอบถามความพึงพอใจของผู้ป่วย (cont.)

(Patient Satisfaction Evaluation)

17. ความรู้สึกมั่นใจต่อผลการรักษาโดยระบบใหม่ (แม้ว่าผู้ป่วยพบเฉพาะเภสัชกรและไม่ได้เข้าพบแพทย์)	5	4	3	2	1
18. ความพึงพอใจโดยรวมต่อระบบ	5	4	3	2	1
19. ความต้องการของท่านในการได้รับการดูแลโดยระบบใหม่นี้ต่อไป	5	4	3	2	1

ข้อเสนอแนะ/ความคิดเห็นเพิ่มเติม

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ลงชื่อ .....

วันที่ .....

******** คณะผู้วิจัยขอขอบคุณทุกท่านที่สละเวลาเข้าร่วมการวิจัยและตอบแบบสอบถามนี้ ข้อมูลที่ได้รับจากงานวิจัย จะเป็นประโยชน์อย่างยิ่งในการพัฒนาระบบบริการผู้ป่วยของสถาบันโรคทรวงอกต่อไป *******

APPENDIX D

แบบสอบถามความพึงพอใจของผู้ป่วย

(Patient Satisfaction Evaluation)

โปรดให้ระดับความพึงพอใจกับบริการที่ท่านได้รับขณะร่วมการวิจัยนี้ โดยให้คะแนนในคำถามแต่ละข้อดังต่อไปนี้

5 พอใจมากที่สุด 4 พอใจ 3 ปานกลาง 2 ควรปรับปรุง 1 ไม่พอใจอย่างมาก

1. ระยะเวลาในการรอพบแพทย์	5	4	3	2	1
2. ความถี่ในการพบแพทย์	5	4	3	2	1
3. ระยะเวลาในการเจาะเลือด	5	4	3	2	1
4. คุณภาพของบริการที่ได้รับจากแพทย์	5	4	3	2	1
5. คุณภาพของบริการที่ได้รับจากพยาบาล	5	4	3	2	1
6. คุณภาพของบริการที่ได้รับจากบุคลากรโดยรวม	5	4	3	2	1
7. เวลาที่ใช้ในการให้บริการในแต่ละครั้ง (ใช้เวลามากไป น้อยไป มีโอกาสซักถามเพียงพอหรือไม่)	5	4	3	2	1
8. คุณภาพของคำอธิบาย/ความรู้เรื่องโรคและเรื่องการใช้ยาที่ได้รับ	5	4	3	2	1
9. การได้รับความรู้/ความเข้าใจเกี่ยวกับโรคและการดูแลตัวเอง	5	4	3	2	1
10. การได้รับความรู้/ความเข้าใจเกี่ยวกับการใช้ยาอย่างถูกต้อง	5	4	3	2	1
11. ความรู้สึกมีส่วนร่วมในการดูแลสุขภาพของตนเอง	5	4	3	2	1
12. ความสามารถในการเข้าถึงบริการหรือขอคำแนะนำนอกเวลานัด	5	4	3	2	1
13. ความช่วยเหลือที่ได้รับเมื่อเกิดปัญหาจากการใช้ยา ปัญหาจากโรค หรือปัญหาจากการตรวจเลือด	5	4	3	2	1
14. ความพึงพอใจโดยรวมต่อระบบ	5	4	3	2	1

แบบสอบถามความพึงพอใจของผู้ป่วย (cont.)

(Patient Satisfaction Evaluation)

ข้อเสนอแนะ/ความคิดเห็นเพิ่มเติม

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ลงชื่อ .....

วันที่ .....

******** คณะผู้วิจัยขอขอบคุณทุกท่านที่สละเวลาเข้าร่วมการวิจัยและตอบแบบสอบถามนี้ ข้อมูลที่ได้รับจากงานวิจัย จะเป็นประโยชน์อย่างยิ่งในการพัฒนาระบบบริการผู้ป่วยของสถาบันโรคทรวงอกต่อไป *******

APPENDIX E

WARFARIN CALENDAR

ปฏิทินยาวาร์ฟาริน

ข้อควรปฏิบัติ

1. กินยาวาร์ฟารินหลังอาหารเย็น หรือ ก่อนนอน ของทุกวัน

2. เจาะเลือดตรวจค่า INR โดยใช้เครื่องที่ได้รับจากรพ. และบันทึกค่า INR ลงในสมุดทุกครั้ง

3. เก็บแผ่นตรวจเลือดที่อุณหภูมิห้อง (ไม่เกิน 30°C) หลีกเลี่ยงความร้อน, ความชื้น และปิดฝาขวดให้สนิททุกครั้ง

4. ห้ามเพิ่มขนาดยาที่รับประทานเป็น 2 เท่าโดยเด็ดขาด

5. ถ้าลืมกินยายังไม่ถึง 12 ชั่วโมง ให้รีบกินยาทันทีที่นึกได้ในขนาดเดิม

6. ถ้าลืมกินยาหลังจากผ่านไป 12 ชั่วโมงแล้ว ให้ข้ามยามื้อนั้น และกินยาวันถัดไปในขนาดเดิม

7. กินยาตามแพทย์สั่งอย่างต่อเนื่อง หากมีเลือดออกผิดปกติให้รีบมาพบแพทย์

ธันวาคม 2551 — **สถาบันโรคทรวงอก**

อาทิตย์	จันทร์	อังคาร	พุธ	พฤหัสบดี	ศุกร์	เสาร์
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

อย่าลืมลงเวลารับประทานยาในตารางทุกวันนะคะ

(ขนาดยาที่รับประทาน.....)

APPENDIX F

Table 23. CONSORT 2010 CHECKLIST

Section/ Topic	Item number	Checklist item
Title and abstract	1a	Identification as a randomized trial in the title
	1b	Structured summary of trial design, methods, results, and conclusion (for specific guidance, see CONSORT for abstracts
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypothesis
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomization Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomization; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),

Table 23. CONSORT 2010 CHECKLIST (cont.)

Section/ Topic	Item number	Checklist item
Method (cont.)		
Allocation concealment mechanism (cont.)	9	describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome
	13b	For each group, losses and exclusions after randomization, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Table 23. CONSORT 2010 CHECKLIST (cont.)

Section/ Topic	Item number	Checklist item
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)
Discussion		
Limitations	20	Trial limitations; addressing sources of potential bias; imprecision; and, if relevant, multiplicity of analyses
Generalizability	21	Generalizability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

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