IMPACT OF EDUCATION AND COUNSELING BY CLINICAL PHARMACISTS ON ANTICOAGULATION THERAPY IN PATIENTS WITH MECHANICAL HEART VALVES

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IMPACT OF EDUCATION AND COUNSELING BY CLINICAL PHARMACISTS ON ANTICOAGULATION THERAPY IN PATIENTS WITH MECHANICAL HEART VALVES

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ABSTRACT

This historical cohort study evaluated the impact of education and counseling provided by clinical pharmacists on the control of anticoagulation therapy, thromboembolic/hemorrhagic complications and drug-related problems. Medical charts of 284 patients with mechanical heart valves at the Cardiovascular Thoracic Surgery clinic, Siriraj Hospital were reviewed. Data from pre- and post-interventions were collected. The mean age of the study population was 50 years old (range 19-82). The mean follow-up period was 11.6 months (range 6-15 months) in both periods. The proportion of patients having anticoagulation therapy in therapeutic range was significantly higher in the post-intervention period (51.79% VS 46.47%, p= 0.016). The proportion of patients with low anticoagulation variability significantly increased by 50% (19.4% vs 29.2% in pre- and post-intervention periods, respectively; p = 0.005). The rate of thromboembolic events was 47% lower in the post-intervention period (5.5 vs 2.9 event/100 patient-year in pre- and post-intervention periods, respectively; p=0.20). Hemorrhagic complications were slightly lower in the post-intervention period (15.6 vs 14.9 event/100 patient-year in pre- and post-intervention periods, respectively; p=0.81). However, these promising trends did not reach statistical significance. In addition, non-compliance was less frequently encountered in the post-intervention period while drug interactions were effectively identified by clinical pharmacists. These results indicate the benefits of education and counseling by clinical pharmacists in the improvement of anticoagulation control which have a potential reduction in complications and drug-related problems such as noncompliance and drug interactions.

KEY WORDS: WARFARIN/INR/PHARMACIST/ORAL ANTICOAGULATION/ANTICOAGULATION CONTROL/ANTICOAGULATION VARIABILITY

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ผลของการให้ความรู้และคำปรึกษาโดยเภสัชกรคลินิกในผู้ป่วยที่มีลิ้นหัวใจเทียมที่ได้รับยาต้านการแข็งตัวของเลือด
(IMPACT OF EDUCATION AND COUNSELING BY CLINICAL PHARMACISTS ON ANTICOAGULATION THERAPY IN PATIENTS WITH MECHANICAL HEART VALVES)

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บทคัดย่อ

การศึกษานี้เป็นการวิจัยแบบย้อนหลังเปรียบเทียบกับการติดตามผลไปข้างหน้าเพื่อประเมินผลของการให้ความรู้และคำปรึกษาเรื่องการใช้ยาวาร์ฟารินโดยเภสัชกรคลินิกต่อการควบคุมระดับการต้านการแข็งตัวของเลือดและภาวะแทรกซ้อนจากการใช้ยาวาร์ฟารินในผู้ป่วยที่ใส่ลิ้นหัวใจเทียมชนิดโลหะจากสาขาวิชาศัลยศาสตร์หัวใจและทรวงอก โรงพยาบาลศิริราช ลักษณะของการวิจัยเป็นการทบทวนแฟ้มประวัติของผู้ป่วยในช่วงก่อนและหลังการได้รับความรู้และคำปรึกษาจากเภสัชกรคลินิก มีผู้ป่วยจำนวน 284 คนที่ผ่านเกณฑ์การคัดเลือก อายุเฉลี่ยของกลุ่มผู้ป่วยที่ศึกษาเท่ากับ 50 ปี (19-82 ปี) ระยะเวลาการติดตามเฉลี่ยในแต่ละช่วงเท่ากับ 11.6 เดือน (6-15 เดือน) สัดส่วนของระดับ INR ที่อยู่ในช่วง 2.0-3.0 ของช่วงหลังมีมากกว่าช่วงก่อนได้รับความรู้และคำปรึกษาอย่างมีนัยสำคัญ (ร้อยละ 51.79 และ 46.47 p=0.016) สัดส่วนของผู้ป่วยที่มี low anticoagulation variability เพิ่มขึ้นร้อยละ 50 หลังได้รับความรู้และคำปรึกษา (ร้อยละ 19.4 และ 29.2 ของผู้ป่วยก่อนและหลังการได้รับคำแนะนำตามลำดับ, p=0.005) อัตราการเกิด thromboembolic complications (stroke และ transient ischemic attack [TIA]) ลดลงร้อยละ 47 หลังได้รับคำแนะนำ (5.5 และ 2.9 event/100 patient-year; p=0.20), อัตราการเกิดภาวะเลือดออก (ชนิดรุนแรงและไม่รุนแรง) เท่ากับ 15.6 และ 14.9 event/100 patient-year (p=0.81) ในช่วงก่อนและหลังได้รับความรู้และคำปรึกษาจากเภสัชกรตามลำดับ แต่ความแตกต่างเหล่านี้ไม่มีนัยสำคัญทางสถิติ นอกจากนี้ การไม่ให้ความร่วมมือในการรักษาลดลงหลังได้รับคำแนะนำจากเภสัชกร เภสัชกรค้นหาปฏิกิริยาระหว่างยาได้อย่างมีประสิทธิภาพ ผลการศึกษานี้แสดงให้เห็นว่า การให้ความรู้และคำปรึกษาในการใช้ยาวาร์ฟารินโดยเภสัชกรคลินิกแก่ผู้ป่วยที่ใส่ลิ้นหัวใจเทียมชนิดโลหะ ส่งเสริมให้การควบคุมระดับการต้านการแข็งตัวของเลือดมีประสิทธิภาพที่ดีขึ้น และมีแนวโน้มที่จะช่วยลด thromboembolic complications ภาวะเลือดออกจากการใช้ยาวาร์ฟารินและปัญหาจากการใช้ยา เช่น การไม่ให้ความร่วมมือในการรักษาและการค้นหาปฏิกิริยาระหว่างยาอีกด้วย

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LIST OF ABBREVIATIONS

A	Aortic
AC	Anticoagulation clinic
ACCP	American College of Chest Physicians
AF	Atrial fibillation
AHA	American Heart Association
AM	Aortic and mitral
aPTT	Activated Partial Thromboplastin Time
ASA	Aspirin
BPH	Benign Prostate Hypertropy
BS	Bjork-Shiley
Bx	Biopsy
CA	Cancer
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CHF	Congestive Heart Failure
CI	Confidence Interval
CM	Carbomedic
CNS	Central Nervous System
CRF	Chronic Renal Failure
CVA	Cerebrovascular Accident
CVT	Cardiovascular and Thoracic
D/F	Drug-food interaction
D/I	Drug-drug interaction
DM	Diabetes Mellitus
EF	Ejection Fraction
F	Female
FFP	Fresh Frozen Plasma

LIST OF ABBREVIATIONS (Continued)

g/day	Gram per day
GI	Gastrointestinal
HM	Medtronic Hall
HMG-CoA	3-hydoxy-3-methylglutaryl coenzyme A reductase
HT	Hypertension
Hx	History of
INR	International Normalized Ratio
IU	International Unit
IV	Intravenous
K_1	Phytonadione
K_2	Menaquinone
K_3	Menadione
K_4	Menadiol sodium diphosphate
KH_2	Hydroquinone
L	Levo-
LN	Lymph node
Lt	Left
LV	Left Ventricular
M	Male
mcg/kg/day	Microgram per kilogram per day
mg	Milligram
mg/day	Milligram per day
mg/wk	Milligram per week
Mi	Mitral
mL	Milliliter
N	Non compliance
No	Number
NSAIDs	Non Steroidal anti-inflammatory drugs
PAF	Platelet Aggregation Factor

LIST OF ABBREVIATIONS (Continued)

PG	Prostaglandin
PT	Prothrombin Time
RDA	Recommended Daily Allowance
Rt	Right
S/P	Status post-
SD	Standard deviation
SE	Starr-Edward
SJ	Saint Jude
SLE	Systemic Lupus Erythematosus
SMZ-TMP	Sulfamethoxazole Trimethoprim
SR	Sorin bileaflet
St.	Saint
Sx	Surgery
T	Tricuspid
TB	Tuberculosis
TE	Thromboembolic
TIA	Transient Ischemic Attack
TXA	Thromboxane A_2
UGIB	Upper Gastrointestinal Bleeding
UMC	Usual Medical Care
Unk	Unknown
US	United States
vs	versus
yr	Year

CHAPTER 1
INTRODUCTION

The efficacy of warfarin has been unequivocally demonstrated for many indications, such as treatment and prevention of thromboembolism, prophylaxis of venous thrombosis (high risk surgery), prevention of systemic embolism in tissue/ mechanical prosthetic valve (prevention of valve thrombosis and systemic emboli) (1-5), acute myocardial infarction, valvular heart disease, atrial fibillation (AF) and treatment of pulmonary embolism, and venous thrombosis. (4)

Warfarin is a vitamin K antagonist that exerts their anticoagulant effect through interference of the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is an important cofactor for the activation of vitamin K-dependent coagulation factors. Inhibition of such interconversion with warfarin results in the production of partially carboxylated and decarboxylated coagulation factors with reduced procoagulant activity. Warfarin is a racemic mixture of two optically active isomers, the R and S forms in equal proportion. It is rapidly absorbed from the gastrointestinal tract. Warfarin has a half-life of 36-42 hours and is highly bound to plasma proteins (mainly albumin). The two isomers of warfarin are metabolized by different cytochrome pathways. The anticoagulant response to warfarin is influenced by pharmacokinetic factors, including drug interactions that affect the absorption, metabolic clearance of warfarin or drug-food interactions. Major problems such as bleeding or thromboembolic complications may be caused by above problems. (4-12) These adverse outcomes have a negative impact on the quality of life of patients, therefore warfarin therapy requires careful monitoring. (13-15) Unlike other drugs with a narrow margin of safety, optimum warfarin dosing can not be determined by a simple serum concentration. The drug is monitored indirectly by measuring its pharmacodynamic effects on the body's hemostatic system; International Normalized Ratio (INR). The hemostatic system is

complex and is affected by numerous variables at many steps in the clotting process. Therefore, warfarin is associated with a high frequency of complications such as hemorrhagic complications (15-20) and the risk of warfarin associated hemorrhagic complications may be greatest during the first month of therapy (21) and previous hemorrhagic event raises the risk of hemorrhagic complications. (21-22)

There is a strong relationship between the intensity of anticoagulation therapy and the risk of hemorrhage that has been reported in patients with mechanical prosthetic valve. Hemorrhagic episodes of moderate intensity (prothrombin time-ratio 1.5) and high intensity (prothrombin time-ratio 2.5) were 0.9 vs 2.1 episodes/100 patient-year ($p<0.001$) for major hemorrhage and 6.2 vs 12.1 episodes/100 patient-year ($p<0.002$) for minor hemorrhage, respectively. (23) In multiple logistic models, the prothrombin time-ratio remained the dominant independent risk factor for both intracerebral and subdural hemorrhage. The estimated odds of subdural hemorrhage increased 7.6- fold as the prothrombin time-ratio increase from 2.0 to 2.5, and the risk rose 4- fold for each unit increase in prothrombin time-ratio (The corresponding odds ratio for a 0.5 increase in prothrombin time-ratio was 2.1). (24) In some studies , when INR rose to 5.0 or above, the incidence of adverse events increase 4.8 per 100 patient – year (95% CI 2.6-7.7) for an INR of 5.0-5.5 and 75 per 100 patient-year (95% CI 54-101) for INR of 6.5 or above. This corresponded to a 37.5 fold increase in the risk of adverse events. (25)

A number of studies have demonstrated that the risk of hemorrhagic or thromboembolism may be effectively reduced with the use of specialized clinic such anticoagulation clinic (AC). This measure has been proved to increase the optimal anticoagulation control, reduce hemorrhagic/thromboembolic complications and decrease the total cost of care. (15-20) However these studies were conducted mainly in the US and European countries. Since March of 2002, the Department of Cardiovascular and Thoracic (CVT), Faculty of Medicine at Siriraj Hospital has implemented a multidisciplinary approach in caring for their patients. Such approach includes incorporating clinical pharmacists in the management of warfarin therapy in patients with mechanical heart valve requiring long-term anticoagulation. This is a collaboration among CVT medical staff, pharmacists, nurses, laboratory personal,

physical therapists and social workers. Clinical pharmacists, working as a part of this clinic, are dedicated to the optimization of warfarin therapy through continuous patient education/counseling, providing supporting materials aiming at improving patient's compliance, screening of drug interactions, and assisting medical staff in warfarin dosage adjustment. This service is named "Drug Counseling Program for Warfarin Therapy" or "Warfarin Project" in short. Patient's understanding regarding warfarin therapy is assessed using pre- and post-education test entailing 10 questions designed to test patient's knowledge of warfarin therapy (Appendix A). Each patient also receives a booklet with important information on warfarin therapy (Appendix B). Patient compliance is evaluated every visit. Information on patient non-compliance, drug interactions or complications of warfarin therapy including hemorrhagic or thromboembolic events are collected and communicated to patient's primary care provider along with suggestions on how to solve those problems. Impact of patient education on patients' knowledge regarding warfarin therapy was previously reported and the results indicated that this service significantly improved patients' knowledge about warfarin therapy. (26) However, the impact of such service on anticoagulation control and rates of warfarin complications have never been reported from this project. Consequently, the efficacy of this clinic in promoting optimum anticoagulation control and reducing complications of warfarin should formally be analyzed.

This study was aimed to evaluate whether clinical pharmacists' interventions can help achieve optimum anticoagulation control while minimize complications from warfarin in Thai patients with mechanical heart valve by using historical cohort study. The medical record of patients participating in the Warfarin Project from March to December, 2002 were historically reviewed and prospectively followed until June 2003. Data on anticoagulation control, anticoagulation variability and complications of anticoagulation therapy pre- and post-intervention periods were compared. The results of this study may be used to justify the development of AC elsewhere in Thailand.

CHAPTER 2
LITERATURE REVIEW

A. Mechanical Heart Valve Replacement

The replacement of diseased and malfunctioning heart valves has been a routine procedure for almost four decades. During this time, there have been many developments in both surgical technique and prosthetic valve design. Notwithstanding the advances made, there is no ideal prosthetic valve. Two major types of replacement valves, namely, mechanical or tissue (bioprosthetic), have their own particular advantages and disadvantages as shown in table 1.

Table 1. Advantages and Disadvantages of Mechanical and Tissue valves

Valve type	Advantages	Disadvantages
Mechanical	Long-term durability, consistency of manufacturing	Unnatural form, patient usually requires long-term anticoagulant therapy
Tissue	More natural form and function, less need for long-term anticoagulant therapy	Unproven long-term durability, inconsistency of manufacturing

Since mechanical prosthetic valves have gained more popularity in the past decades and this study is focused on patients with mechanical valves, the information regarding the three most common mechanical prostheses valves is reviewed briefly here. These include caged-ball, tilting disc and bi-leaflet valves.

1. Caged-ball valves.

The long-established Starr-Edwards caged-ball valve (Figure1.) is by far the most commonly used example of its type. The presence of the cage is also likely to increase flow abnormalities leading to turbulence during the forward flow phase. In addition, the high profile of this valve is particularly significant in large sizes. With mitral

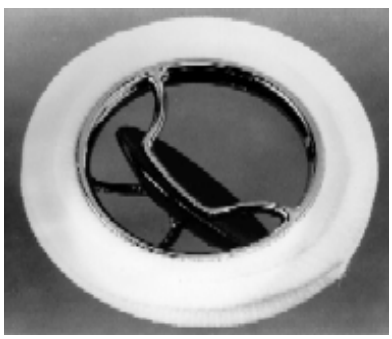
prostheses, the cage may contact the ventricular wall during systole, particularly in the case of small left ventricle. This may ultimately lead to myocardial conduction disturbances or ventricular rupture. In the aortic position, size discrepancy may lead to secondary stenosis caused by the ball itself.

Figure 1. Starr-Edward valve

2. Tilting disk valves

The tilting disk valve has the advantages of a significantly lower profile and quasicentral flow. An example of a disk configuration, the Bjork-Shiley monostrut valve, is illustrated in Figure 2A. Flow through the valve is distorted by the presence of the occluder and supporting strut; however, the disturbance is significantly less than that observed with a caged-ball valve.

Medtronic Hall valve disc (Figure 2B.) substrate is tungsten-impregnated graphite with pyrolytic carbon coating. The round, flat disc is designed to maximize flow characteristics by introducing the lowest possible disturbance to natural blood flow.



2A

2B

Figure 2A. Bjork-shilley valve, 2B:Medtronic Hall

3. Bileaflet valves

Bileaflet valves represent the latest development in mechanical valve design. St. Jude (Figure 3.) and Carbomedic are by far the most commonly use example of its type. The wide opening angle and thin cross-sectional area presented by the open leaflets present minimal disturbance to flow. Closing regurgitation is also minimized by the size and shape of the leaflets; however, the additional central gap between the leaflets will contribute to the leakage regurgitation.

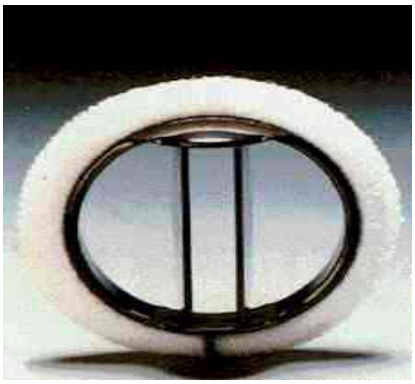


Figure 3. St. Jude valves

Prostheses most prone to thrombosis are those that produce turbulence (with associated high shear stresses), and stasis in close proximity to thrombogenic surfaces. The prostheses differ in their thrombogenicity, optimum anticoagulation levels for each need to be defined in order to ensure maximum safety in long term management (2-5,27-29)

The incidence of embolism following valve replacement probably underestimate the size of the problem because many small emboli go to clinically silent areas of the body or the brain, the fact remains that the majority of patients appear to escape significant embolic complications such as transient ischemic attack (TIA) or cerebrovascular accident (CVA).

Oral anticoagulation, especially with warfarin, has been proved to be highly effective in the prevention of valve thrombosis and embolism from prosthetic source. Warfarin is a coumarin derivative and indirect-acting anticoagulants (vitamin K antagonist). The drug is commercially available as a racemic mixture (S and R) in the equal proportion of the 2 optical isomers of the sodium salt. (4)

B. Pharmacology of warfarin

Warfarin alters the synthesis of blood coagulation factors II (prothrombin), VII (proconvertin), IX (Chirstmas factor or Plasma thromboplastin component), and X (Stuart prower factor) in the liver by interfering with the cyclic inter-conversion of vitamin K and its 2,3 epoxide (vitamin K epoxide), which is necessary for the γ-carboxylation of several glutamic acid residues in the precursor protein of these coagulation factors. The γ-carboxylation requires the reduced form of vitamin K (vitamin KH_2), molecule oxygen and carbon dioxide and is linked to the oxidation of vitamin KH_2 to vitamin K epoxide. Vitamin K epoxide is then recycled to vitamin KH_2 through two reductase steps. (Figure 4.) The first, which is sensitive to warfarin, reduces vitamin K epoxide to vitamin K_1 (in plant material or vitamin K-containing supplements), while the second, which is relatively insensitive to warfarin, reduces vitamin K_1 to vitamin KH_2. The result is the synthesis of dysfunction but immunologically detectable forms of coagulation factors II, VII, IX and X. In adequate dosage, phytonadione (vitamin K_1) in plant material or vitamin K-containing supplements reverses the effect of warfarin on the hepatic synthesis of vitamin K–dependent clotting factors. In contrast to heparin, warfarin has no anticoagulant effect in vitro. Because warfarin does not alter catabolism of blood coagulation factors, depletion of circulating functional vitamin K-dependent coagulation factors must occur before the effect of the drug becomes apparent. The rates of depletion of functional coagulation factors II, VII, IX, and X depend on the their individual rates of degradation. Following initiation of warfarin therapy, blood concentration of functional coagulation factor VII (plasma half-life of 4-6 hours) is depressed first, followed by those of factor IX (plasma half-life of 20-24 hours), X (plasma half-life of about 48-72 hours), and finally factor II (plasma half-life of 60 hours or longer). When warfarin therapy is discontinued or phytonadione is administered, blood concentrations of functional vitamin K-dependent coagulation factors return to the pretreatment concentrations.

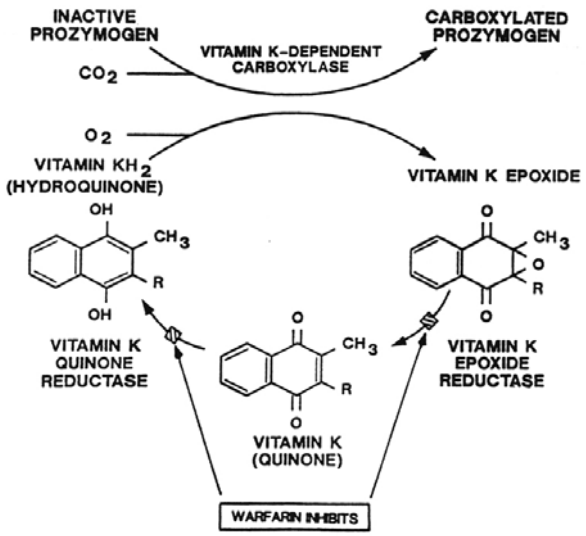


Figure 4. Vitamin K cycle

The enantiomers of warfarin have different half-lives, potencies, and rates of elimination. The S-isomer (elimination half-life 33 hours) has 2-5 times the anticoagulant activity of the R-isomer (elimination half-life 45.4 hours). An anticoagulant effect generally occurs within 24 hours following administration of warfarin, but peak anticoagulant effects may be delayed for 72-96 hours. Antithrombogenic effects of warfarin generally occur only after concentrations of functional coagulation factors IX and X are diminished, which may not occur until 2-7 days following initiation of therapy, and there is a period of latency following discontinuation of the drug until blood concentrations of functional vitamin K-dependent coagulation factors return to the pretreatment level. Warfarin therapy inhibits thrombus formation when stasis is induced and may prevent extension of existing thrombi. The drug has no direct effect on established thrombi and appears to have little, if any, effect on the pathogenesis of arterial thrombi that results from interaction of platelet with an abnormal vessel wall. Because warfarin affects synthesis of blood coagulation factors that are involved in both intrinsic and extrinsic coagulation, the drug prolongs both the prothrombin time (PT) which measures the integrity of the extrinsic system and activated partial prothrombin time (aPTT) which measures the integrity of the intrinsic system. (Figure 5.) Warfarin inhibits carboxylation of regulatory anticoagulant protein C and S and therefore has the potential to exert a procoagulation effect. (4,30-31) Protein C is synthesized in

endothelial of vessels and hepatic microsome (as proenzyme). It acts as anticoagulant by activating the specific proteolysis of activated factor V and VII and activates fibrinolysis by increasing tissue plasminogen activator concentration. These reactions need protein S to be a cofactor. (32)

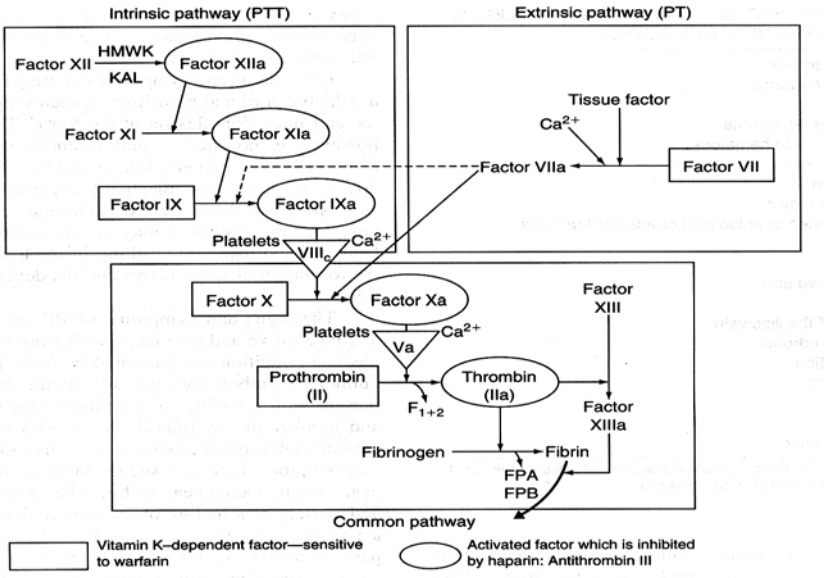


Figure 5. Hemostasis pathways

Warfarin is used to reduce the incidence of thromboembolism associated with prosthetic mechanical or bioprosthetic valves. The risk of systemic embolism is higher with prosthetic mechanical than bioprosthetic heart valves, higher with first-generation mechanical (e.g., caged ball, caged disc) valves than with newer mechanical (e.g., bileaflet, Medtronic Hall tilting disk) heart valves, higher with multiple valves than one prosthetic valve, and higher with mitral than aortic positions. The risk also increases in the presence of atrial fibrillation. All patients with mechanical heart valves require lifelong anticoagulant therapy because of the high risk of thromboembolism associated with these valves. With anticoagulant therapy, the risk is approximately 0.71-4.0% annually. (23,25,33) The treatment recommendations are differ in each consensus recommendations, risk of thromboembolism appears to be higher in the first few days or months (21-22) following the replacement of a mechanical or bioprosthetic valves. For patients with the newer , bileaflet or Medtronic Hall tilting disk in aortic position, anticoagulant therapy with a target INR of 2.5 (range 2.0-3.0) is recommended in patients who have no additional factors for

thromboembolism (i.e., atrial fibrillation, left ventricular dysfunction, history of thromboembolism, hypercoagulable condition). (3) Anticoagulation therapy with a target INR of 3.0 (range 2.5-3.5) is recommended in patients with bileaflet or tilting disk in mitral position. Anticoagulant therapy with a target INR of 3.0 (range 2.5-3.5) is recommended in patients with first-generation mechanical heart valves (caged ball, caged disk) (3) or 3.0-4.5 (31) in the aortic position and no additional thromboembolic risk factors, or a mechanical heart valve in the mitral position. Life-long anticoagulant therapy with a target INR of 2.5 (range 2.0-3.0) is recommended in patients with a bioprosthetic aortic heart valve (3,31) and additional risk factors for thromboembolism (atrial fibrillation), and a higher intensity of oral anticoagulation (target INR of 3.0, range 2.5-3.5) is recommended by some clinicians for patients with a mitral bioprosthetic heart valve and additional risk factors. (3) Table 2. shows the summary of difference in anticoagulation intensity for patients with mechanical valve.

Table 2. The summary of difference in anticoagulation intensity for patients with mechanical valve

Type of mechanical heart valve	Position	Target INR
Bileaflet or HM	A*	2.5 (2.0-3.0)
Bileaflet,Tilting disk	M*	3.0 (2.5-3.5)
Caged ball, Caged disc	A*	3.0 (2.5-3.5)
Caged ball, Caged disc	M*	3.0-4.5

*No additional factors for TE such as AF, LV dysfunction, Hx of TE, hypercoagulable condition

Aspirin and dipyridamole have been used in conjunction with warfarin to reduce the incidence of thrombosis in patients with prosthesis mechanical valves if warfarin alone does not completely prevent thrombosis. (3,34) In a randomized, placebo-controlled study in patients with prosthetic heart valves who were at high risk for systemic emboli, the addition of delayed-release, enteric-coated aspirin (100 mg/day) to warfarin therapy (adjusted to maintain an INR of 3.0-4.5) resulted in a substantial reduction in major systemic embolism or death, particularly from vascular

causes, compared with warfarin therapy alone. Although the risk of hemorrhagic complications with combined aspirin-warfarin therapy was considerably higher than that of warfarin alone (8.5% vs 6.6% per year, respectively) (31), the combined end point of major systemic embolism were 1.9%/year with combined therapy compared to 8.5%/year with warfarin alone. Patients with prosthetic heart valves who have a breakthrough embolic event despite prophylactic antithrombotic therapy (aspirin and/ or warfarin) should have the dosage of their antithrombotic therapy increased or should receive additional therapy. For example, patients receiving warfarin therapy adjusted to maintain an INR of 2.0-3.0 or 2.5-3.5 who suffer thromboembolic complications, should have their warfarin dosage increased to achieve and maintain an INR of 2.5-3.5 or 3.5-4.5, respectively. (3) If patients are not receiving aspirin therapy, aspirin should be initiated at a dosage of 80-100 mg daily. In patients receiving the combination of low dose aspirin (80-100 mg daily) and warfarin, the dosage of warfarin should be increased first, followed by an increase in the aspirin dosage (to 325 mg daily) if the higher warfarin dosage dose not prevent embolic events. In patients receiving aspirin alone, the aspirin dosage may be increased to 325 mg daily or warfarin therapy may be initiated and titrated to achieve and maintain an INR of 2.0-3.0. (3)

In patients with a prosthetic heart valves receiving long-term oral antithrombotic therapy (warfarin and/or aspirin) who require additional surgical procedures, the risk of perioperative bleeding should be weighed against the increased risk of thromboembolism that may occur as a result of temporary discontinuance of oral antithrombotic therapy. Oral antithrombotic therapy should not be discontinued for procedures in which bleeding is unlikely or inconsequential, such as local skin surgery, teeth cleaning, or treatment of dental caries. Therapy with warfarin should be discontinued approximately 48-72 hours or 4 days prior to procedures (noncardiac and cardiac) that have a risk of perioperative bleeding, and the procedure should not be performed before the anticoagulant effects of warfarin largely have dissipated (as indicated by a INR of 1.5 or less). Aspirin should be discontinued 1 week before noncardiac procedures in patients with prosthetic heart valves but need not be withheld in cardiac procedures such as cardiac catherization or angiography. (2)

Perioperative heparin should be considered for noncardiac procedures in patients with prosthetic heart valves who are at very high risk for thrombosis without oral anticoagulation therapy, including those with a history of thrombosis or embolus within 1 year (arbitrarily) of the procedure, patients with thromboembolic events after previous discontinuation of anticoagulant therapy, those with Bjork-Shiley valves, and those with 3 or more of the following risk factors: atrial fibrillation, previous thromboembolism, hypercoagulable condition, mechanical prosthetic, and perhaps left ventricular dysfunction (ejection fraction less than 30%). Heparin should also be considered in patients with mechanical heart valve in the mitral position, in whom a single risk factor for thromboembolism would be considered sufficient reason for antithrombotic therapy. In such high-risk patients undergoing noncardiac procedures, heparin should be initiated after discontinuation of warfarin therapy when the INR is below 2 (approximately 48 hours before surgery) and discontinued 4-6 hours before the procedure. In patients undergoing noncardiac procedures associated with an appreciable incidence of postoperative hemorrhage, adjusted-dose heparin should be initiated as soon after surgery as hemostasis has been established. Adjusted-dose heparin should be reinitiated approximately 24 hours after surgery in high-risk patients undergoing noncardiac procedures. Therapy with warfarin generally is administered for follow-up treatment after heparin therapy in patients undergoing noncardiac procedures, and therapy with the 2 drugs is usually overlapped for 3-5 days until an adequate response to the warfarin is obtained (as indicated by the INR of 2.0 or greater). Long-term therapy with aspirin may be reinstituted in surgical patients with prosthetic heart valves the day after the noncardiac procedure or after control of active bleeding. In patients with prosthetic heart valves who require urgent cardiac catheterization and are receiving warfarin therapy, the procedure may be performed, but warfarin preferably should be discontinued prior to (approximately 72 hours before) the procedure to allow the INR to fall to 1.5 or less. Patients with one or more risk factors for thromboembolism should receive heparin therapy when the INR fall below 2.0 and continue to receive heparin until warfarin is restarted and the desired INR is achieved. In warfarin-treated patients with prosthetic heart valves who require cardiac catheterization and a transeptal or left ventricular incision, antithrombotic

therapy should be discontinued and the INR allowed to fall to 1.2 or less prior to the procedure. (2)

C. Adverse drug reactions of warfarin

The most common adverse effect of warfarin is hemorrhagic events which is the extension of the drug's pharmacologic action. Hemorrhagic events can range from minor local ecchymosis to major bleeding complications, which occasionally may result in death. Relatively minor bleeding episodes occur in 2-10% of patients receiving warfarin. (25,33,35) The major bleeding is most prone in the GI tract or genitourinary sites. (21-22,35) Although bleeding results principally from overdose or excessive prolongation of the INR, bleeding complications may occur when the INR is in the usual therapeutic range. (35) A severe elevation (greater than 50 seconds) in activated partial thromboplastin time (aPTT) with a PT ratio or international normalized ratio (INR) in the desired range reportedly may suggest an increased risk of postoperative hemorrhage. Bleeding complications may be manifested by signs or symptoms that do not indicate obvious bleeding, such as paralysis, headache, pain in the chest, abdomen, joints, muscles or other areas, dizziness, shortness of breath, difficult breathing or swallowing, unexplained swelling, weakness, hypotension, or unexplained shock. Paralytic ileus and intestinal obstruction also have been reported from submucosal or intramural hemorrhage. Therefore, the possibility of bleeding should be considered in any anticoagulated patients with complaints that do not indicate an obvious diagnosis. The frequency and severity of bleeding may be minimized by careful clinical management of the patient, including frequent INR determinations. Early manifestations of overdosage including microsopic or gross hematuria, melena, excessive uterine or menstrual bleeding, petechiae, ecchymosis, bleeding from gums or other mucous membranes, and oozing from nicks made while shaving. If any unexpected bleeding occurs during anticoagulant therapy, the patient's condition must be evaluated immediately.

In the treatment of overdose or excessive INR, therapy should be determined by the severity of the effect, the urgency of the need to store normal hemostasis, and whether or not therapy with the anticoagulant is to be maintained. Minor hemorrhage or an overly INR will usually respond to a decrease in dosage or to withholding 1 or

more doses of the drug. If moderate or severe hemorrhage occurs or if the INR is excessively high, warfarin should be discontinued immediately and phytonadione administered. Other available vitamin K derivatives (menadiol sodium diphosphate) are ineffective and should not be used in the treatment of warfarin overdose. (36) Several hours are usually required for the effects of phytonadione to occur whether the drug is administered orally or parenterally. Therefore, if bleeding is severe and immediate restoration of functional vitamin K-dependent blood coagulation factors is necessary, fresh, whole blood, plasma, or commercial factor VII and factor X complex should be administered concomitantly. Vitamin K is an essential fat-soluble vitamin that occurs in two natural forms, K_1 and K_2. Vitamin K_1 or phytonadione (phylloquinone) is synthesized by plants and algae, concentrated in the chloroplast lamellae and is the natural vitamin available for therapeutic use. Green leafy vegetables such as spinach, kale, broccoli, cabbage, brussel sprouts and lettuce contain the highest concentration of vitamin K_1. (37) Vitamin K_2 (menaquinones) is synthesized by gram positive bacteria and bacteria in the intestinal tract. The Recommended Daily Allowance (RDA) of vitamin K is 1 mcg/kg/day of phylloquinones for adults; infants require 10 times that amount to maintain normal homeostasis. Plasma vitamin K is mainly in the form of phylloquinones, whereas liver stores are 90% menaquinones and 10% phylloquinones. Phylloquinones are more biologically active. The healthy liver has approximately a 30-day store of vitamin K. Vitamin K_3 (menadione) is a precursor for vitamin K_2. Vitamin K_4 (menadiol sodium diphosphate) has 50% of the potency of vitamin K_3. Vitamin K_3 and K_4 (only advantage is that they do not require bile for absorption) may produce hemolysis, hyperbilirubinemia, and kernicterus in neonates and hemolysis in glucose-6-phosphate-dehydrogenase-deficient patients. They are not interchangeable with, or a substitute for, vitamin K_1 when anticoagulant are responsible for coagulation deficits. (36,38)

D. Recommendations for warfarin dosing (2,36-56)

Practical Dosing

For the initiation and maintenance dosing of warfarin, the dose of 5 mg is recommended (2A). Starting dose of < 5 mg might be appropriate for elderly

patients, patients with impaired nutrition or liver disease and patients who are at high risk of bleeding.

Management of nontherapeutic INRs

1. The INR greater than therapeutic range but less than 5.0 and no significant bleeding.
   - Lower the dose or omit a dose
   - When INR at therapeutic-range, resume therapy at lower dose

   If INR only minimally greater than therapeutic-range
   - No dose reduction (2C)
2. The INR greater than 5.0 but less than 9.0 and no significant bleeding.
   - Omit the next one or two doses
   - Monitor INR frequently
   - When INR is in therapeutic-range, resume therapy at lower dose

   Alternatively
   - Oral vitamin K_1 1-2.5 mg
   - If increased risk of bleeding, oral vitamin K_1 2-4 mg (INR reduction in 24 hours)
   - INR still high, oral vitamin K_1 1-2 mg additional dose (2C)
3. The INRs greater than 9.0 and no significant bleeding.
   - Hold off warfarin
   - Oral vitamin K_1 3-5 mg (INR reduction in 24-48 hours)
   - Monitor INR frequency
   - Administer additional vitamin K_1 if necessary
   - Resume therapy at lower dose (2C)
4. INRs greater than 20.0 and serious bleeding occur.
   - Hold off warfarin
   - Slow IV vitamin K_1 10 mg
   - Supplement with FFP (fresh frozen plasma) or prothrombin complex
   - Vitamin K_1 can be repeated every 12 hours (2C)

5. Life-threatening bleeding
   - Hold off warfarin
   - Administer prothrombin complex
   - Supplemented with slow IV vitamin K_1 10 mg, repeat this therapy as necessary (2C)

There are four methodologic grades; grade A, B, C and C+. Grade A recommendations are base on randomized trials with consistent results. Grade B recommendations are made when randomized trials have inconsistent results or have substantial methodologic weakness. Grade C recommendations are base on observational studies or from generalization from randomized trials from one group of patients to a different group. When experts consider that the data from observational studies are overwhelming, then the grade C recommendation is upgraded to grade C+. Grade 1 is a very strong recommendation base on the results of well-designed, randomized trails with consistent results. Grade 2 recommendation need further trials or further evaluations of cost benefit. (57)

Vitamin K_1 if given in excessive dosage, may make the patient unresponsive for several days or weeks to subsequent warfarin therapy and probably should not be used in patients with minor hemorrhage in whom anticoagulant therapy must be continued. (2,44)

Necrosis

Necrosis, potentially fatal necrosis and/or gangrene of skin or other tissues with subcutaneous infarction, vasculitis, and local thrombosis have occurred rarely in patients receiving warfarin. This reaction , which can occurs on the first exposure to the drug or during subsequent course of therapy, usually appears early (1-10 days) (58) after initiation of therapy. Tissue damage occurs principally at sites of fat tissue such as the abdomen, breasts, buttocks, and thighs. Limb ischemia, necrosis, and gangrene also have been reported in patients with heparin-induced thrombocytopenia when heparin treatment was discontinued and warfarin was started or continued. Most cases of warfarin-induced necrosis have been reported in women. The necrosis lesions generally begin as painful, erythematous, patchs on the skin that progress rapidly to dark, hemorrhagic areas. Necrosis may involve skin, soft tissue, and muscle; gangrene

and, frequently infection may follow. In severe cases, surgical debridgement of the affected tissue, skin grafting, or amputation may be necessary.

Patients with hereditary, familial, or clinical deficiencies of protein C or its cofactor, protein S, appear to have an increase risk of developing necrosis during warfarin therapy; however necrosis can occur in the absence of protein C deficiency. It has been suggested that necrotic reactions occur because initiation of warfarin therapy causes plasma concentrations of protein C to decrease more rapidly than plasma concentration of factor II, IX and X. Protein C generally inhibits coagulation by inactivating factor V and VIII and facilitating fibrinolysis; therefore, a rapid decline in plasma concentrations of protein C may result in a hypercoagulable state. If necrosis occurs during therapy with warfarin, decisions regarding diagnostic testing and therapy must be made on an individualized basis. If necrosis is suspected to be induced by warfarin and is not associated with heparin-induced thrombocytopenia, the drug should be discontinued, vitamin K or fresh frozen plasma should be administered, and heparin therapy should be considered both to treat the underlying thromboembolic disease and possibly prevent additional microvascular thrombosis. In addition, protein C concentrate or epoprostenol (prostacyclin) reportedly has been used with some success to treat warfarin-induced necrosis. It has been suggested that if warfarin anticoagulant therapy is discontinued before actual tissue necrosis occurs, it may be possible to limit the extent of tissue damage. In addition, initiation of anticoagulant therapy with heparin for 4-5 days before initiation of warfarin therapy or overlapping therapy with the two drugs for 5-6 days may minimize the risk of warfarin-induced necrosis. (58)

Warfarin should be used with caution in patients with heparin-induced thrombocytopenia and deep vein thrombosis because of the risk of venous limb ischemia, necrosis, and gangrene occurring when heparin treatment is discontinued and warfarin therapy started or continued in such patients. (59) Patients with hereditary, familial or clinical deficiencies of protein C or its cofactor, protein S, appear to have an increased risk of developing tissue necrosis during warfarin therapy and the drug should be used with caution in patients with known or suspected deficiency in protein C-mediated anticoagulant response. Warfarin or coumarin derivatives are generally contraindicated in patients with recent or completed eye,

brain or spinal cord surgery or prostectomy and in those with open ulcerative, traumatic, or surgical wounds. Major regional or lumbar block anesthesia, continuous tube drainage of the small intestines or any orifice and spinal puncture or other diagnostic or therapeutic procedures with potential for uncontrolled bleeding are also contraindications to the use of these drugs. Many minor dental and surgical procedures, however, may be performed if necessary in patients receiving an anticoagulant if meticulous surgical hemostasis is maintained. If anticoagulant therapy is administered prior to, during or immediately following minor dental or surgical procedures, minimal anticoagulation should be maintained. Some clinicians recommend that for minor dental or surgical procedures the INR should be maintained at less than 1.5. When emergency surgery is necessary in patients with warfarin therapy, blood coagulation can be returned to normal by administration of fresh frozen plasma. (2)

Warfarin is considered contraindicated during pregnancy, but the drug has been used in the certain pregnant women (those with prosthetic heart valves) considered at increased risk for thrombosis. Fetal or neonatal hemorrhage and intrauterine death have occurred, even when maternal PT values were within the generally accepted therapeutic range. Hypoplastic nasal structures and other abnormalities consistent with a diagnosis of chondrodysplasia punctata have occurred rarely in children whose mothers received warfarin or coumarin derivatives during the first trimester of pregnancy. (60) CNS abnormality also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy.

Ventral midline dysplasia, characterized by optic atrophy and eye abnormalities have been observed. Mental retardation, blindness, and other CNS abnormalities have been reported in association with second- and third- trimester exposure to warfarin. Other teratogenic effects reported rarely following in utero exposure to the drug include urinary tract abnormalities (single kidney), asplenia, anencephaly, spinal bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly. Spontaneous abortion and stillbirth are known to occur and the use of warfarin is

associated with a high risk of fetal mortality. Low birth weight and growth retardation also have been reported. If a woman becomes pregnant while receiving warfarin or coumadin derivatives, she should be informed of the potential risk to the fetus. Despite the risk of these drugs to the fetus, these agents have been used in pregnant woman with prosthetic heart valves at an increased risk for valve thrombosis. The need for anticoagulant therapy must be critically evaluated in pregnant woman and the risk of not administering the drug must be carefully weighted against the possible risks to both the mother and fetus. As no prospective, controlled clinical trials have been performed in pregnant women with prosthetic mechanical heart valves, optimal antithrombotic therapy remains to be established.

The risk of valve thrombosis in pregnant women with prosthetic mechanical heart valves appears to be lowest with the use of oral anticoagulants. Heparin is considered safer for the fetus than warfarin but has been associated with an increased maternal risk of valve thrombosis, death and major bleeding complications compared with oral anticoagulant therapy. The decision whether to use heparin during the first trimester or continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner of the risks associated with available anticoagulant therapies. If anticoagulant therapy is required in pregnant women, especially during the first trimester, most clinicians recommend that heparin be used since it dose not cross the placenta. (60-61) In pregnant women at high risk (history of thromboembolism, first-generation mechanical mitral valve) for valve thrombosis, some clinicians recommended continuous IV infusion of heparin or subcutaneous adjusted-dose heparin therapy during the first trimester (particularly between weeks 6 through 12) followed by conversion to adjusted-dose warfarin therapy (target INR of 2.5-3.5) until the patient is close to term (36 weeks or middle of the third trimester). Low-dose aspirin (80 mg) (60) may used in conjunction with anticoagulant therapy to further reduce the incidence of valvular thrombosis, although such combination therapy increases the risk of hemorrhage. Pregnant women at low risk of valve thrombosis (no history of thromboembolism, newer prosthetic mechanical valves) may receive adjusted-dose subcutaneous heparin therapy throughout pregnancy.

Some clinicians suggest that pregnant women close to term who have prosthetic mechanical heart valves receiving oral anticoagulation should be transferred

to subcutaneous adjusted-dose heparin in order to avoid bleeding complications in the neonate secondary to the trauma of delivery. Should labor begin before successful transfer from oral anticoagulation to heparin, some clinicians suggest that cesarean section be performed. In the absence of appreciable bleeding, combined therapy with heparin and warfarin may be resumed 4-6 hours after delivery. For lactation, neonate are particularly sensitive to warfarin as a result of vitamin K deficiency. The drug should be used with caution in nursing women, and nursing infants should be carefully observed for evidence of bleeding. (58)

E. Pharmacokinetics of warfarin:

Warfarin sodium is well absorbed from the gastrointestinal tract (GI tract). Absorption of the drug is dissolution-rate controlled. Presence of food in GI tract decreases the rate, but not the extent, of absorption. Warfarin is usually detectable in plasma within 1 hour following oral administration, and peak plasma concentration of the drugs are usually attained within 1-12 hours. However, plasma concentration of warfarin is not necessary related to antithrombogenic effects and is not a useful determinant of anticoagulant dosage requirement. Warfarin is 97.4-99.0% bound to plasma proteins, primarily albumin. Uptake of drug by erythrocytes is variable. The drug is distributed to liver, lungs, spleen, and kidneys. Warfarin crosses placenta, and fetal plasma drug concentrations may be equal to maternal plasma concentrations. Based on a one compartment model and assuming complete bioavailability, the estimated volumes of distribution for S- and R- isomer are similar. Warfarin is almost 100% hydroxylated by hepatic cytochrome P-450 (microsomal) enzymes to inactive metabolites. The cytochrome P-450 isoenzymes involved in warfarin metabolism include CYP2C9, CYP2D6, CYP2C8, CYP2C18, CYP1A2, and CYP3A4. S-isomer is metabolized principally by cytochrome P-450 isoenzyme CYP2C9 to the inactive metabolite 7-hydroxywarfarin. R-isomer is metabolized by CYP1A2 and CYP3A4 isoenzymes to diastereoisomeric alcohols, which have some anticoagulant activity but considerably less than the parent compound. The CYP2C9 isoenzymes is likely to be the principal hepatic cytochrome P-450 isoenzyme that modulates the in-vivo anticoagulant activity of warfarin. Warfarin is excreted in bile as inactive metabolites, reabsorbed, and excreted in urine. (4,57) Patients with CYP2C9 enzyme activity

deficiency may require a lower warfarin dose or more frequent monitoring and may be at high risk for bleeding episodes. (62-63)

Table 3. Metabolism pathway of warfarin

Isomer	% of metabolism	Cytochrome	Metabolites
R	60% oxidation	CYP1A2	R-6-OH-warfarin
			R-7-OH-warfarin
			R-8-OH-warfarin
		CYP3A4	R-10-OH-warfarin
			R-4-OH-warfarin
	40% reduction	-	RS-alcohol
			RR-alcohol
S	90% oxidation	CYP2C9	S-6-OH-warfarin
			S-7-OH-warfarin
		CYP3A4	S-10-OH-warfarin
			S-4-OH-warfarin
	10% reduction	-	SS-alcohol
			SR-alcohol

F. Drug interaction

Multiple pathways exist for interference with warfarin, and interactions may lead to either hemorrhage or thrombotic episodes by increasing or reducing this agent's effect. Therefore, close monitoring of therapy and knowledge of potential interactions of drugs or herbs with warfarin are extremely important.

Drugs may increase patient's sensitivity to warfarin by

- decreasing intestinal synthesis or absorption of vitamin K
- affecting distribution or metabolism of vitamin K
- decreasing the rate of anticoagulant metabolism by competing for sites of metabolism
- inhibiting the function or synthesis of metabolic enzymes

- decreasing synthesis and/or increasing catabolism of functional blood coagulation factors II, VII, IX, X
- interfering with other components of normal hemostasis such as platelet function or fibrinolysis.
- competitively or noncompetitively interfering with protein binding of warfarin producing increased concentrations of unbound anticoagulant and potentiation of anticoagulant effects.

Certain drugs may decrease patient's response to warfarin by decreasing absorption and increasing the rate of metabolism by enzyme induction. Because S-isomer of warfarin is about 2-5 times more potent than R-isomer, drugs that preferentially alter (increase or decrease) the metabolism of S-isomer are more likely to be associated with alteration in INR. Vitamin K_1 (phytonadione) intake (500 mcg, RDA 70-100 mcg/day or 1 mcg/kg/day) (45) may causes a decrease in INR because vitamin K_1 acts through the warfarin-insensitive reductase reaction by generating the active hydroquinone cofactor shown in Figure 4. (4,43) The following drugs, vitamins, minerals and herbal products reportedly may increase or decrease patient response to warfarin. (4,9,64-69)

Table 4. Drug interaction

Pharmacokinetic	**Pharmacodynamic**
Increase warfarin level	**Increase antithrombotic effect**
Amiodarone (S and R –isomer)	Aspirin
SMZ-TMP (S-isomer)	NSAIDs: fenoprofen, indomethacin, ibuprofen, ketoprofen,medclofenamate, naproxen,piroxicam, sulindac, tolmetin,diclofenac
Metronidazole (S-isomer)	Ticlopidine/clopidogrel
Phenylbutazone (S-isomer)	Moxolactam/cefoperazone
Sulfinpyrazone (S-isomer)	High dose penicillin
Disulfiram (S-isomer)	Heparin
Cimetidine (R-isomer)	L-thyroxine/thyroid hormones
Omeprazole (R-isomer)	Long-term alcohol abuse. Occasional consumption of low to moderate amounts of ethanol (41 to 54 g/day) dose not appear to affect warfarin anticoagulation. The effect of chronic ingestion of large amounts of ethanol is less clear. More than 250 g/day of ethanol for over 3 months has been shown to prolong the half-life of warfarin, but had no effect on INR. The effect of short-term consumption of large amount of ethanol is unknown.
Clofibrate/gemfibrozil	$2^{nd}/3^{rd}$ generation cephalosporin
Azole antifungal: fluconazole, Itraconozole, ketoconazole, miconazole	Vitamin K deficiency (poor intake)

Table 4. Drug interaction (Continued)

Pharmacokinetic	Pharmacodynamic
Increase warfarin level	**Increase antithrombotic effect**
Macrolide antibiotic: Azithromycin, erythromycin, clarithromycin	Alpha-tocopheral in large doses
HMG-CoA reductase inhibitors	
Decrease warfarin level	**Decrease antithrombotic effect**
Sucralfate	Estrogen
Chronic alcohol ingestion	Multivitamins or food supplements
Carbamazepine (onset 10-35 days)	
Phenobarbital (onset 7-30 days)	
Phenytoin	
Griseofulvin (onset 60 days)	
Rifampin/rifabutin (onset < 7 days)	
Dicloxacillin/cloxacillin/nafcillin (onset < 7days)	

Table 5. Herbal and vitamins interaction

Herbal products	Interaction
Cinchona (*Chincona spp*.), source of quinine	Potentiated anticoagulant action of warfarin
Coenzyme Q10, also known as ubiquinone	Reduced INR (compound is structurally similar to vitamin K)
Danshen (*Salvia miltiorrhiza*), also known as tan seng	Increased INR and prolonged PT/PTT (i.e., altered pharmacokinetics) by reducing elimination of warfarin; reduced platelet aggregation and TXA formation
Devil's claw (*Harpagaphytum procumbens*)	Increased action of warfarin (by unknown of mechanism); cause purpura
Dong quai (*Angelica sinensis*)	Active ingredient (ferulic acid) inhibits PAF; herb contains coumarins; increased risk of bleeding because of reduced platelet aggregation ; increase INR, leading to widespread bruising
Garlic (*Allium sativum*), fresh or commercially pressed, in large amounts	Increase risk of bleeding by reduced platelet aggregation; increased INR and reduced TXA production; reports of bleeding (postoperative bleeding and spontaneous spinal epidural hematoma reported with garlic alone); may increase hypoprothrombinemia

Table 5. Herbal and vitamins interaction (Continued)

Herbal products	Interaction
Ginkgo (*Ginkgo biloba*)	Increase risk of bleeding by reduced platelet aggregation; ginkolides and terpinoids inhibit PAF; intracerebral hemorrhage reported in patients taking ASA with or without warfarin
Ginseng	Altered INR (both increase and decrease have been reported) by unknown mechanism; may increase risk of bleeding by reduced platelet aggregation ; may inhibit PAF and conversion of fibrin to fibrinogen; may induce CYP3A4 liver enzymes (and thereby increase warfarin metabolism)
Green tea and herbal teas (made with tonka beans melilot, or woodruff)	Reduced INR because of high vitamin K content; teas contain natural coumarins
Papaya (*Carica papaya*), source of papain	Increase INR
St John's wort (*Hypericum perforatum*)	Reduced INR by inducing CYP3A4 (and thereby increasing warfarin metabolism
Bromelain*, a proteolytic enzyme found in pineapple	May potentiate anticoagulant action of warfarin
Cayenne* (*Capsicum spp*.)	May potentiate anticoagulant action of warfarin and antiplatelet aggregation

Table 5. Herbal and vitamins interaction (Continued)

Herbal products	Interaction
Echinacea	May increase INR by decreasing elimination of warfarin; may inhibit CYP3A4 (thereby decreasing warfarin metabolism)
Feverfew (*Tanacetum parthenium*)	May increase risk of bleeding by preventing platelet aggregation, reduces production of PG and TXA, inhibit phospholipase A2 and cyclooxgenase
Flaxseed (*Linum usitatissimum*), a source of mucilage	May reduce absorption of warfarin
Ginger (*Zingiber officinale*)	May increase risk of bleeding by antiplatelet aggregation
Iron,magnesium,zinc	Reduces warfarin absorption (by binding) separate administration by 2 hours (theoretical interaction)
Vitamin C	Reduces anticoagulant effect of warfarin (more than 10 times daily recommendation intake; 600mg/day)
Vitamin E	Increases anticoagulant effect of warfarin ; may inhibit oxidation of reduced vitamin K, antiplatelet effect (more than 10 times daily recommendation intake; 300IU)
Vitamin K	Reduces INR from observed study (500 mcg/day)

Table 5. Herbal and vitamins interaction (Continued)

Herbal products**	Interaction
Angelica root, licorice root, melilot, sweet cloer, sweet woodruff, tonka bean	Potentiate anticoagulant action of warfarin
Angelica root, arnica flower, celery, chamomile, danshen, dong quai, eleuthero (Siberian ginseng) root,fenugreek, feverfew, garlic, ginkgo, ginseng, horse chestnut, licorice root, passion flower herb, red clover, sweet clover,sweet woodruff, sweet clover	Potentiate anticoagulant action of warfarin

* Theoretical interaction (in vitro)

**Herbs and herbal products containing coumarin, coumarin derivatives or p-coumaric acid

Cigarette smoking dose not alter the pharmacokinetics of the warfarin enantionmers, as a result, no dosage adjustment is required. (68)

Chronic ingestion of large doses of acetaminophen has been reported to potentiate the effects of warfarin although conflicting data exists and the clinical importance of such interaction has been questioned. The results of an observational study in patients who are stabilized on warfarin therapy indicate an association between ingestion even low to moderate doses of acetaminophen (9 or more tablets weekly) and excessively high INR. (4,58)

The anticoagulant response to warfarin is influenced by pharmacokinetic factors, including drug interactions that affect the absorption, metabolic clearance of warfarin or drug-food interactions. Major problems such as bleeding or thromboembolic complications may be caused by above problems. (4-12) These adverse outcomes have a negative impact on the quality of life of patients, therefore

warfarin therapy requires careful monitoring. (13-14,16) Unlike other drugs with narrow margin of safety, optimum warfarin dosing can not be determined by a simple serum concentration. The drug is monitored indirectly by measuring its pharmacodynamic effects on the body's hemostatic system using the international normalized ratio (INR). The hemostatic system is complex and is effected by numerous variables at many steps in the clotting process. Therefore, warfarin is associated with a high frequency of complications. (22)

G. Role of pharmacist in anticoagulation services

A number of studies have documented that pharmacists' interventions help achieve optimum anticoagulation control and reduce the rate of adverse effects. (15-20) Gray et al in 1985 (18) performed a retrospective controlled trial to investigate the effects of pharmacist-managed anticoagulation clinic (AC) compared with usual medical care (control) on anticoagulation control, hospitalization from recurrent thromboembolism or hemorrhage and the cost-benefit of the clinic. There were 26 patients who were referred to AC based on judgment of physicians while 26 patients not attending AC were randomly selected as a control group. Interventions included dosage adjustment and patient education on importance of compliance, drug-drug and drug-diet interactions and self-monitoring for hemorrhage. At the end of the study, anticoagulation control in the AC group was significantly superior to that of the control group. In the AC group, prothrombin time ratios outside the therapeutic range were reduced from approximately 36 % to 15% in the pre-AC and post-AC periods, respectively. No significant change of such ratio was observed in the control group. In the AC group, hospitalization rate from anticoagulant-induced hemorrhage or thromboembolism was reduced from 38.5% to 3.8% in the pre-AC and post-AC periods, respectively. No significant change in hospitalization rate was observed in the control group. The cost-benefit analysis revealed a net saving of $ 860.88 per patient-year from the prevention of hospitalization in the AC group compared to the control group.

Cortelazzo et al in 1993 (15) assessed the quality of an AC by evaluating the incidence of hemostatic complications in 271 patients on oral anticoagulation for mechanical heart valve prosthesis before and after their enrollment in the AC. After a

median followed-up period of 34 months, the incidences of hemorrhagic events and thrombosis were significantly lower after the enrollment into the AC compared to before the enrollment period (1.0 vs 4.9%/patient-year for hemorrhagic events and 0.6 vs 6.6%/patient-year for thrombosis). The authors postulated that better dose regulation of warfarin, continuous patient education and early identification of clinical conditions potentially at risk for thrombosis and hemorrhage may contribute to these improved outcomes. However lack of a parallel control group and partly retrospective nature of the study could partially weaken the overall conclusions.

Wilt et al in 1995 (16) performed a retrospective chart review to assess differences in the clinical outcomes between patients enrolled in an AC and patients receiving usual medical care. Interventions included dosage adjustment and continuous patient education on importance of compliance, drug-drug and drug-diet interactions and self-monitoring for hemorrhage or thromboembolism. Outcomes of interest included the number of thromboembolic and hemorrhagic events, unplanned clinic visits, emergency room visits and hospital admissions. Cost of hospital admissions, emergency room visits and participation in the AC were analyzed. During 28 person-years of treatment, control subjects experienced 12 thromboembolic events, 2 minor and 5 major hemorrhagic events. On the contrary, the AC group reported 2 minor bleeding episodes during 60 person-years of treatment. A potential cost avoidance of $4,073 per person-year of follow-up was reported if the control group had been enrolled in the AC.

Lee et al in 1996 (20) conducted a non-randomized prospective trial using matched controls to determine whether an AC would reduce warfarin-related readmission within 90 days after patients were discharged with warfarin. Pharmacists' interventions in the AC included patient counseling, monitoring of changes in medications/diet, adverse effects and drug interaction screening. Sixty eight patients were enrolled in AC group while matched controls of the same size were randomly selected. At 90 days, the rates of warfarin-related readmission in the AC group were less than that of the control group (9% vs 41.7%; $p = 0.01$). While this result showed that patients under the care of the AC had fewer warfarin-related hospital readmissions than did the control group, however, small sample size and short follow-up period were limitations of this study.

Chiquette et al (17) reviewed the inpatient and outpatient medical records to assess the impact of an AC compared to usual medical care (UMC) on clinical outcomes. There were 142 newly anticoagulated patients in the UMC group while 176 patients were enrolled in the AC group. Outcomes of interest were anticoagulation control, hemorrhagic and thromboembolic events and difference in the cost of hospitalizations and emergency department visits. Among patients who received lower range anticoagulation (INR = 2.0-3.0), patients in the AC group had fewer INR greater than 5.0 (7% vs 14.7%), spent more time in therapeutic range; 2.0-3.0 (40% vs 37%) and spent less time at an INR greater than 5 (3.5% vs 9.8%). Among patients who received higher range anticoagulation (2.5-4.5), patients in the AC group had more INRs within range (50.4% vs 35%), had fewer INRs less than 2 (13% vs 23.8%), and spent more time within range (64% vs 51%). The rates of thromboembolic and hemorrhagic complications were significantly lower in the AC group. There was also a trend toward a lower mortality rate in the AC group. Lower rates of warfarin-related admissions and emergency room visits were observed and calculated into an annual savings in healthcare costs of $29,972 per 100 patients. The non-randomized nature of the study was a limitation of this study.

Dager et al (19) conducted a non-randomized prospective study using historical matched controls to compare the effect of daily consultation by a team of hospital pharmacists on the accuracy and rapidity of optimizing warfarin therapy to usual medical care (UMC). Sixty consecutive patients were enrolled in the study group while 60 historical patients with matched indications were included in the control group. Outcomes of interest were time required to achieve a stable INR within target range, frequency of excessive anticoagulation, reduction in drug interactions and length of hospital stay. At the end of the study, the study group had a shorter hospital stay than the control group (9.5 $\pm$ 5.6 vs 6.8 $\pm$ 4.4 days; 95% CI 1.0-3.0, p=0.009). The rate of achieving target INRs were significantly higher in the study group than the control group. Also, the incidence of major drug interactions was significantly lower in the study group. The authors concluded that daily consultation by pharmacists significantly decreased the length of hospital stay, the number of patients with excessive anticoagulation therapy and incidence of major drug interactions with warfarin.

Tang et al (13) conducted a study to evaluate patient's knowledge of warfarin and its relationship to anticoagulation control in 122 Chinese patients. Their knowledge of warfarin therapy and adherence to medical advice were tested by 9 questions (Table 6). The maximum score was 1.0 which was based on the total points divided by the highest possible points. Overall, patient's warfarin knowledge was poor (mean score of 0.48±0.18). The score did not differ between men and women. Participants generally knew the colors of their warfarin tablets (Q1a) and took them regularly (Q4). They almost always informed their physicians and dentists of their warfarin therapy (Q9). Only 40-45% of patients knew the strengths of their warfarin tablets (Q1b), the reason for taking warfarin (Q2), and its effect on the body (Q3). Their deficiency in knowledge was even more obvious with respect to the possible consequences of under or over-anticoagulation (Q6 and 7), drugs or medicated oils that may interact with warfarin (Q8), and management of a missed dose (Q5). There was an inverse relationship between age and the knowledge score of the patients ($r = -0.43$; $p<0.001$). There was a positive association between the duration of warfarin therapy and patients' knowledge ($r = 0.18$; $p=0.044$). About half of the patients had read the booklet before and their knowledge of warfarin therapy was better than those who had not read the booklet (0.53 ± 0.20 vs 0.42 ± 0.20; $p<0.001$). In the latter group, illiteracy was the main reason for not reading the booklet. There was a positive correlation between patients' knowledge of warfarin therapy and number of INR values that were within the target range ($r = 0.20$; $p=0.024$). This study emphasizes the importance of patient education on warfarin therapy.

Table 6. Questions designed to test patients' knowledge of warfarin therapy and adherence to medical advice.

Questions designed to test patients' knowledge of warfarin therapy and adherence to medical advice (13)
Q1. What is the (a) and (b) strength of your warfarin tablet(s)?
Q2. Do you know the indication for your warfarin therapy?
Q3. Do you know what warfarin does to your body?
Q4. Do you take your warfarin tablet regularly (say in the past 1 week)?
Q5. What will you do if you missed dose?
Q6. Do you know what may happen with under-anticoagulation?
Q7. Do you know what may happen with over-anticoagulation?
Q8. Do you know what drugs or medicated oils may interact with warfarin?
Q9. When you visit a doctor or dentist, will you always tell them of your warfarin therapy?

H. Role of pharmacists in anticoagulation services in Thailand

Tipawan et al (71) performed a prospective, randomized, controlled study to determine the impact of warfarin monitoring service by pharmacist on the achievement of optimal anticoagulation intensity (INR between 2.0-2.5 according to Rajvithi Hospital's recommendation) and episodes of TE or bleeding in patients with mechanical heart valve. There were 74 and 71 patients in the study and control groups, respectively. The follow-up period was 3 consecutive clinic visits (1 year). Interventions included patient education, detection of drug-related problems and providing recommendation on dosage changes to physicians. The results showed that the number of patients with optimal INR of 2.0-2.5 were not statistically different in both groups in each of the follow-up visits (18.9, 23.6, 19.4% vs 11.3, 22.2, 28.3 in the study and control groups, respectively). More than 50% of patients in both groups had sub-optimal INRs. There were 2 episodes of TIA in the study group and none in control group. Minor bleeding in the study group were greater than the control group (4,5,12 and 1,1,1 at visit 1,2 and 3 in the study and control groups, respectively). Drug-related problems, non-compliance, drug interactions and medication error were

identified in the study group. This study was unable to show significant impact of pharmacist interventions on the anticoagulation control, most likely, due to short follow-up time, small sample size and therapeutic range that was too narrow (2.0-2.5 instead of 2.0-3.0). Nonetheless, the study still showed the ability of a clinical pharmacist in identifying drug-related problems as well as providing proper education for patients receiving warfarin therapy.

Umporn et al (26) evaluated the impact of pharmacist's interventions on the knowledge of warfarin therapy in 179 patients with mechanical heart valve pre- and post-warfarin education program. The satisfaction of health care team and drug related problems were also assessed. Patients' knowledge regarding warfarin therapy was tested by 10 questions (Appendix A). At the end of the study, patients scored higher in the post-education than the pre- education programs (9.25 vs 2.34; $p<0.001$). Twenty-five (80.65%) of 35 drug-related problems were solved by the clinical pharmacist. Physicians and nurses were satisfied with the service of the clinical pharmacist and rated the quality of the service as "very good". However, the impact of such service on anticoagulation control and rates of warfarin complications has not been evaluated.

Suparat et al (72) performed a prospective study to compare the impact of pharmaceutical care in anticoagulation control, drug-related problems and dosage adjustment between pre- and post-pharmaceutical care periods. One-hundred and sixty-seven patients were enrolled in the study group while two-hundred and seventy-five patients' medical charts were used as a historical control (pre-pharmaceutical care). The majority of patients received warfarin therapy due to rheumatic heart disease and atrial fibrillation while patients with mechanical valve were a minority population. The primary outcome was the achievement of "stable INR" which was characterized by having INR within range for 3 consecutive visits. After 5 months of follow-up period, more patients in the study group had stable INR than the control group (31.74 vs 3.27%; $p<0.05$). There were 12 major bleeding events in the pre-pharmaceutical care while none occurred in the post-pharmaceutical care period ($p<0.05$). Despite having favorable results, this study had several limitations. First, the outcome used in this study (stable INR) is not the standard outcome in measuring anticoagulation control and has not been shown to correlate with long-term clinical outcomes. Second, the follow-up period of the study was relatively short. Thirdly,

there are some statistical flaws in the data analysis. Nonetheless, this study showed that pharmacist interventions help increase the achievement rate of INR goals while minimizing hemorrhagic complications from warfarin therapy.

In conclusion, anticoagulation clinic has been proved to increase optimal anticoagulation control, reduce bleeding /TE complications and reduce total cost of care in the US and European countries. In Thailand, there were a few studies evaluating the impact of anticoagulation clinic on anticoagulation control and bleeding/TE complications, especially in patients with mechanical heart valve who need life-long anticoagulation therapy. These studies have limitations and are still inconclusive. As a result, this study aimed to evaluate whether education and counseling by clinical pharmacists can improve anticoagulation control while minimize complications from warfarin in Thai patients with mechanical heart valve.

CHAPTER 3
MATERIALS AND METHODS

Materials

1. Patient profile (Appendix C)
2. Drug interaction screening (Appendix D)
3. Outcomes Assessment (Appendix E)

Methods

1. Study Design

This study was designed as a historical cohort study comparing anticoagulation control, anticoagulation variability, rate of thromboembolic events and incidence of major and minor bleedings between pre-and post-implementation of the Warfarin Project periods. Data from patients during the pre-implementation period (prior to March 2002) were retrospectively collected and served as our control. Data during the post-implementation period (March 2002 to June 2003) of the same patients were prospectively collected. The follow-up time for pre- and post-implementation periods were equal and each period was no less than 6-month in duration.

2. Ethical approval

The study protocol was approved by the Ethical Committee of the Faculty of Medicine Siriraj Hospital.

3. Population

Patients with mechanical heart valve attending CVT clinic at Siriraj Hospital participating in the Warfarin Project served as our pool population. These patients had one or more of the following conditions.

3.1. Sub- or supra-therapeutic INRs

3.2. Without prior education on warfarin therapy by clinical pharmacists or other healthcare professionals

3.3 Voluntary referral from his/her primary care provider

Medical records of these patients were reviewed. Patients who met the following inclusion criteria in the absence of exclusion criteria were enrolled into the study.

Inclusion criteria

1. Attending the anticoagulation clinic during March-December, 2002
2. Receiving warfarin therapy prior to the study period (prior to March 2002) for at least 6 months
3. Follow-up period (after March 2002) with clinical pharmacists of CVT clinic was no less than 6 months (maximum 15 months)

Exclusion criteria

1. Patients with follow-up period less than 6 months
2. Patients with pre-study period lasting less than 6 months
3. Patients who were lost to follow-up or died from causes other than thromboembolic events or hemorrhagic complications of warfarin

4. Number of studied patients

We estimated that post-implementation of the Warfarin project would lead to an improvement in the rate of anticoagulation control and expected to detect a 50% decrease in INRs outside therapeutic range compared to pre-intervention period. We estimated that INRs in the pre-implementation period were outside therapeutic range for at least 40% of the time. Therefore we calculated a sample size that allowed us to detect a 50% decrease in INR outside therapeutic range using the following formula (73)

$$Np = \frac{[Z_\alpha + Z_\beta]^2 f}{d^2}$$

where Np = number of paired observation

d = difference in the proportion of successes

d = P_I-P_C

P_I = probability in intervention group

P_C = probability in control group

f = discordant rate

Z_α = the Z value corresponding to the 2-tailed alpha (α =0.10)

Z_β = the Z value corresponding to the 1-tailed beta (β =0.10)

$$Np = \frac{[1.96+1.282]^2 (0.5)}{(0.4-0.2)^2} = 132$$

A dropout rate of 13% was expected. (71) Accordingly, the lowest number of patients needed in the analysis to show a 50% difference in the anticoagulation control between pre- and post- intervention periods was 150.

5. Outcome measures

5.1 Anticoagulation control

Although guidelines from western countries recommend higher intensity of anticoagulation therapy in patients with mechanical heart valve, an INR in the range of 2-3 was selected as the therapeutic range in this study. Studies conducted in Thailand (74-75) and other Asian countries (76-79) suggest that this range of INR (1.9-3.0) may be comparably effective in the prevention of thromboembolic complications in Asian population. In this study, anticoagulation control both pre- and post-interventions periods was expressed in two ways including percentage of INRs within therapeutic range and anticoagulation variability. (80) All pre- and post-intervention INRs of each patient were collected and calculated as % of INR in the therapeutic range for each period. For anticoagulation variability, patients were divided into 2 groups based on the percentage of INR outside the target range. Those with therapeutic INR less than or equal 70% and more than 70% of the time were classified as high- and low-variability groups. Anticoagulation variability has

been shown to correlate with morbidity and mortality in patients with prosthetic heart valves.(80)

5.2 Thromboembolic events

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

5.2.1 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. (15,17,23,25,74,81)

5.2.2 Transient ischemic attack (TIA) is defined as a sudden neurological deficit that persists for less than or equal to 24 hours. (17,74)

5.2.3 Valve thrombosis is defined as the deposition of thrombus on the valve, documented by two-dimensional echocardiography and resulting in hemodynamic dysfunction.

5.2.4 Peripheral or systemic embolism is defined as the occurrence of acute ischemia caused by an arterial embolism documented by angiography or surgery. (15,23)

For the purpose of data analysis, these events were collected and expressed individually and in combination as number of events per 100 patient-year. To illustrate the calculation, total patient-year of observation was obtained by simple addition of follow-up time contributed by each subject. The number of event of interest was then multiplied by 100 and divided by the total follow-up time. The result can then be expressed as case or event per 100 patient-year. (80)

5.3 Hemorrhagic complications

Hemorrhagic complications are divided into two parts including major and minor hemorrhage. The definition of each event is described below.

5.3.1. Major hemorrhage

5.3.1.1 Decrease in hemoglobin of greater than or equal to 2.0 g/dL (15)

5.3.1.2 Either death or morbidity or leading to admission (21-22,25,70,74)

5.3.1.3 Need blood transfusion at least 2 units (range 1-3 units of blood transfusion) (17,21-22)

5.3.1.4 Gross hematuria, major hematoma, upper gastrointestinal bleeding (22)

5.3.2. Minor hemorrhage

5.3.2.1 All type of bleeding; increased bruising, bleeding gums, bleeding from minor trauma site, epistaxis (22-23,33,70)

5.3.2.2 Decreasing of packed cell volume 4 hematocrit unit (range 3-4 hematocrit unit) even if no bleeding (17,22,70)

Similar to thromboembolic events, these hemorrhagic events were collected and expressed individually and in combination as number of events per 100 patient-year.

5.4. Drug-related problems

In this study, drug-related problems of interest were drug interactions and non-compliance. Literatures and database of warfarin drug-interactions were reviewed and used a source for evaluating drug interactions for this study. (64-68) The occurrence of drug interactions were collected and reported to the patient's care provider. Non-compliance was evaluated at each visit by patient interview. The patient's care provider was notified when non-compliance was detected. Clinical pharmacists provided education and other assisting devices such as pill calendar, pill box and other methods of reminder as appropriate.

5.5. Non-compliance

This term was defined as failure to take a medication as prescribed.

6. Criteria for termination

Patients were terminated from the study according to the following criteria

- Patient who had lost to follow-up or passed away from causes other than thromboembolic events or hemorrhagic complication of warfarin.
- Patient died during follow-up period from causes other than thromboembolic events or hemorrhagic complications of warfarin.
- Patient desired to withdraw from the Warfarin Project.

7. Step of investigation

There were two clinical pharmacists (one of which was the investigator) providing interventions to patients. Standard interventions by clinical pharmacists of the CVT clinic were described in Appendix F. The flow of the clinic was depicted in Appendix G and H

7.1 Medical records screening and selection

The medical records of the patients who met the inclusion criteria were reviewed.

7.2. Data collection

Information on all INR tests performed, doses and preparations of warfarin used in every visit were obtained. Reason (s) for any subsequent unscheduled physician visits or emergency room visits or hospitalizations were collected. If any of such reason was either hemorrhagic or thromboembolic event, data from hospital records including INR, length of hospitalization, medications received, blood and blood products; and all diagnostic procedures perform were collected. All thromboembolic events and hemorrhagic complications were reviewed by physicians (criteria shown in page 38-40). In addition, assessment of warfarin compliance, drug interactions and other drug-related problems were collected (Appendix E).

8. **Data analysis**

8.1 Patients' characteristics and drug-related problems were analyzed by descriptive statistics.

8.2 The anticoagulation controls of pre- and post-interventions were compared as follow.

8.2.1. For the percentage of time with INR in the therapeutic range, a paired-t test was performed.

8.2.2. For anticoagulation variability, McNemar's chi-square test was used to compare the proportion of patients with high- and low-variability in pre- and post-intervention periods.

8.2.3. Event rates such as bleeding or thromboembolism during pre- and post-intervention periods were reported as number of events per 100 patient-year and compared using Chi-square.

8.2.4. Non-compliance were reported as number of events and events per 100 patient-year

CHAPTER 4
RESULTS

I. Population characteristics

Three-hundred and ninety-five patients in the Warfarin Project served as our pool population. After reviewing medical records of these patients, one-hundred and eleven medical records (28.1%) were excluded. Twenty three patients were lost to follow up (5.8%), 75 patients were with incomplete history during pre-intervention period
(19.0%), 2 patients denied counseling (0.5%), 6 patients were referred back to local hospitals (1.5%), 2 patients were with only one INR value in 6 months (0.5%) and 3 patients died (0.8%). Causes of death in 2 patients were vehicle accident and heart failure, respectively. No cause of death was identified in the remaining deceased patient.

Finally, medical records of 284 patients who met the inclusion criteria were reviewed and included in the analysis. There were 124 males (43.7%) and 160 females (56.3%).The average (mean±SD) age and time of valve replacement were 49.75±12.43 years old, and 8.01±5.6 years, respectively. Figure 6 showed distribution of age. The total follow-up time was 23.28±6.08 months (range 11-30 months) which was equally divided into pre- and post-intervention periods. Based on this follow-up time, there was a total of 550 patient-year of follow-up in our study with 275 patient-year of follow-up for both pre- and post-intervention periods. Atrial fibrillation was the most common comorbidity in these patients (132 of 284 patients or 46.5%). For valve position, there were 77 cases of aortic position (27.1%), 143 cases of mitral valve position (50.4%), 59 cases of both aortic and mitral (20.8%) positions, one case of aortic, mitral and tricuspid positions (0.4%), three cases with mitral and tricuspid positions (1.1%). Figure 7 showed distribution of valve position. For valve models, there were 118 cases with monoleaflet valve (41.6%), 105 cases with bileaflet valve

(37%), 48 cases with caged ball valve (16.9%), 3 cases with a combination of bileaflet and monoleaflet valves (1.1%), 4 cases with monoleaflet and caged ball valves (1.5%), 1 case with a combination of bileaflet and caged ball valves (0.4%). There were 5 cases for which types of valve were not documented (1.8%). Figure 8 showed distribution of valve model. The demographic characteristics, underlying diseases, dosage of warfarin in pre- and post-intervention and concurrent drugs in patients with high risk of TE were presented in Table 7-10.

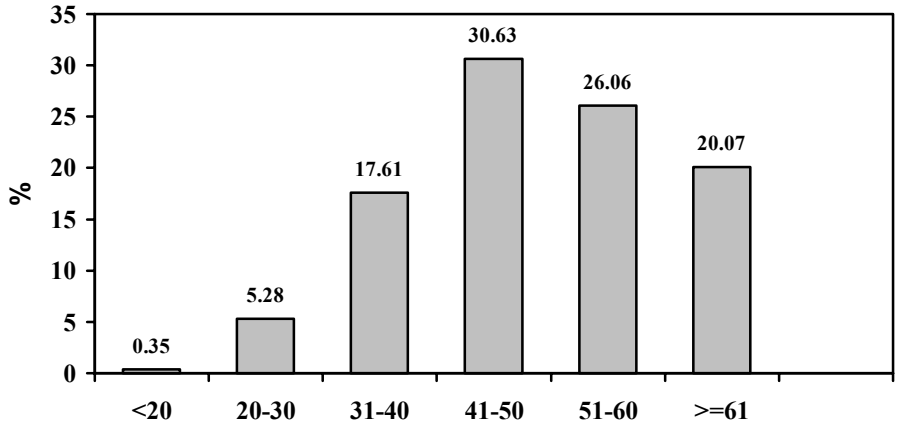
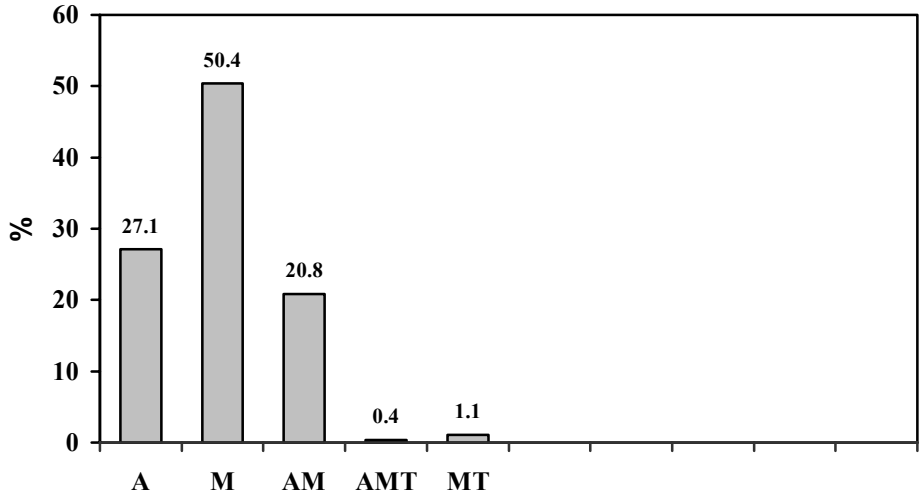
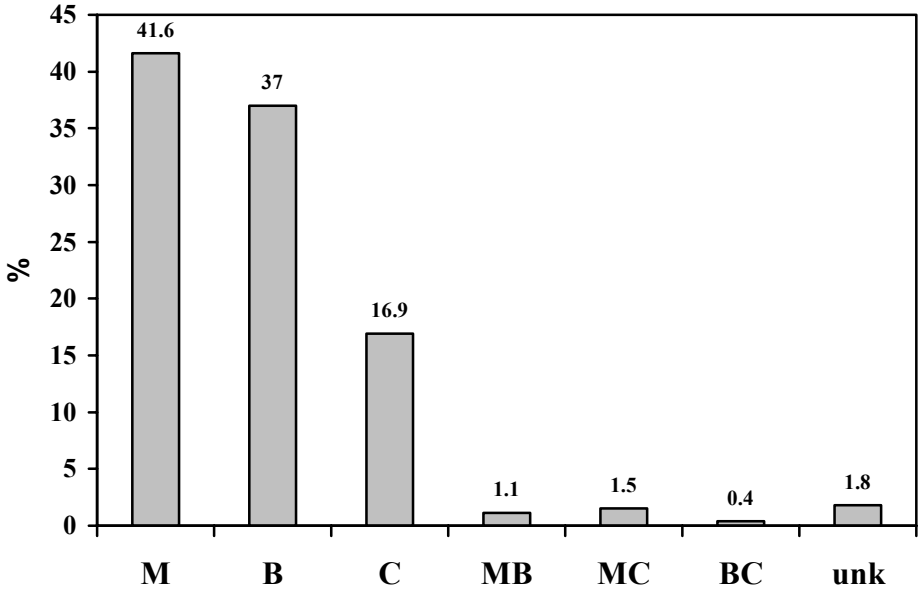


Figure 6. Distribution of age



A = aortic, M = Mitral, T = tricuspid

Figure 7. Distribution of position of valve replacement



M = Monoleaflet, B = Bileaflet, C = caged ball, unk = unknown

Figure 8. Distribution of valve model

Table 7. Characteristic of the patients

Characteristics	
Patients	284
Patient-years	550
Age (range 19-82 year)	
Mean± SD	49.75± 12.43
Range	19-82
Median	50.00
Mode	41*
AF	132(46.5%)
Sex: Male	124(43.7%)
Female	160(56.3%)
Valve position	
Aortic	77(27.1%)
Mitral	143(50.4%)
Aortic+mitral	59(20.8%)
Aortic+mitral+tricuspid	1(0.4%)
Tricuspid	1(0.4%)
Mitral+tricuspid	3(1.1%)
Valve model	
Bileaflet	105(37%)
Monoleaflet	118(41.6%)
Caged ball	48(16.9%)
Bileaflet+Monoleaflet	3(1.1%)
Monoleaflet+caged ball	4(1.5%)
Bileaflet+caged ball	1(0.4%)
Unknown	5(1.8%)
Time of valve replacement ± SD (year)	8.01± 5.6
Time of followed up ± SD (month)	11.64±3.04

* multiple mode exist. The smallest value is shown.

Table 8. Underlying diseases

Underlying disease*	Frequency
Anemia	1
Asthma	1
BPH	2
Bradycardia	1
Bradycardia with pacemaker	1
CA breast s/p radiation	1
CA cervic s/p surgery	1
Cataract	1
CHF	28
Chronic renal failure	3
Cirrhosis	1
Coronary artery disease	11
DM	19
Dyslipidemia	9
Gall stone	1
Gout	4
Hemolytic anemia	1
Hepatitis B	1
Hypertension	20
Hypothyroid	4
Left hemiparesis	2
LV dysfunction	1
Marfan syndrome	3
Migraine	1
Nasal polyp	1
Peptic ulcer	1
Psychosis	1
Pulmonary hypertension	1
Rheumatoid arthritis	2
SLE	1
TB	1
Tension headache	1
Thallassemia	1
Total	128

* 92 patients

Table 9. Dosage of warfarin (mg/week) in pre- and post-intervention periods

	Group	N	Mean	SD	P value
Warfarin	Pre-	284	24.12	9.7	0.195
	Post-	284	24.53	9.8	

Table 10. Concurrent drugs in patient with high risk of TE in pre- and post-intervention period

Drug	Dosage (mg)	Number of patient (%)	
		Pre-	Post-
ASA	60	14(4.9)	16(5.6)
ASA	300	1(0.3)	1(0.3)
Atorvastatin	20	0	1(0.3)
Dipyridamole	75	1(0.4)	2(0.7)
Gemfibrozil	300	2(0.7)	3(1.1)
Simvastatin	20	4(1.4)	7(2.5)

II. Anticoagulation control

There were 1,686 and 1,348 INRs measurements in pre- and post-intervention groups, respectively. The average (mean±SD) INR values were 2.35±0.79 and 2.35±0.89 in pre- and post-intervention groups, respectively. ($p = 0.803$) Figure 9 showed distribution of INR in both groups and Figure 10-11 showed scatter plot of INRs in pre- and post-intervention periods. The anticoagulation control based on the percentage of INR within therapeutic range (INR of 2.0-3.0) was significantly better in the post-intervention compared to pre-intervention periods (51.8% vs 46.7% in the post- and pre-intervention groups, respectively; $p = 0.016$). For anticoagulation variability, there were 19.4% and 29.2% of patients with low anticoagulation variability (INR in range for > 70% of the time) in pre- and post-intervention periods, respectively. (Table 11.) This change corresponds to approximately 50% improvement in anticoagulation variability ($p = 0.005$, $df = 1$, $\chi^2 = 7.755$)

Table 11. Distribution of patients based on intervention periods and anticoagulation variability

		Pre-intervention period	
Post- intervention period	High variability	Low variability	Total
High variability	168	33	201
Low variability	61	22	83
Total	229	55	284

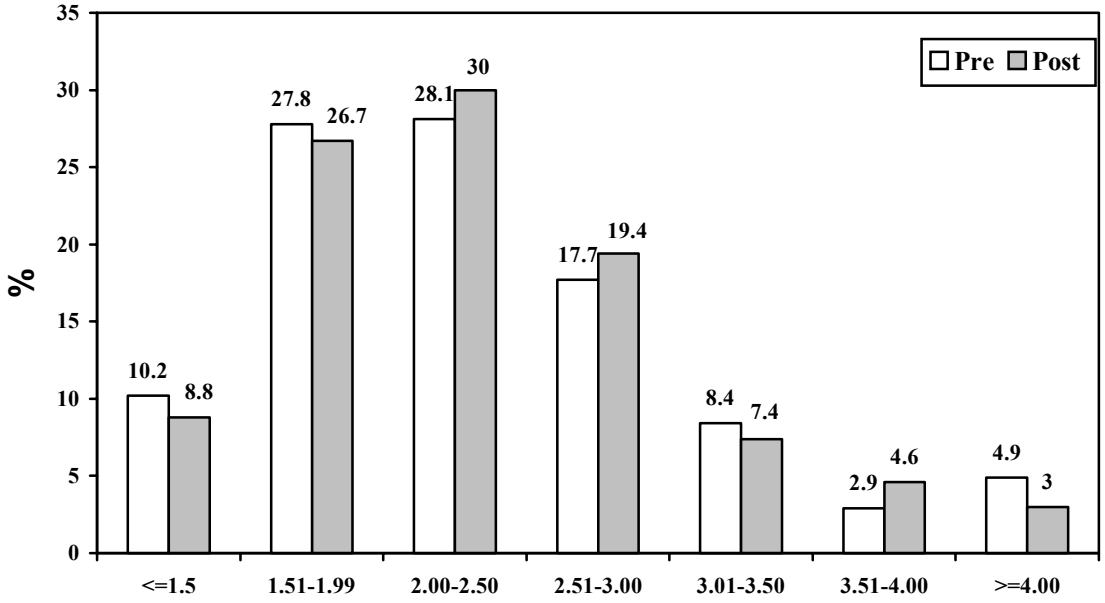


Figure 9. Distribution of INRs in both groups

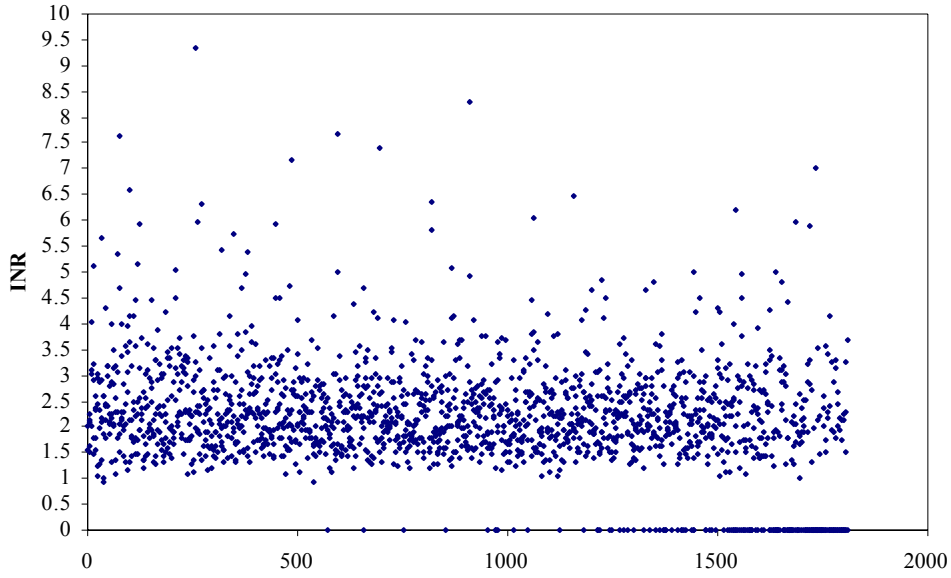


Figure 10. Scatter plot of INRs in pre-intervention period

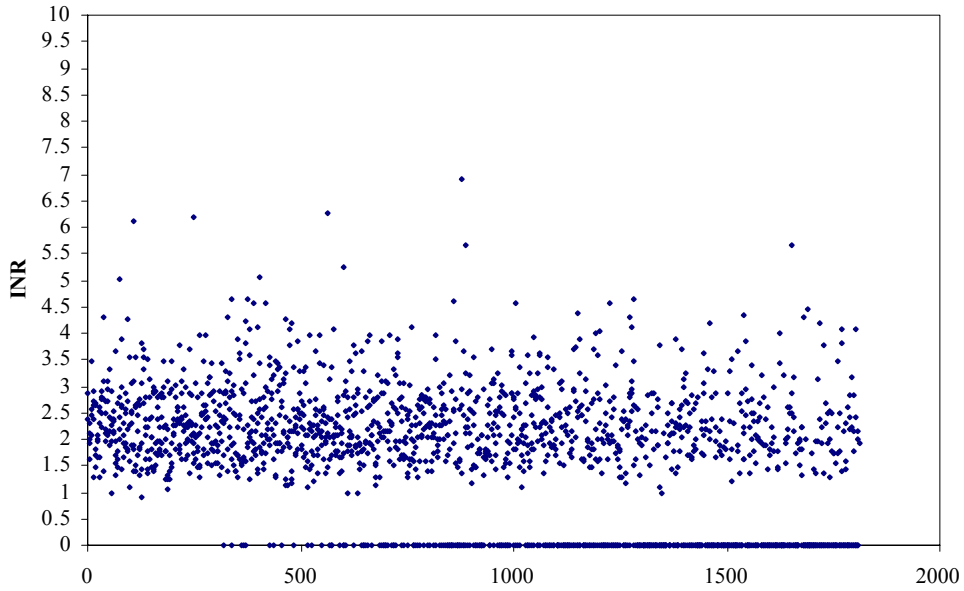


Figure 11. Scatter plot of INRs in post-intervention period

III. Hemorrhagic complications

1. Major bleeding

During the pre-intervention period, 6 major bleedings occurred in 5 patients. These events included 3 upper gastrointestinal bleedings (UGIB), 1 gross hematuria and 1 retroperitoneal hematoma. (Detail listed in Table 12.)

The first patient was a 71 years old male with Metronic Hall valve at aortic position. He experienced UGIB with INR at the time of the event was 6.49 with 27.5 mg/wk of warfarin. The second patient was a 66 years old male with Saint Jude valve at aortic position. He experienced two episodes of UGIB. In the first event, INR at the time of bleeding was 4.1 with 21 mg/wk of warfarin. The INR in the second event was not available because patient stopped warfarin days before admission. This patient had a long history of non-compliance and uses of unknown herbal medicine.

The third patient was a 24 years old woman with Medtronic Hall valve at both aortic and mitral positions. She experienced retroperitoneal hematoma with INR at admission of 2.35 with 43.75 mg/wk of warfarin. Four units of blood were used for transfusion. The forth patient was a 45 year old male with Starr-Edward valve at mitral position, AF and a history of alcohol abuse. He experienced gross hematuria with INR of 9.35 with 21 mg/wk of warfarin. The fifth patient was a 50 year old male with Medtronic Hall at mitral position and AF. He had hematuria with unknown INR on admission.

Based on this data, the incidence of major bleeding in this period is 2.18 event/100 patient-year.

During the post-intervention period, 6 major bleedings occurred in 6 patients. These events included 1 upper gastrointestinal bleeding (UGIB), 1 gross hematuria and 4 hematoma. (Detail listed in Table 13.)

The first patient was a 59 years old woman with Carbomedic valve at mitral position and AF. She experienced UGIB with unknown INR. The dosage of warfarin was 12 mg/week. No detail admission was available to us since she was admitted to Jaehom hospital in Lampang province. The second patient was a 50 years old male with Saint Jude valves at both aortic and mitral positions and AF who experienced

gross hematuria. The INR at admission was 2.11 with 35 mg/wk of warfarin. He was admitted for a total of 7 days and received five units of blood transfusion. The third patient was a 43 years old female with Carbomedic and Medtronic Hall valves in atrial and mitral positions and a history of alcohol abuse. The INR at admission was 1.5, however warfarin therapy was stopped previously for unknown period prior to admission. She received a weekly warfarin dose of 22.5 mg. The forth patient were a 51 years old female with Saint Jude valve in atrial position. She experienced major hematoma after receiving a course of Thai traditional massage. The INR at admission was 7.85 with 26.25 mg/wk of warfarin. The fifth patient was a 67 years old male with unknown type of valve in mitral position, hypothyroidism and bradycardia with pacemaker. He experienced major hematoma at unknown INR level. The sixth patient was a 31 years old female with Medtronic Hall valve in mitral position and atrial fibrillation. She experienced major hematoma with INR of 7.7 on admission with 35 mg/wk of warfarin.

Based on this data, the incidence of major bleeding in this period is 2.18 event/100 patient-year. However, with the exclusion of one patient whose cause of bleeding was trauma, the incidence of major bleeding is 1.81 event/100 patient-year. This represents a 17% reduction in major bleeding compared to the pre-intervention period. However, this difference did not reach statistical significance ($p = 1.0$).

Table 12.Data of patients experiencing major bleeding in pre-intervention period

No	Major bleeding	Sex	Age	AF	Valve	Position	INR	Dose/wk	underlying	note
42620	UGIB,EC	M	71	No	HM	A	6.49	27.5	HT, gout	-
39376	UGIB	M	66	No	SJ	A	4.1	21.0	-	Herbal consumed, UGIB last year
39376	UGIB	M	66	No	SJ	A	1.1	21.0	-	Herbal consumed and stopped warfarin before admission
41726	Retroperito-neal hematoma	F	24	No	HM	AM	2.35	43.75	-	-
31091	Hematuria	M	45	Yes	SE	M	9.35	21.0	-	Alcohol, abused, smoking
41693	Hematuria	M	50	Yes	HM	M	unk	52.5	-	-

Note: Sex;F = female, M=male,AF= Atrial fibillation, valve; SJ=Saint Jude, HM=Medtronic Hall, SE=Starr-Edward, unk=unknown, position;A=aortic, M=mitral, AM=Aortic and mitral, underlying=underlying disease, HT=hypertension, UGIB=Upper gastrointestinal tract bleeding, EC=Ecchymosis

Table 13. Data of patients experiencing major bleeding in post-intervention period

No	Major bleeding	Sex	Age	AF	Valve	Position	INR	Dose/wk	Rx	underlying	note
33415	UGIB	F	59	Yes	CM	M	unk	12.0	2	-	Hx UGIB last year
43610	Hematuria	M	50	Yes	SJ	AM	2.11	35.0	1	-	-
33101	Hematoma	F	43	Yes	HM, CM	AM	1.50	22.5	3	-	Alcohol abused, unknown about warfarin stopping
39667	Hematoma*	F	51	No	SJ	A	7.85	26.25	2	-	massaged
42463	Hematoma	M	67	No	unk	M	unk	26.25	2	Hypothyroid, bradycardia with pacemaker	-
41167	Hematoma	F	31	Yes	HM	M	7.7	35.0	1	-	-

* cause of bleeding was trauma

Note: Sex;F=female, M=male,AF=Atrial fibillation, valve;CM=Carbmedric, SJ= Saint Jude, HM=Medtronic Hall, unk=unknown, position;A=aortic, M=mitral, AM=Aortic and mitral, Rx=number of pharmacist visit, underlying=underlying disease, Hx=history of

2. Minor bleeding

During the pre-intervention period, 37 minor bleedings occurred in 32 patients. These events included 19 ecchymosis, 10 gum bleeding, 1 minor hematoma, 3 hypermenorrhea, 2 epistaxis, 1 subclinical hematuria and 1 subconjunctival bleeding. Detail of all events listed by patient is depicted in Table 14.

During the post-intervention period, 36 minor bleedings occurred in 31 patients. These events included 20 ecchymosis, 7 gum bleeding, 3 hypermenorrhea, 2 epistaxis, 2 subconjunctival bleeding, 1 hemoptysis and 1 lower GI bleeding (positive occult blood). Detail of all events listed by patient is depicted in Table 15.

Based on this data, the incidences of minor bleeding in the pre- and post intervention periods are 13.5 and 13.1 event/100 patient-year, respectively. This difference did not reach statistical significance ($p = 0.9$).

Table 14. Data of patients experiencing minor bleeding in pre-intervention period

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	underlying	Note
30297	EC	F	36	Yes	HM	M	5.95	17.5	-	Used NSAIDs for 7 days
32335	Hematoma*	F	55	Yes	HM	M	1.82	26.25	-	Minor trauma
36163	GUM	F	52	No	HM	M	5.03	35.0	-	Stop warfarin 10 days
36330	Hematoma*	F	63	Yes	SE	M	4.48	42.0	-	Minor trauma
37442	EC	F	63	No	HM	M	2.29	26.25	-	-
40314	EYE	M	53	Yes	SJ	M	1.35	31.25	-	Stop warfarin 3 days
41463	EC	F	62	Yes	SE	T	1.43	22.5	-	-
41470	EC	F	39	Yes	SE	T	4.25	26.25	-	-
41693	Hematuria	M	50	Yes	HM	M	5.40	52.5	-	Minor bleeding
42206	EC	F	49	Yes	BS	M	2.48	21.0	LV dilated	-
42234	EC	F	24	No	SJ	A	4.70	35.0	-	-
42338	GUM	F	33	No	HM	M	2.12	21.0	-	-
42352	EC	F	28	No	SJ	A	4.69	21.0	-	-
42411	EC	F	59	No	HM	A	3.36	43.75	SLE,CRF, HT	Rt. Hemiparesis before valve replacement
42436	EC	M	57	Yes	HM	M	2.89	26.25	-	-
42436	EC	M	57	Yes	HM	M	1.39	26.25	-	-
42620	EC	M	70	No	HM	A	8.3	27.5	-	Stop warfarin 3 days
42629	GUM	F	38	Yes	SR	M	4.38	26.25	-	-
43301	GUM	M	39	Yes	SJ	AM	4.32	26.25	-	-
43474	EC	F	51	Yes	SE	M	1.37	Unk	CAD	Stop warfarin 10 days
43653	GUM	F	35	No	SR	M	2.32	26.25	-	-
43858	EC	F	53	Yes	HM	M	4.30	35.0	-	-

* excluded because bleeding from minor trauma

Table 14. Data of patients experiencing minor bleeding in pre-intervention period (Continued)

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	underlying	Note
21142	GUM	M	51	No	BS	M	2.35	21.0	-	-
23103	Menses	F	43	Yes	BS	M	1.75	21.0	CVA	-
30380	EC	F	73	Yes	HM	M	1.05	0	-	Stop warfarin 1 week
33101	EC	F	43	Yes	HM, CM	AM	3.32	17.5	-	LV dysfunction in 2001
33127	EC	F	48	Yes	HM	M	2.34	18.75	-	-
33230	GUM	M	45	Yes	SE	M	2.34	26.25	-	TIA last year
36470	Menses	F	33	No	SE	M	1.46	43.75	-	Stop warfarin 3 days
36470	Menses	F	33	No	SE	M	1.25	43.75	-	Stop warfarin 3 days
37515	GUM	F	49	No	HM, SE	AM	4.24	35.0	-	-
39226	EC	F	42	Yes	SJ	AM	3.02	26.25	HT	-
39226	EC	F	42	Yes	SJ	AM	4.49	26.25	HT	-
39393	EP	F	71	No	SJ	A	2.08	22.50	-	-
39393	EP	F	71	No	SJ	A	2.02	22.50	-	-
39667	Hematoma*	F	51	No	SJ	A	3.74	26.25	-	Massaged
39667	Hematoma	F	51	No	SJ	A	1.68	26.25	-	-
40526	GUM	F	48	Yes	HM	M	4.98	17.5	-	Stop warfarin 2 days
40607	GUM	F	56	Yes	HM	AM	2.15	35.0	-	-
41334	EC	F	59	Yes	HM	AM	2.43	15.75	CVA	-

* excluded because bleeding from minor trauma

Note: Sex;F = female, M=male,AF= Atrial fibillation, valve;CM=Carbmedric, SJ= Saint Jude, HM =Medtronic Hall, BS=Bjork Shiley, SE=Starr-Edward, unk=unknown, position;A=aortic, M=mitral, AM= Aortic and mitral, T=Tricuspid,

underlying= underlying disease, HT=hypertension, CAD=coronary artery disease, CRF= chronic renal failure, LV dilated=left ventricular dilated, DM=diabetic millitus,CHF=congestive heart failure,CA=cancer,
s/p=status post,Hx=history of, Sx= surgery, GUM= Bleeding per gum,
EC=Ecchymosis, EP=Epistaxis, EYE=Subconjunctival bleeding,
Menses= Hypermenorrhea

Table 15. Data of patients experiencing minor bleeding in post-intervention period

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	Rx	underlying	Note
30380	GUM	F	73	Yes	HM	M	2.12	8.75	3	-	-
32248	EC	M	39	No	HM	M	6.20	17.5	2	-	-
32248	GUM	M	39	No	HM	M	6.20	17.5	2	-	-
33127	EC	F	48	Yes	HM	M	3.70	18.75	1	-	-
38469	Menses	F	41	No	HM	M	1.79	15.75	2	CHF	Valve thrombosis in 1995 (tissue obstructed)
39282	EC	F	57	Yes	SJ	A	3.89	21.0	3	-	-
39491	Hemoptysis	M	70	Yes	SE	M	3.55	20.0	1	-	-
39497	EC	F	59	Yes	SJ	AM	3.48	21.0	1	-	-
39721	EYE	M	41	No	SJ	A	3.31	29.0	2	-	-
40004	EC	F	46	Yes	HM	M	2.84	27.5	2	-	TIA in 2002
40029	EC	F	67	No	CM, SJ	AM	3.80	21.0	3	-	-
40138	EC	F	29	No	SJ	A	2.86	21.0	2	-	Unscheduled LN Bx
40432	EC	F	47	Yes	HM	M	3.33	36.25	2	-	-
40526	Menses	F	48	Yes	HM	M	2.69	10.5	2	-	-
41032	EYE	F	58	Yes	SE	M	5.05	16.5	2	-	-
41221	EP	M	41	No	SR	M	4.10	52.5	3	-	Alcohol abused
41448	EC	M	46	Yes	SE	M	3.21	21.0	2	CAD s/p stent in 2002	-
41470	EP	F	39	Yes	SE	T	1.83	17.5	3	-	-
41693	EC	M	50	Yes	HM	M	1.11	26.25	2	-	Stop warfarin
42032	EC	M	69	Yes	SJ	AM	4.65	35.0	2	CHF	-
42338	GUM	F	33	No	HM	M	2.51	21.0	1	-	-
42429	GUM	M	31	No	HM	A	2.81	43.75	3	-	Alcohol abused
42429	GUM	M	31	No	HM	A	2.64	43.75	3	-	Alcohol abused
42436	EC	M	57	Yes	HM	M	2.67	30.0	3	-	-
42588	EC	F	37	No	SJ	M	3.90	17.5	1	-	-
42588	Menses	F	37	No	SJ	M	2.86	17.5	1	-	-

Table 15. Data of patients experiencing minor bleeding in post-intervention period (Continued)

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	Rx	underlying	Note
34123	EC	F	52	No	CM	A	4.11	27.5	3	Rt.side weakness in 1993	-
42606	EC	F	31	No	HM	AM	3.26	17.5	1	-	-
34162	EC	F	50	Yes	CM	AM	4.32	21.1	1	-	-
37442	EC	F	63	No	HM	M	1.95	21.25	2	-	-
37442	GUM	F	63	No	HM	M	1.95	21.25	2	-	-
42746	EC	F	49	No	SJ	A	4.36	26.25	4	-	-
43475	EC	F	27	No	SJ	AM	5.24	16.50	3	-	Pregnancy
43475	EC	F	27	No	SJ	AM	3.99	17.50	3	-	Pregnancy
44034	Occult	M	40	No	HM	A	12.64	23.25	2	-	Medication error
44046	EC	F	55	Yes	SJ	A	4.09	26.25	3	-	Amiodarone
44194	Hematoma*	F	53	No	HM	MT	1.97	17.5	2	-	Minor trauma

* excluded because bleeding from minor trauma

Note: Sex;F = female, M=male,AF= Atrial fibillation, valve;CM=Carbmedric, SJ= Saint Jude, HM =Medtronic Hall, BS=Bjork Shiley, SE=Starr-Edward, unk=unknown, position;A=aortic, M=mitral, AM= Aortic and mitral, T=Tricuspid, Rx=number of pharmacist visit, underlying= underlying disease, HT=hypertension, CAD=coronary artery disease, CRF= chronic renal failure, LV dilated=left ventricular dilated, DM=diabetic millitus,CHF=congestive heart failure,CA=cancer, s/p=status post,Hx=history of, Sx= surgery, GUM= Bleeding per gum, EC=Ecchymosis, EP=Epistaxis, EYE=Subconjunctival bleeding, Menses= Hypermenorrhea

3. Combined bleeding

When combining both major and minor bleeding, the incidences of the combined bleeding are 15.6 and 14.9 event/ 100 patient-year in pre- and post-intervention periods, respectively. The difference of major and minor bleeding rates in pre- and post-intervention periods were not statistically significant either analyzed individually or combined (p=1.00 and p=0.90 for major and minor bleeding and p=0.81 for combined bleeding). Table 16. showed distribution of bleeding complications of warfarin therapy in pre- and post-intervention periods. Table 17. showed distribution of INRs of minor bleeding in pre- and post-intervention periods, Table 18. showed distribution of patients experiencing minor bleeding in pre- and post-intervention periods based on age. Table 19-20 showed distribution of valves and positions of patients experiencing minor bleeding in pre- and post-intervention periods. Figure 12-13 showed scatter plot of INRs of combined bleeding in pre- and post-intervention periods.

Table 16. Distribution of bleeding complications from warfarin therapy in pre- and post-intervention periods

Type of bleeding	Number of patient-time			
	Major bleeding		Minor bleeding	
	Pre_	Post_	Pre_	Post_
1.Gastrointestinal	3	1	0	0
2.hematuria	2	1	1	0
3. ecchymosis	0	0	19	20
4.hematoma	1	3	1	0
5. bleeding per gum	0	0	10	7
6. hemoptysis	0	0	0	1
7. epistaxis	0	0	2	2
8. gynecologic	0	0	3	3
9.subconjunctival	0	0	1	2
10.occult	0	0	0	1
Total	6	5	37	36

Table 17. Distribution of INRs of minor bleeding in pre- and post-intervention periods

INR	Pre-intervention		Post-intervention	
	Patient-time	%	Patient-time	%
<1.50	2*	6.3	0*	0
1.51-2.00	2	6.3	3	9.0
2.01-2.50	11	34.4	1	3.0
2.51-3.00	1	3.1	8	24.2
3.01-3.50	3	9.4	5	15.2
3.51-4.00	0	0	6	18.2
>4.01	13	40.6	10	30.3

* Excluding patients whose warfarin therapy was stopped prior to the measurement of INR

Table 18. Age distribution of patients experiencing minor bleeding in pre- and post-intervention periods

Age	Pre-intervention*		Post-intervention**	
	Number	%	Number	%
<20	0	0	0	0
21-30	2	6.3	2	6.7
31-40	7	21.9	6	20.0
41-50	9	28.1	11	36.7
51-60	9	28.1	6	20.0
>=61	5	15.6	5	16.7

* AF 57% **AF 52%

Table 19. Distribution of valve types and positions in patients experiencing minor bleeding in pre-intervention period

Valve/Position	A(%)	M(%)	AM(%)	T(%)
Monoleaflet	3 (9.4)	12 (37.5)	2 (6.3)	0
Bileaflet	3 (9.4)	3 (9.4)	2 (6.3)	0
Caged ball	0	3 (9.4)	0	2 (6.3)
Bi*+Caged ball	0	0	1 (3.1)	0
Mono**+ Caged ball	0	0	1 (3.1)	0

* bileaflet ** monoleaflet

A=aortic, M=mitral, AM= Aortic and mitral, T=Tricuspid

Table 20. Distribution of valve types and positions of patients experiencing minor bleeding in post-intervention period

Valve/Position	A(%)	M(%)	AM(%)	T(%)
Monoleaflet	1 (3.3)	11 (36.7)	1 (3.3)	0
Bileaflet	6 (20.0)	2 (6.7)	5 (16.7)	0
Caged ball	0	3 (10.0)	0	1 (3.3)

A=aortic, M=mitral, AM= Aortic and mitral, T=Tricuspid

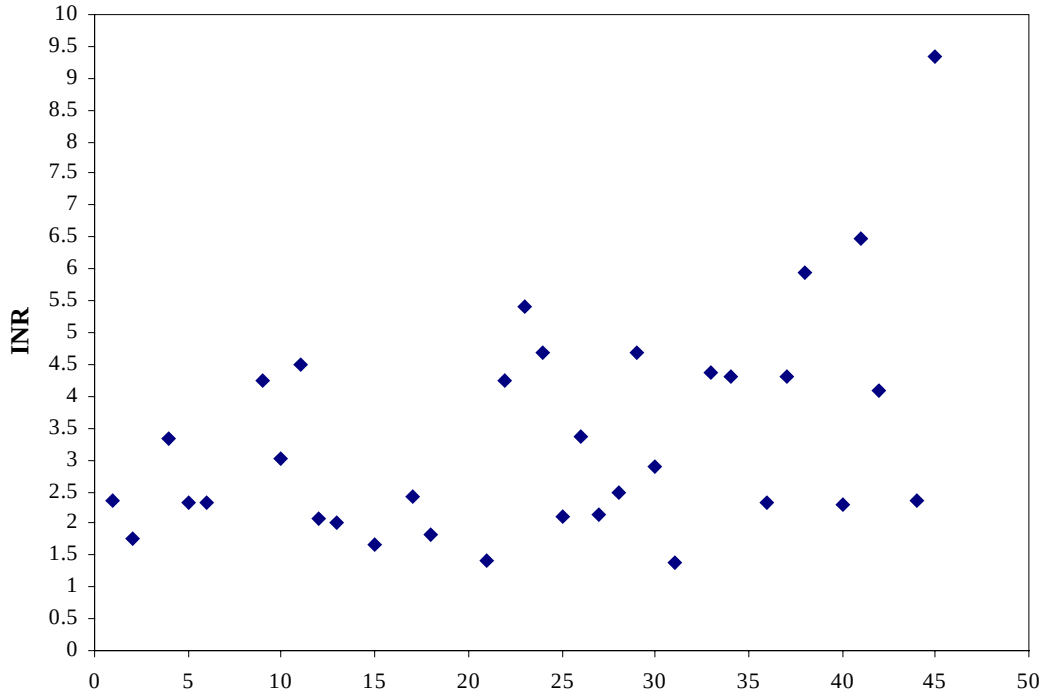


Figure 12. Scatter plot of INRs of combined bleeding in pre-intervention period

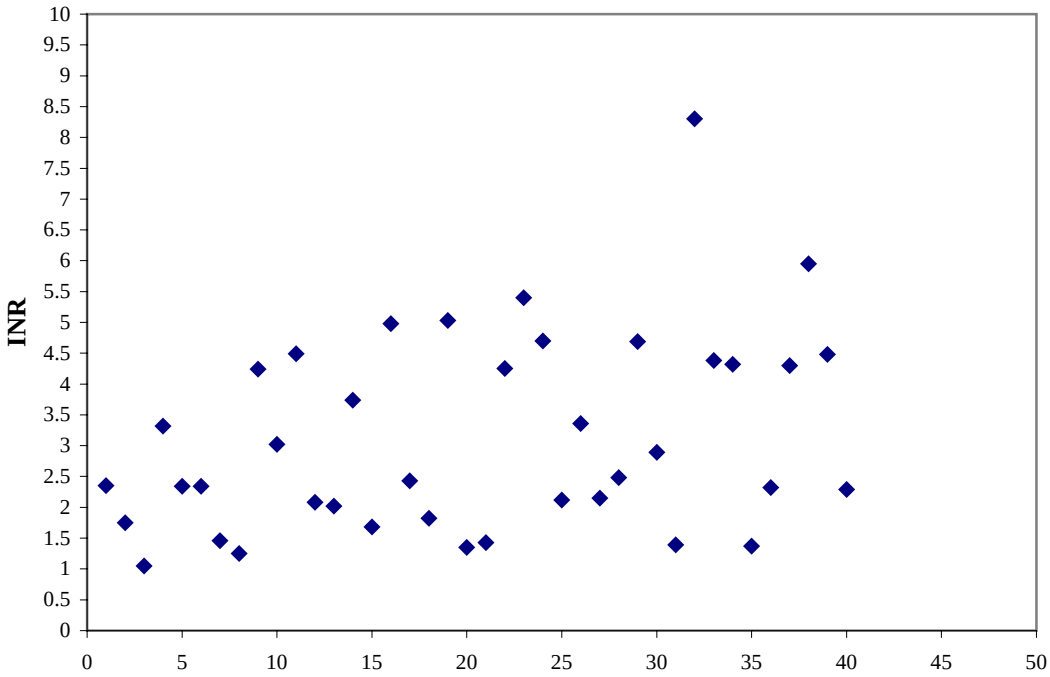


Figure 13. Scatter plot of INRs of combined bleeding in post-intervention period

IV. Thromboembolic complications

During the pre-intervention period, cerebrovascular accident (CVA) occurred in 1 patient. The patient was a 56 years old with Medtronic Hall valve at both aortic and mitral positions and AF. The INR on admission was 1.93 with 17.5 mg/wk of warfarin. There were 14 occurrences of transient ischemic attack (TIA) in 13 patients during this period. These events occurred in 5 males and 8 females. Detail of the events listed by patient is depicted in Table 21. The incidence of thromboembolic events in this period is therefore calculated to be 5.46 event/100 patient-year with 0.36 event/100 patient-year for CVA and 5.1 event/100 patient-year for TIA.

During the post-intervention period, cerebrovascular accident (CVA) occurred in 3 patients. The first patient was a 79 years old with Medtronic Hall valve at both aortic and mitral positions, coronary artery disease and AF. He was admitted to Nakornpathom hospital with a chief complaints of right side weakness. The INR on admission was unknown. The second patient was a 46 years old female with Medtronic Hall valves at both aortic and mitral positions. She was admitted to Nonthawej hospital with a chief complaint of left side weakness. The INR on admission was 1.7. She later received a diagnosis of acute brain infarct in temporal region. The third patient was a 48 years old female with Medtronic Hall valve at mitral position and AF. The event occurred while patient stopped taking warfarin for 6 days as a preparation to a dental procedure. The INR on admission is unknown.

There were confounding factors in 2 of 3 patients experiencing CVA in this period which may explain the occurrence of CVA. The first patient had the diagnosis of coronary artery disease, a major risk factor for CVA. In addition, the patient experienced a right-sided weakness which suggested that the occluded lesion was in the left hemisphere of the brain. However, considering the type of stroke caused by mechanical heart valve in mitral and aortic positions, the majority of lesion are in the right hemisphere which generally leads to left-side weakness. This is due to the anatomical preference which facilitates the passage of thromboemboli to the right more than the left side of the brain. Due to these factors, the exact cause of CVA in this patients is inconclusive. The second patient suffered a CVA event while her warfarin therapy was interrupted as a preparation to a dental procedure. From patient's INR record, her anticoagulation control prior to interruption was adequate. As a result,

the CVA event in this patient can be explained by the planned interruption of warfarin therapy. Such interruption, although some may consider it controversial, is a typical medical practice and recommended by respected guidelines.

There were 7 occurrences of transient ischemic attack (TIA) in 6 patients (1 male and 5 females) during this period. All patients had AF as a comorbidity. One patient had multiple risk factors for thromboembolism including coronary artery disease and left ventricular dysfunction. Based on this data, the incidence of thromboembolic events in this period was 3.59 event/100 patient-year with 1.09 event/100 patient-year for CVA and 2.5 event/100 patient-year for TIA. However, with the exclusion of two CVA cases due to the presence of confounding factors, the incidence of thromboembolic events in this period was 2.9 event/100 patient-year with 0.36 event/100 patient-year for CVA and 2.5 event/100 patient-year for TIA. (Detail of events listed in Table 22).

For thromboembolic complications, there was no significant difference in the incidence of CVA between the two periods either with or without the exclusion of cases with confounding factors ($p=1.0$). The rate of TIA in the post-intervention periods was less than that of the pre-intervention period (5.1 vs 2.5 events/100 patient-year; $p=0.19$). On the combined incidences of CVA and TIA or combined TE, there were less combined TE events in the post-intervention period. (5.46 vs 2.9 events/100-patient year; $p =0.21$).These differences, however, did not reach statistical significance

Distribution of the INRs when CVA and TIA complications occurred in pre- and post-intervention periods were shown in Table 23. Scatter plot of INRs of combined TE in pre- and post-intervention periods were depicted in Figure 14-15.

Table 21. Data of patients experiencing thromboembolic events in the pre-intervention period

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	underlying	Note
31148	TIA	F	73	No	HM	M	1.69	17.5	DM,CA cervix s/p Sx	-
31345	TIA	M	54	No	Unk	M	1.11	17.5	-	-
32365	TIA	M	46	No	HM	M	2.52	35.0	-	-
32446	TIA	F	52	No	SE	M	1.50	21.0	-	Eye emboli
37442	TIA	F	63	No	HM	M	1.58	21.25	-	-
37442	TIA	F	63	No	HM	M	2.29	26.25	-	-
40607	CVA	F	56	Yes	HM	AM	1.93	17.5	-	-
41108	TIA	M	67	No	HM	M	1.58	21.25	-	Eye emboli
41343	TIA	F	47	Yes	SJ	M	2.65	21.25	DM,CRF, HT,hypothyroid , gall stone	Amiodarone, Elthoxin,ASA
42016	TIA	M	66	No	SJ	A	1.18	21.0	-	No care giver
42206	TIA	F	49	Yes	BS	M	1.95	21.0	LV dilated	EF 40%
42234	TIA	F	24	No	SJ	A	2.20	26.25	-	2 months after decrease dosage
43419	TIA	M	71	No	SE	A	1.48	15.75	HT	Eye emboli
43653	TIA	F	35	No	SR	M	1.03	21.0	-	Eye emboli
44281	TIA	F	38	Yes	SJ	M	1.63	21.0	Pulmonary Edema	-

Table 22. Data of patients experiencing thromboembolic events in the post-intervention period

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	Rx	underlying	Note
26375	TIA	F	56	Yes	SE	M	2.00	15.75	3	-	-
33127	CVA*	F	48	Yes	HM	M	unk	0	1	-	Stop warfairin 6 days for dental operation
35294	TIA	F	53	Yes	HM	M	1.82	15.75	3	HT	-
39667	TIA	F	51	No	SJ	A	1.50	26.25	2	-	-
40035	TIA	F	53	Yes	SJ	M	1.55	52.5	2	-	-
42219	TIA	M	63	Yes	HM	M	1.97	18.75	2	CAD, LV dilated	EF 40% CABGx2
42219	TIA	M	63	Yes	HM	M	1.66	12.75	2	CAD, LV dilated	EF 40% CABGx2
42264	CVA	F	46	No	HM	AM	1.70	17.5	1	-	-
42606	TIA	F	31	No	HM	AM	1.47	17.5	1	-	-
43434	CVA*	M	79	Yes	HM	AM	Unk	21.0	2	CAD	-

* excluded because CVA cause from other cause

Table 23. Distribution of the INRs when CVA and TIA complications occurred in the pre- and post-intervention periods

INR	**TIA(%)**		**CVA(%)**	
	Pre-	Post-	Pre-	Post-
<1.50	5(35.7)	2(28.6)	0	0
1.51-2.00	5(35.7)	5(71.4)	1(100)	1(100)
2.01-2.50	4(28.6)	0	0	0

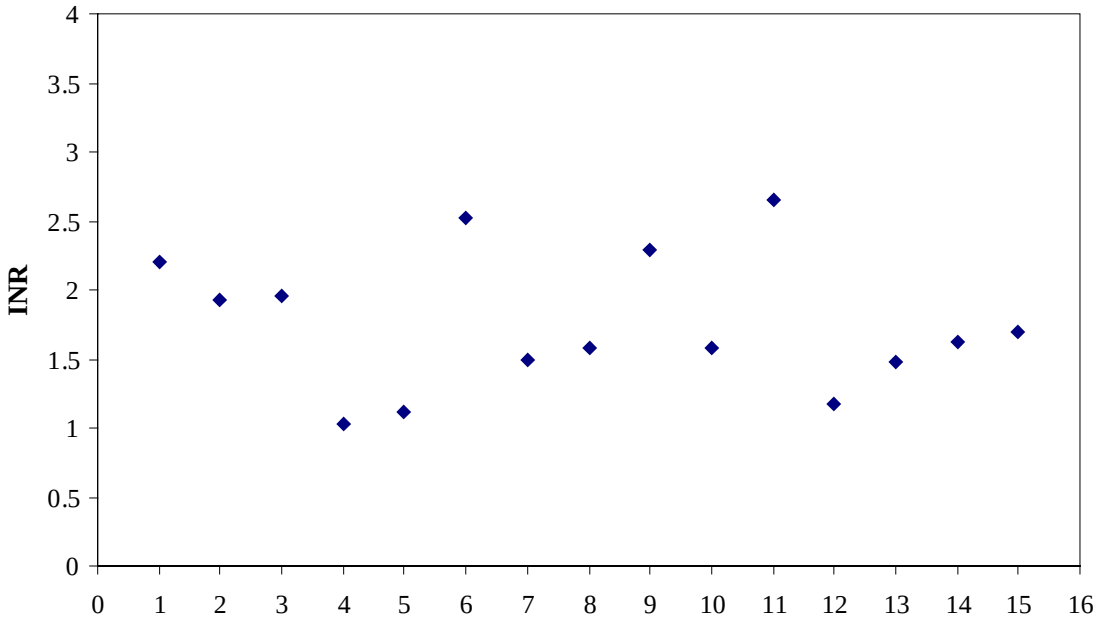


Figure 14. Scatter plot of INRs of combined TE in pre-intervention period

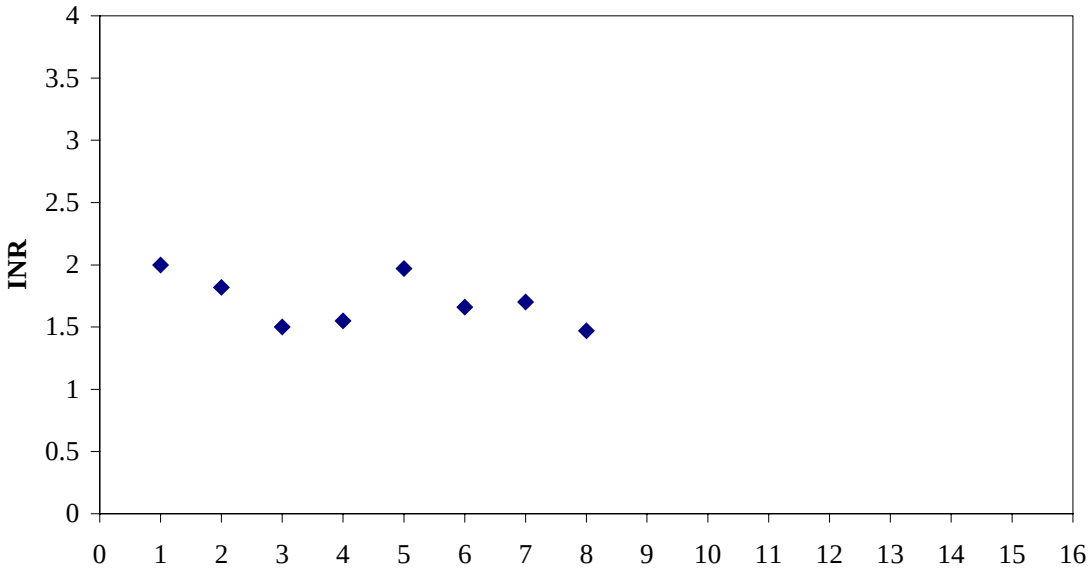


Figure 15. Scatter plot of INRs of combined TE in post-intervention period

When combining the pre- and post-intervention periods (table 24), we have found that thromboembolic events occurred at the rate of 3.3, 0.9 and 0 event/100 patient-year when INR were < 2.0, 2.0-2.99 and $\geq$ 3, respectively. On the other hand,

bleeding occurred at the rate of 1.5, 3.8 and 6.5 event/100 patient-year when INR were < 2.0, 2.0-2.99 and ≥ 3, respectively. Comparing these events to studies conducted in Europe or the United States, the INR of 2.0-3.0 appears to be adequate and lead to similar outcomes.

Table 24 Distribution of thromboembolic and bleeding events per INR levels

INR	Combined TE				Combined Bleeding			
	Pre-	Post-	Total	Rate*	Pre-	Post-	Total	Rate*
≤ 1.50	5	2	7	1.3	2	0	2	0.4
1.51-1.99	6	5	11	2.0	2	4	6	1.1
2.00-2.49	2	1	3	0.5	11	1	12	2.2
2.50-2.99	2	0	2	0.4	1	8	9	1.6
3.00-3.50	0	0	0	0	3	5	8	1.5
≥ 3.51	0	0	0	0	10	17	27	5.0

* event/100 patient-year

V. Unscheduled physician visit

In the pre-intervention period, there were 2 unscheduled visits but none were related to warfarin complications (tension headache and dental care). Four patients were admitted with heart failure, dyspnea, paravalvular leakage and unknown cause. (Detail of events listed in table 25)

In post-intervention period, there were 6 unscheduled visits however only one was considered to be related to warfarin complications (minor bleeding). These included ascites, dyspnea, edema, lymnode biopsy, palpitation and dizziness, pethichea and animal bite. There were 16 hospital admissions during post-intervention period. Six patients were admitted to Siriraj hospital; 3 with a chief complaints of dyspnea, 1 patient with a diagnosis of right side heart failure, 1 patient with a diagnosis of cellulitis and 1 patient with a diagnosis pulmonary edema. Ten patients were admitted to other hospitals. The reasons for admission of these patients were heart failure (6 patients), brain surgery (1 patient), complete heart block (1), chest pain (1) and dizziness/tinnitus (1). (Detail of events listed in table 26)

Table 25. Data of patients admitted in pre-intervention period

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	underlying	Note
42778	Admit	F	45	No	HM	A	1.98	26.25	-	Unk cause
43079	Admit	F	70	No	HM	A	4.15	35.0	DM,CAD, Dyslipidemia, Catarax	Valve good function , LV dysfunction
43623	Admit	F	30	No	SJ	M	3.68	26.25	Paravalvular Leakage	-
43703	Admit	F	54	Yes	HM	AM	2.31	26.25	-	Dyspnea

Table 26. Data of patients admitted in post-intervention period

No	Complication	Sex	Age	AF	Valve	Position	INR	Dose/wk	Rx	underlying	Note
37155	Admit	F	49	No	HM, SE	AM	2.22	35.0	1	-	Cellulitis
37269	Admit	M	67	Yes	SE	M	4.18	21.25	2	-	Dyspnea
38152	Admit	M	44	No	SJ	A	4.27	14.5	2	CHF	Dyspnea improved after furosemide injected
40706	Admit	M	53	No	HM	AM	4.04	10.0	3	Rt.side heart failure	-
43703	Admit	F	54	Yes	HM	AM	2.15	10.5	3	Ascites	Rt.side heart failure
44194	Admit	F	53	No	HM	MT	1.94	10.5	2	-	Pulmonary edema

VI. Compliance to warfarin therapy

There were 62 documented events of non-compliance to warfarin therapy during the pre-intervention period. In the post-intervention period, 40 events were found during patient interview.

Table 27. Number of events of non compliance in pre- and post-intervention periods

	Number of events (%)	
Non compliance to warfarin therapy	Pre-	Post-
	62(22.5*)	40(14.5*)

*events/100 patient-year

VII. Detection of drug interactions

During the intervention period, clinical pharmacists were able to detect 52 significant drug interactions that may lead to interference with anticoagulation therapy. All drug interactions were reported to the patient's primary care provider. Interestingly, a number of interactions were caused by non-prescription drugs, nutritional supplements or herbal products.

Table 28. Drug interaction with warfarin during followed up periods

Drug	Number of events	
	Pre-intervention	Post-intervention
Aspirin	15	18
NSAIDs	5	5+9*
Antimicrobial	No data available	2*
Amiodarone	5	4
Omeprazole	1	1*
Cimetidine	1	1*
Paracetamol >20 tab/week	No data available	1*
Eltroxin	5	4
Ethinyl estradiol	No data available	3
Rifampicin	No data available	3
Gemfibrozil	No data available	4
Nutritional supplement or herbal products		
Noni juice	0	3*
Soy milk	0	1*
Spirulina	0	1*
Total	12	52

* not prescribe by physician

VIII. Interventions

During the intervention period, there were 39 additional interventions performed by clinical pharmacists. All interventions were accepted by physicians in the clinic. The distribution of interventions from pharmacists were showed in Table 29.

Table 29. The distribution of interventions from pharmacists

Intervention	**Frequency**	Percent
Dosage adjustment*	31	79.5
Monitoring of efficacy**	5	12.8
Monitoring of safety***	3	7.7
Total	39	100

*increase, decrease or unchanged dosage

**follow-up frequency

***CBC, Hematocrit

CHAPTER 5

DISCUSSION

Lifetime oral anticoagulation is recommended to reduce the risk of thromboembolic complications in patients with mechanical heart valve. Warfarin, the most commonly used oral anticoagulant, has narrow therapeutic index and complicated pharmacokinetics/pharmacodynamic profiles. As a result, managing warfarin therapy is a challenging task. A number of studies in western countries have documented that pharmacists' interventions help achieve optimum anticoagulation control. This may lead to the reduction of both thromboembolic and hemorrhagic complications. (15-24)

This study is a historical cohort study evaluating the effects of pharmacist interventions on clinical outcomes of anticoagulation therapy in Thai patients with mechanical heart valve. Anticoagulation control, thromboembolic events and hemorrhagic complications between pre- and post-intervention periods were our main outcomes of interest. Historical data of study patients was chosen as control to reduce selection bias that was introduced due to patient selection criteria of the Warfarin Project.

In this study, an INR in the range of 2-3 was selected as the therapeutic range which was lower than INR of 2.5-3.5, the range recommended by guidelines from western countries. Studies conducted in Thailand and other Asian countries suggest that lower range of INR may be comparably effective in the prevention of thromboembolic complications in this population. (74-79)

There were two clinical pharmacists participating in this study. Although interpersonal variation may occur, the supervising pharmacist trained and oversaw interventions of the other pharmacist. In addition, both had to follow similar clinic protocols and worked under the same set of physicians. This may help lessen the variation that may occur.

From baseline characteristics, three fourth of our patient population were over 40 years old and almost half of them had atrial fibrillation which posses additional risk of CVA. This was due to the fact that most of these patients had rheumatic heart disease as the primary cause. As for the valve positions, over 70% were in the mitral position while 27% were in the aortic position. These characteristics represent general population of patients with mechanical valve in Thailand. The two most common valves used in our study population were monoleaflet and bileaflet valves. Although bileaflet valve is currently more popular, based on the average time post-operation (8 years), the usage pattern of these valves reflected the practice of such period where bileaflet valves were still expensive and relatively new in the market. Therefore, the result of our study should be applicable to real-life practice in the country.

Warfarin dose

There has long been a belief that Thai patients may need less warfarin to achieve the same INR goal than westerner patients (5 mg daily). Su-arpa Ploylearmsaeng conducted a study to determine the usual dose required to obtain therapeutic INRs of 2-3 in patients with mechanical heart valve. Ninety five patients from Rajvithi Hospital were included in the study. The result showed that the average dose required to obtain INR of 2-3 was 3.34 $\pm$ 0.94 mg/day. In our study, the average warfarin doses both in pre- and post-intervention periods were approximately 24 mg/week or 3.5 mg/day with the average INR of 2.35±0.79 and 2.35±0.89 in pre- and post-intervention groups, respectively. As a result, our study along with Su-arpa study confirmed that the average warfarin dose required to obtain INR of 2-3 in Thai patients is, in fact, lower than that of Westerners.

Anticoagulation control

Anticoagulation control both pre- and post-interventions was expressed in two ways including percentage of INRs within therapeutic range and anticoagulation variability. Although the first is a common way of expressing anticoagulation control in earlier studies, anticoagulation variability has recently been shown to correlate with morbidity and mortality in patients with prosthetic heart valves. (80) In our study, there was a significant improvement in the anticoagulation control from pre- to post-

intervention periods irrespective of analyzing methods. There was an 11% increase in the percentage of therapeutic INRs and 50% increase in the number of patients with low anticoagulation variability in the post- compared to the pre-intervention periods. Generally, our results are consistent with previous studies conducted in the US and Europe. Studies by Gray et al, Cortellazzo et al, Wilt et al, Chiquette et al and others, all showed that pharmacists' interventions help promote the achievement of anticoagulation control in a variety of patient populations. We believe that the main factor that may be accounted for this improvement is the structured, continuous patient education that may help promote awareness and compliance to warfarin therapy. In addition, drug interaction screenings, and compliance boosting devices may play some part in this improvement.

There were 2 previous studies evaluating the impact of clinical pharmacists on anticoagulation therapy in Thailand. Tipawan et al conducted a study in the setting of mechanical heart valve while Suparat et al performed the study in a mixed population including mostly patients with atrial fibrillation and to a lessor extent, patients with mechanical heart valve. Despite showing that pharmacists helped identified drug-related problems and provided patient education, Tipawan study failed to show significant impact of pharmacist interventions on the anticoagulation control. A number of factors may be attributable to this negative finding. The small number of patients, short follow-up time, and limited number of visits may diminish the chance of finding such impact which may require sufficient time to show an effect. In addition, the unconventionally narrow therapeutic range used in the study (2.0-2.5 instead of 2.0-3.0) may play a part in the difficulties of achieving INR goals, especially when considering the nature of variation of INR test itself. Suparat et al, on the other hand, reported a significant increase in the, so called, "stable INR" in the post- compared to the pre-intervention periods. In addition, the incidence of major bleeding was significantly reduced compared to the pre-intervention period. Despite having favorable results, this study had several limitations. First, the outcome used in this study (stable INR) is not the standard outcome in measuring anticoagulation control and has not been shown to correlate with long-term clinical outcomes. Second, the follow-up period of the study was relatively short. Nonetheless, this study showed

that pharmacist interventions help increase the achievement rate of INR goals while minimizing hemorrhagic complications from warfarin therapy.

Comparing with previous local studies, our study has certain advantages and limitations. Having the larger sample size and longer follow-up time, the study has more power to detect significant and long-term impact of interventions. Using anticoagulation variability, a surrogate marker shown to correlate with morbidity/mortality, as a way to express anticoagulation control increases the strength of our finding comparing to previous studies. Nevertheless, the important limitation of our study is the study design. The most robust and ideal design for an intervention study is the randomized, double-blinded, controlled trial. Due to the nature of our interventions, it is impractical to use a double-blinded design. We did not randomize patients since the interventions provided to our patients were considered standard interventions that are to be given to all patients in the Warfarin Project at Siriraj Hospital.

In contrast to Tipawan study which enrolled similar patient population, we found significant improvement in the anticoagulation control in the post- compared to the pre-intervention period. The 50% increase in proportion of patients with low anticoagulation variability is considered highly significant not only in terms of statistical analysis but also clinical management. Our findings along with those of Suparat help support the role of pharmacists in the management of warfarin therapy in Thailand.

Thromboembolic complications

Cerebrovascular accident (CVA)

The rates of CVA in our study were 0.36 and 1.09 event/100 patient-year in the pre- and post-intervention periods, respectively. Although it may seem that CVA rate was higher in the post-intervention period, this difference did not reach statistical significance and, in fact, there were confounding factors that may help explain this finding.

There were 3 patients experiecing CVA in the post-intervention period. Two of these patients had confounding factors that may explain the occurrence of CVA events. The first patient was a 79 years old male with Medtronic Hall valve at both

aortic and mitral positions, coronary artery disease and AF. He was admitted to Nakornpathom hospital with a chief complaints of right side weakness. The INR on admission was unknown. The cause of CVA in this patient was confounded by the fact that this patient had atherosclerosis, a major risk factor for CVA. In addition, the patient experienced a right-sided weakness which suggested that the occluded lesion was in the left hemisphere of the brain. However, considering the type of stroke caused by mechanical heart valve in mitral and aortic positions, the majority of lesion are in the right hemisphere which generally leads to left-side weakness. This is due to the anatomical preference which facilitates the passage of thromboemboli to the right more than the left sides of the brain. Due to these factors, the exact cause of CVA in this patients is inconclusive. The second patient was a 48 years old female with Medtronic Hall valve at mitral position and AF. The event occurred while patient stopped taking warfarin for 6 days as a preparation to a dental procedure. From patient's INR record, her anticoagulation control prior to interruption was adequate. As a result, the CVA event in this patient can be explained by the interruption of warfarin therapy for dental procedure. Such interruption, although some may consider it controversial, is a typical medical practice and recommended by respected guidelines. Excluding these two cases, the indicence of CVA in the pre- and post-intervention periods were equal at the rate of 0.36 event/100 patient-year.

In contrast to CVA, there were 50% less TIA events in the post- compared to the pre-intervention periods (5.1 vs 2.5 event/100 patient-year; p =0.18). When combining these thromboembolic events, there were less combined TE events in the post-intervention period (5.46 vs 2.9 events/100-patient year; p = 0.20). Although these trend toward benefit did not reach statistical significance, they were consistent and could be explained by the improvement of anticoagulation control seen in our study. Due to the low frequency of these events, we may need larger sample size and longer follow-up time to have adequate statistical power to show difference on this outcome. Nonetheless, this result suggests that pharmacists' interventions have the potential to reduce thromboembolic complications in patients with mechanical heart valve through the improvement of anticoagulation control.

Comparing with other studies, our study is the only local study that reported a trend toward lower thromboembolism rate. For international studies, Cortelazzo et al

found that the thromboembolism rate was significantly lower after the enrollment into the AC compared to before the enrollment period (0.6 vs 6.6%/patient-year). Other studies also reported signficant improvement of thromboembolism rate with pharamcists' interventions, however patients with mechanical heart valve were a minority in those studies. Due to differences in types of valve, valve positions and comorbidities, comparison of thromboembolism rates of our study with others are with limitations.

There are interesting findings regarding the relationship of thromboembolic events and INR range. Over 80% of thromboembolic events occurred when INR was below 2 while none occurred at the INR over 2.5. During the post-intervention period where the documentation was more completed, no thromboembolic events occurred when the INR was above 2. These findings are consistent with the proposed INR range of 2.0 – 3.0 in Thai population.

Hemorrhagic complications

Major bleeding

Major bleeding occurred at the rate of 2.18 event/100 patient-year in both pre- and post-intervention periods. There was, however, 1 event in the post-intervention period which was caused by trauma. When excluding this patient, the incidence of major bleeding in this period was 1.81 event/100 patient-year which is 17% lower than the pre-intervention period. However, this difference did not reach statistical signficance.

Comparing with other studies, the result of our study is consistent with those international studies and the local study by Suparat et al, though with less effect. Chiquette et al reported that the incidence of major to fatal bleeding was reduced from 3.9 to 1.6 event/100 patient-year. Cortellazzo et al showed that incidence of major bleeding was lowered from 4.7 to 1.0 event/100 patient-year. Suparat et al reported that there were 12 vs 0 major bleedings in the pre- and post-intervention periods, respectively but the number of event/100 patient-year were not calculated nor reported. Considering the already low rate of major bleeding at baseline in our study, it is therefore difficult to show significant impact on the reduction of major bleeding.

However, the trend toward lower rate of major bleeding in our study is consistent with results from other studies.

Minor bleeding

Minor bleeding occurred at the rate of 13.8 vs 13.1 event/100 patient-year in the pre- and post-intervention period, respectively. For the INR of 2.0 – 3.0, the incidence of minor bleeding were 4.4 vs 3.3 event/100 patient-year. This result is consistent with other local studies. Tientadakul et al reported the rate of minor bleeding at 4.3 event/100 patient-year with INR between 2.0 – 2.9. The difference in rates of minor bleeding in our study was not statistically significant. One limitation that may explain the seemingly lack of effect on the outcomes is the incomplete documentation, especially in the pre-intervention period since meticulous documentation on the outcomes only started during interventions. Comparing to international studies, studies by Wilt et al and Chiquette et al also showed a non-significant trend toward lower incidence of minor bleeding.

Combined bleeding

The rates of combined bleeding were 16.0 vs 14.9 event/100 patient-year in the pre- and post-intervention periods, respectively. This difference did not reach statistical significance.

There were interesting findings on the relationship of hemorrhagic events and INR values. For patients experiencing major bleeding, most of them had supratherapeutic INR on admission. Meanwhile, over 50% of minor bleedings occurred when INR values over 3.0. This result emphasizes the importance of achieving optimal anticoagulation control to reduce hemorrhagic complications in Thai population.

Optimal anticoagulation intensity

There has been no conclusive data derived from randomized controlled trials to confirm that the INR of 2-3 is the optimal anticoagulation intensity in Asian population. Most reports were small retrospective studies or studies using surrogate markers instead of hard outcomes. Although our study was not designed to answer this

question, there were interesting findings on the relationship of INR and outcomes in the study which may help support the use of lower INR target (2-3) than those used in Westerners (2.5-3.5). In table 24, when combining the pre- and post-intervention periods, we have found that thromboembolic events occurred at the rate of 3.3, 0.9 and 0 event/100 patient-year when INR were < 2.0, 2.0-2.99 and $\geq$ 3, respectively. On the other hand, bleeding occurred at the rate of 1.5, 3.8 and 6.5 event/100 patient-year when INR were < 2.0, 2.0-2.99 and $\geq$ 3, respectively. Comparing these events to studies conducted in Europe or the United States, the INR of 2-3 appears to be adequate and lead to similar outcomes. As a result, data from this study help provide more evidence to support the INR target of 2-3 for Thai population. However, randomized controlled trials designed to tackle this question are still warranted.

Unscheduled physician visit

There were 0 and 1 warfarin-related, unscheduled physician visit in the pre- and post-intervention periods, respectively. However, due to the incompleteness of data, especially during the pre-intervention period on this regard, we were unable to find any meaningful interpretation on this aspect.

Drug related problems

In addition to better anticoagulation control, clinical pharmacists also helped detect and solve drug related problems encountered in the study population. These problems include noncompliance and drug interactions which are major problems with anticoagulation therapy.

There were 62 vs 40 documented events of non-compliance to warfarin therapy (22.5 vs 14.5 event/100 patient-year) during the pre- and post-intervention periods, respectively. This result is consistent and may be attributable to the improvement in anticoagulation control observed in the study.

During the intervention period, 52 significant drug interactions were detected and reported to the patient's primary care provider. This may also be attributable to the improvement in INR control since drug interactions are one of the most common causes of sub- or supratherapeutic INRs. Interestingly, a number of interactions were caused by non-prescription drugs, nutritional supplements or herbal products. This

may indicate that the use of these products are very common in Thai population. This finding clearly indicate that pharmacists may have an important role in the detection and management of drug interactions in patients receiving warfarin therapy.

There were 39 additional interventions performed by clinical pharmacists. All interventions were accepted by physicians in the clinic. The majority of interventions were providing recommendations for dosage adjustment while the rest were providing recommendations on monitoring of efficacy and safety.

Study Limitations

Our study has several limitations. The important limitation of our study is the study design. The most robust and ideal design for an intervention study is the randomized, double-blinded, controlled trial. Due to the nature of our interventions, it is impractical to use a double-blinded design. We did not randomize patients since the interventions provided to our patients were considered standard interventions that are to be given to all patients in the Warfarin Project at Siriraj Hospital. Incompleteness of data especially during the pre-intervention period also prevent us to make a fair comparison on certain outcomes. Lack of INR values on admission and other clinical data during acute events occurred at other hospitals did not allow us to investigate the relationship of INR and some complications. Due to the lower incidence of certain outcomes, larger sample size with longer follow-up may be helpful in finding statistical differences on those outcomes.

CHAPTER 6
CONCLUSION

Anticoagulation therapy in patients with mechanical heart valve is of significant benefits yet difficult to manage. Although a number of studies have documented benefits of pharmacist interventions in the management of anticoagulation in this patient population, most studies were conducted in western population. The results from studies in those western countries may not be applicable to Thailand due to a variety of differences in healthcare system. Results from previous local studies are inconsistent. Those studies also have major limitations including small sample size, relatively short follow-up time, different expression of anticoagulation control, statistical flaws and lack of hard outcomes.

We are able to show in our study that anticoagulation control was significantly better either expressed as percentage of INR in range or anticoagulation variability when pharmacists were incorporated in the healthcare team. Although no significant differences were observed in the rates of thromboembolic and hemorrhagic complications, there were non-significant trends toward lower incidence of both complications. This result is consistent and could be explained with the improvement in anticoagulation control seen in our study. In addition, other drug-related problems were reduced or discovered effectively as shown by a decrease in non-compliance and detection of drug interactions.

When combining data in both periods, we have found interesting relationship of INR range and complications. Previously, there were limited published data to support the INR target of 2-3 in Thai patients with mechanical heart valve. This study has provided more evidence to support the INR target of 2-3 as the optimal anticoagulation intensity since this INR range appears to provide low rate of thromboembolic events while minimizing the rate of bleeding in Thai population. However, since this study was not designed to specifically address this question, additional data from well-designed and adequately-powered studies are still warranted.

Overall, despite several limitations, the results of our study strongly support the conclusion that pharmacist interventions led to the improvement of anticoagulation control with a potential reduction in thromboembolic and hemorrhagic complications in Thai patients with mechanical heart valve. We strongly believe that one of the major implications of our study along with other local studies is a call for pharmacists in the country to become involved in the management of warfarin therapy with the goal of promoting safe and effective use of warfarin.

Recommendation

The result of this study supports the development of specialized service aiming at promoting the safe and effective use of warfarin. Due to the lack of such services especially in the upcountry areas, large number of Thai patients with mechanical heart valves have to travel from their hometown to big cities for follow-up visits. This pattern of care creates many problems including high patient loads to those tertiary care facilities and financial burden from traveling and housing costs on the patient side. Therefore, the establishment of warfarin clinic in upcountry areas may help solve these problems.

Recommendation for further studies

Our study evaluated only clinical outcomes while economics and humanistic outcomes were not investigated. As a result, the assessment of impacts on cost-benefit, patient satisfaction and quality of life should be performed.

Recommendation for hospital administrators

The result of this warfarin project clearly showed that this service is of high value to patient care. However, due to the high patient-provider ratio, more pharmacists are needed to provide this beneficial service to all patients.

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APPENDIX A

APPENDIX A. แบบประเมินความรู้ความเข้าใจสำหรับผู้ป่วยที่ได้รับการรักษาด้วยยาวาร์ฟาริน

แบบประเมินความรู้ความเข้าใจสำหรับผู้ป่วยที่ได้รับการรักษาด้วยยาวาร์ฟาริน

☐ ผู้ป่วยใหม่ ☐ ผู้ป่วยเก่า วันที่....……...เดือน.....พ.ศ….....

ชื่อ-สกุล.....อายุ.....ปี HN…….CNS…….

โรคประจำตัว/ประวัติการผ่าตัด.....แพทย์ผู้รับผิดชอบ.....……....

หัวข้อที่ประเมิน	รู้ (1)		ไม่รู้ (0)		เข้าใจผิด (-1)	
	ก่อน	หลัง	ก่อน	หลัง	ก่อน	หลัง
1. ผู้ป่วยทราบหรือไม่ว่ายาเม็ดสีชมพู/สีฟ้าเป็นยาอะไร						
2. ผู้ป่วยทราบหรือไม่ว่ามีความจำเป็นในการกินยานี้อย่างไรบ้าง						
3. ผู้ป่วยทราบหรือไม่ว่ายานี้มีผลข้างเคียงที่สำคัญอะไรบ้าง						
4. ผู้ป่วยทราบหรือไม่ว่าหากลืมกินยาจะทำอย่างไร						
5. ผู้ป่วยทราบหรือไม่ว่าหากไปพบทันตแพทย์หรือแพทย์ด้วยปัญหาอื่นควรบอกอะไรกับทันตแพทย์หรือแพทย์บ้าง						
6. ผู้ป่วยทราบหรือไม่ว่าก่อนที่จะซื้อยา สมุนไพร ยาหม้อ ยาลูกกลอน หรืออาหารเสริม มากินเอง ควรปรึกษาแพทย์หรือเภสัชกร						
7. ผู้ป่วยทราบหรือไม่ว่าหากเกิดอุบัติเหตุ หรือมีบาดแผล ควรปฏิบัติอย่างไรบ้าง						
8. ผู้ป่วยทราบหรือไม่ว่าการดำเนินชีวิตประจำวันบางอย่าง เช่น พฤติกรรมในการบริโภคหรือการสูบบุหรี่ การดื่มเครื่องดื่มที่มีแอลกอฮอล์ อาจส่งผลต่อประสิทธิภาพและอาการข้างเคียงที่จะเกิดขึ้นจากยาได้						
9. ผู้ป่วยทราบหรือไม่ว่าการพกบัตร หรือเอกสารที่แสดงการเป็นผู้ป่วยที่กำลังใช้ยาวาร์ฟารินอยู่จำเป็นหรือไม่อย่างไร						
10.ผู้ป่วยทราบหรือไม่ว่าหากมีการเปลี่ยนที่อยู่หรือเบอร์โทรศัพท์ควรทำอย่างไรบ้างและเพื่ออะไร						

สรุปคะแนนความรู้

Pre-test score .....คะแนน

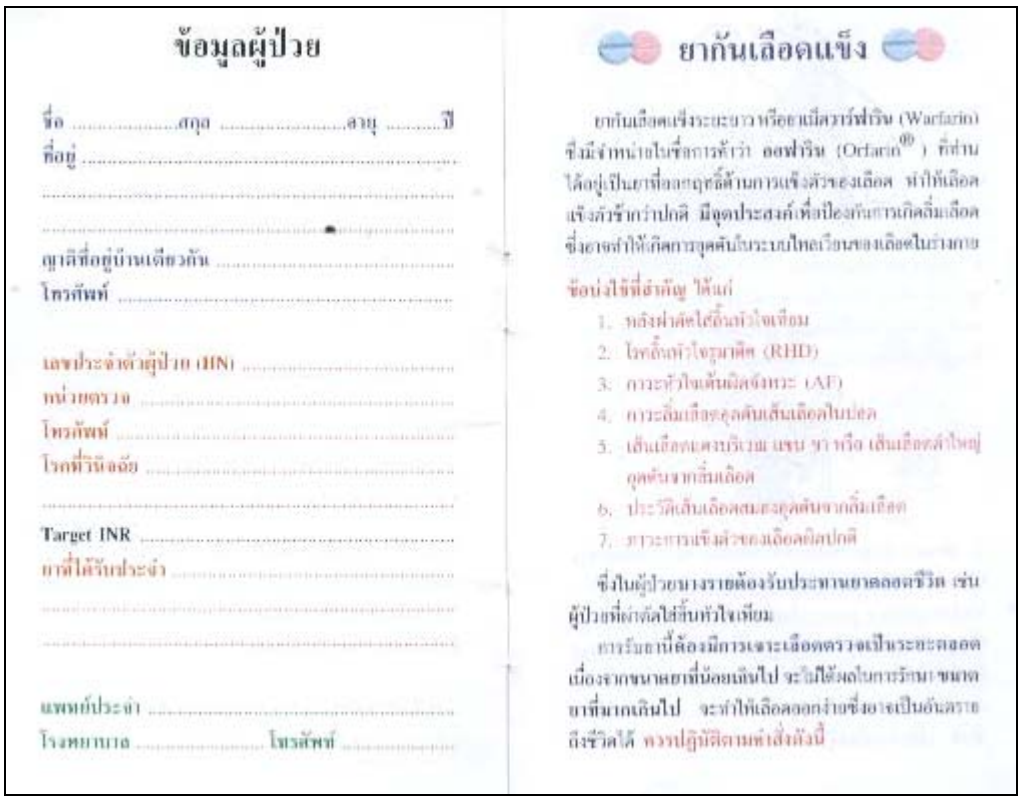
Post-test score .....คะแนน

หมายเหตุ.....

APPENDIX B

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว (Continued)



ข้อมูลผู้ป่วย

ชื่อ .....สกุล .....อายุ .....ปี
ที่อยู่ .....
.....
.....
ญาติที่อยู่บ้านเดียวกัน .....
โทรศัพท์ .....

เลขประจำตัวผู้ป่วย (HN) .....
หน่วยตรวจ .....
โทรศัพท์ .....
โรคที่วินิจฉัย .....
.....
Target INR .....
การได้รับประจำ .....
.....
.....

แพทย์ประจำ .....
โรงพยาบาล ..... โทรศัพท์ .....

ยากันเลือดแข็ง

ยากันเลือดแข็งระยะยาวหรือวาร์ฟาริน (Warfarin) ซึ่งมีจำหน่ายในชื่อการค้าว่า ออฟาริน (Orfarin®) ที่ท่านได้อยู่เป็นยาที่ออกฤทธิ์ต้านการแข็งตัวของเลือด ทำให้เลือดแข็งตัวช้ากว่าปกติ มีจุดประสงค์เพื่อป้องกันการเกิดลิ่มเลือดซึ่งอาจทำให้เกิดการอุดตันในระบบไหลเวียนของเลือดในร่างกาย

ข้อบ่งใช้ที่สำคัญ ได้แก่

1. หลังผ่าตัดใส่ลิ้นหัวใจเทียม
2. โรคลิ้นหัวใจรูมาติค (RHD)
3. การระทึกใจเต้นผิดจังหวะ (AF)
4. การระดับเลือดอุดตันเส้นเลือดในปอด
5. เส้นเลือดดำบริเวณ แขน ขา หรือ เส้นเลือดดำใหญ่อุดตันจากลิ่มเลือด
6. ประวัติเส้นเลือดสมองอุดตันจากลิ่มเลือด
7. ภาวะการแข็งตัวของเลือดผิดปกติ

ซึ่งในผู้ป่วยบางรายต้องรับประทานยาตลอดชีวิต เช่น ผู้ป่วยที่ผ่าตัดใส่ลิ้นหัวใจเทียม

การรับยานี้ต้องมีการเจาะเลือดตรวจเป็นระยะตลอด เนื่องจากขนาดยาที่น้อยเกินไป จะไม่ได้ผลในการรักษา ขนาดยาที่มากเกินไป จะทำให้เลือดออกง่ายซึ่งอาจเป็นอันตรายถึงชีวิตได้ ควรปฏิบัติตามข้อห้ามดังนี้

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว (Continued)

1. มาตรวจตามแพทย์นัด เพื่อเจาะตรวจดูฤทธิ์ของยาที่ให้ทุก 1-3 เดือน และปรับยาตามคำสั่งของแพทย์ ในกรณีไม่สามารถพบแพทย์ได้ตามนัดให้รับประทานยาในขนาดเดิมไว้ก่อน จนกว่าจะได้รับการเจาะเลือดและพบแพทย์

2. ท่านต้องรับประทานยาต่างต่อเนื่อง นอกจากมีอาการเลือดออกผิดปกติ เช่น เลือดกลากรามีรอยฟัน ปัสสาวะเป็นเลือด อาเจียนเป็นเลือด อุจจาระเป็นเลือด หรือเป็นสีดำ มีบาดแผลเลือดออกมาก มีรอยช้ำตามตัว เป็นจ้ำๆ ประจำเดือนออกมากผิดปกติ ไอเป็นเลือด เป็นต้น

ถ้ามีอาการดังกล่าว ให้ หยุดรับประทานยา และมาพบแพทย์ทันที เพื่อเจาะเลือดดูว่ารับประทานยามากหรือน้อยไป

3. ถ้าไปพบแพทย์หรือทันตแพทย์ด้วยปัญหาอื่น ต้องบอกให้แพทย์ทราบว่าท่านกำลังรับประทานยาต้านเลือดแข็งอยู่ โดยเฉพาะในกรณีที่จะต้องทำการผ่าตัด ถอนฟัน หรือต้องรับประทานยาอย่างอื่นเพิ่ม

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว (Continued)

4. ถ้าเกิดอุบัติเหตุ มีบาดแผล เลือดอาจออกไม่หยุด วิธีแก้ไขไม่ให้เลือดออกมาก คือใช้มือกดไว้ให้แน่นตรงบาดแผล เลือดจะหยุดออก หรือออกน้อยลง แล้วให้รีบไปโรงพยาบาลทันที เมื่อพบแพทย์หรือพยาบาลให้แจ้งว่าท่านรับประทานยากันเลือดแข็งอยู่

5. ท่านต้องนำบัตรประจำตัวผู้ป่วยที่ได้รับยาวาร์ฟาริน (warfarin card) ที่ได้รับพร้อมสมุดประจำตัวผู้ป่วย ที่รับการรักษาด้วยยากันเลือดแข็งระยะยาว ติดตัวตลอดเวลา เมื่อไปรับการตรวจรักษาที่สถานพยาบาลอื่น หรือเกิดอุบัติเหตุฉุกเฉิน ให้นำไปให้แพทย์ หรือพันตแพทย์ดู

6. ท่านควรบันทึกความเข้าใจรายละเอียดใน สมุดประจำตัวผู้ป่วย ที่รับการรักษาด้วยยากันเลือดแข็งระยะยาว และนำมาด้วยทุกครั้งที่แพทย์นัด

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว (Continued)

ข้อควรระวัง

7. ถ้ามีการเปลี่ยนแปลงที่อยู่ โปรดแจ้งให้พยาบาลหน่วยตรวจที่เกี่ยวข้อง และแพทย์ประจำตัว ของท่านทราบ เพื่อจะได้ติดต่อสอบถามอาการ และให้คำแนะนำ ในการรักษาได้อย่างต่อเนื่อง

8. ยาบางชนิดอาจเกิดปฏิกิริยากับ วาร์ฟาริน มีผลให้ระดับยาวาร์ฟารินหรือยาเริ่มที่ใช้ร่วมกันมีการเปลี่ยนแปลงระดับยาในกระแสเลือดได้ เช่น

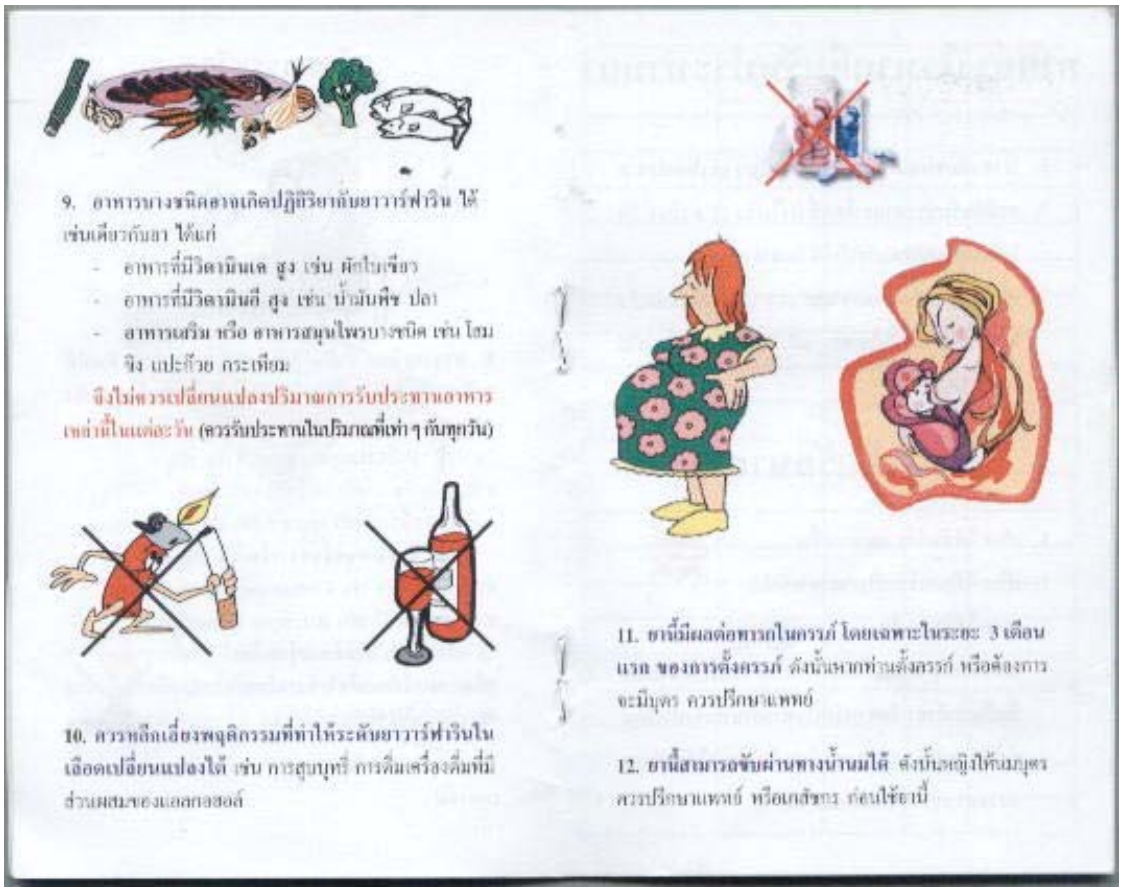
ยาที่เพิ่มฤทธิ์ของวาร์ฟาริน เช่น
ยารักษาโรคข้อ บางตัว เช่น Indomethacin
ยารักษาการติดเชื้อ บางตัว เช่น ยากลุ่ม Cephalosporins

ยาที่ลดฤทธิ์ของวาร์ฟาริน เช่น
ยากันชัก บางตัว เช่น Carbamazepine Phenytoin
ยารักษาวัณโรค บางตัว เช่น Rifampin Griseofulvin

ยาสมุนไพร ยาหม้อ ยาลูกกลอน หรือยาแผนโบราณอื่น ๆ ก็อาจมีผลต่อระดับยาวาร์ฟารินได้เช่นกัน

ดังนั้นจึงควรปรึกษาแพทย์ หรือเภสัชกรก่อนใช้ยาเหล่านั้น

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว (Continued)



9. อาหารบางชนิดอาจเกิดปฏิกิริยากับยาวาร์ฟาริน ได้เช่นเดียวกับยา ได้แก่
- อาหารที่มีวิตามินเค สูง เช่น ผักใบเขียว
- อาหารที่มีวิตามินอี สูง เช่น น้ำมันพืช ปลา
- อาหารเสริม หรือ อาหารสมุนไพรบางชนิด เช่น โสม จิง เปะก๊วย กระเทียม

จึงไม่ควรเปลี่ยนแปลงปริมาณการรับประทานอาหารเหล่านี้ในแต่ละวัน (ควรรับประทานในปริมาณที่เท่า ๆ กันทุกวัน)

10. ควรหลีกเลี่ยงพฤติกรรมที่ทำให้ระดับยาวาร์ฟารินในเลือดเปลี่ยนแปลงได้ เช่น การสูบบุหรี่ การดื่มเครื่องดื่มที่มีส่วนผสมของแอลกอฮอล์

11. ยานี้มีผลต่อทารกในครรภ์ โดยเฉพาะในระยะ 3 เดือนแรก ของการตั้งครรภ์ ดังนั้นหากท่านตั้งครรภ์ หรือต้องการจะมีบุตร ควรปรึกษาแพทย์

12. ยานี้สามารถขับผ่านทางน้ำนมได้ ดังนั้นจะมีให้นมบุตร ควรปรึกษาแพทย์ หรือเภสัชกร ก่อนใช้ยานี้

APPENDIX B. สมุดประจำตัวผู้ป่วยที่การรักษาด้วยยากันเลือดแข็งตัวระยะยาว (Continued)

ทำอย่างไรหากลืมรับประทานยา

1. **ห้าม**เพิ่มขนาดยา ที่รับประทานเป็น 2 เท่าโดยเด็ดขาด
2. กรณีลืมรับประทานยาโดยที่ ยังไม่ถึง 12 ชั่วโมง ให้รีบรับประทานยาทันทีที่นึกได้ ใน**ขนาดเดิม**
3. กรณีที่ลืมรับประทานยา และ เลย 12 ชั่วโมงไปแล้ว ให้**ข้าม**ยาในมื้อนั้นไปเลย แล้วรับประทานยามื้อต่อไปใน**ขนาดเดิม**

การเก็บรักษายา

1. เก็บยาให้พ้นแสง และความชื้น
2. เก็บยาไว้ในภาชนะที่โรงพยาบาลจัดให้
3. เก็บยาให้พ้นมือเด็ก

หมายเหตุ ลักษณะเม็ดยาวาร์ฟาริน จะมีสีไม่สม่ำเสมอ ซึ่งเป็นปกติของเม็ดยาวาร์ฟารินท่านสามารถรับประทานต่อได้ตามปกติ และ*กรุณานำยาที่เหลือมาให้เภสัชกรตรวจสอบทุกครั้งที่มาพบแพทย์*

ว/ด/ป	ขนาดยาที่ได้	PT(sec)	INR	นัดครั้งหน้า

APPENDIX C

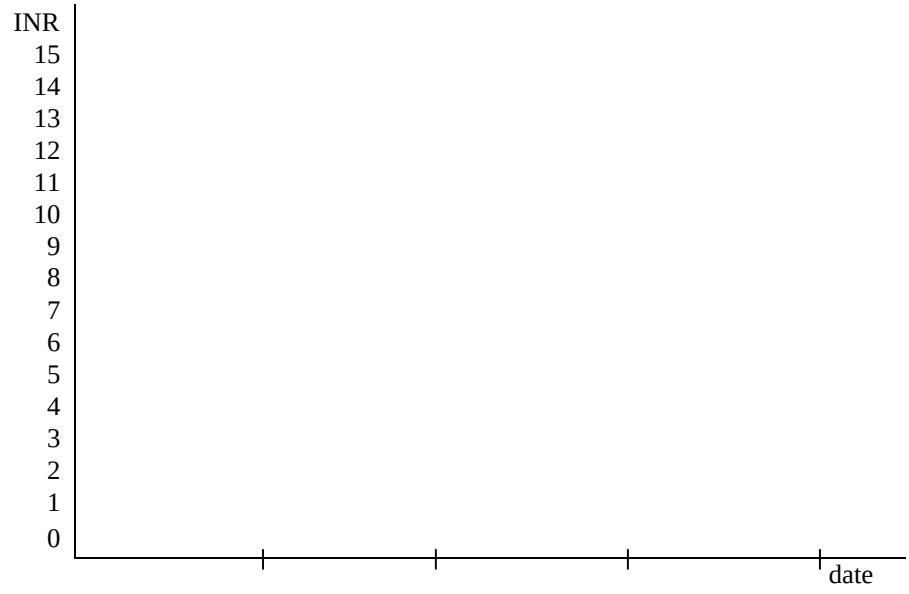
APPENDIX C. Patient Medication Record

Patient Medication Record

Patient name	Age	Sex	HN	CNS
Address		Occupation		Education
Indication for warfarin		Dated treatment started		
Tel.		pharmacist		Physician
History of patient illness				
Family/Social history				
Lifestyle/diet				

Date	Dose	Dose adjustment	INR	Intervention	Progress note

Concurrent drugs



APPENDIX D

APPENDIX D. List of drugs that interact with warfarin

No	Drugs	Sig	Onset	Severity	Doc	Effect	Mechanism	Management
1	Aminoglutethimide	2	Delayed	Mod	suspect	Anticoagulant effect may be decreased	Increased warfrain clearance, probably because of liver microsomal enzyme induction.	Monitor prothrobin time when adding or stopping aminoglutethimide.
2	Amiodarone	1	Delayed	Major	establish	Augments hypoprothrombinemia effect	Inhibit S/R isomer of warfarin metabolism	30%-50% dose of warfarin reduction, monitor INR closely,These effect may persist for weeks-months after discontinuation of amiodarone, necessitating continued warfarin dose adjustment
3	Androgen: danazol, methyltestosterone, oxymetholone	1	Delayed	Major	probable	Augments hypoprothrombinemia effect	Unknown	Avoid the combination if possible, when adding, warfarin dose requirements will be reduced. Monitor INR closely
4	Azole antifungal: fluconazole, Itraconozole, ketoconazole, miconazole	1	Delayed	Major	probable	Anticoagulant effect may be increased	Probably inhibit warfarin metabolism	Monitor closely, adjust dose of warfarin if need
5	Babiturates: amobarbital,phenobarbital,secobarbital	1	Delayed	Major	establish	Reduce the effect of warfarin	Inductuion of hepatic microsomal enzymes	Monitor closely, adjust dose of warfarin if need.Termination of barbiturates therapy will result in decrease warfarin requirements.
6	Carbamazepine	2	Delayed	Mod	suspect	Anticoagulant effect may be decreased	Unknown, however believed to result from induction of hepatic metabolism of warfarin	Monitor INR when start or stopping carbamazepine therapy,dose adjustment may be necessary.
7	Cephalosporins	2	Delayed	Mod	suspect	Anticoagulant effect may be increased	Unknown	May be reduced warfarin doses during administration of parenteral cephalosporins.

APPENDIX D. List of drugs that interact with warfarin (Continued)

No	Drugs	Sig	Onset	Severity	Doc	Effect	Mechanism	Management
8	Chloramphenicol	2	Delayed	Mod	suspect	Anticoagulant effect may be increased	Unknown, animal experiments suggest inhibition of hepatic metabolism of warfarin.	Monitor INR and adjust doses of warfarin if need.
9	Cholestyramine	2	Delayed	Mod	probable	Anticoagulant effect may be decreased	Reduce warfarin absorption and possibly increased elimination.	Separate administration of these agents by at least 3 hours.
10	Cimetidine	1	Delayed	Major	establish	Anticoagulant effect may be increased	Inhibit R isomer of warfarin metabolism	Avoid the combination if possible, when adding, warfarin dose requirements will be reduced. Monitor INR closely
11	Dextrothyroxine	1	Delayed	Major	probable	Augments hypoprothrombi-nemia effect	Unknown	Monitor closely, lower dose of warfarin may be required
12	Disulfuram	2	Delayed	Mod	probable	Anticoagulant effect may be increased	Unknown	Monitor closely, adjust dose of warfarin if need
13	Fibric acids: clofibrate, gemfibrozil, fenofibrate	1	Delayed	Major	establish	Augments hypoprothrombinemia effect	Unknown	Monitor closely, and observe the patient for sign of bleeding.
14	Glucagon	2	Delayed	Mod	probable	Anticoagulant effect may be increased in patients receiving sustained doses of glucagon (bleeding may occur)	Unknown	Monitor patients receiving warfarin and glucagon concurrently daily for prothrombin activity and signs of bleeding. Adjust doses as needed.

APPENDIX D. List of drugs that interact with warfarin (Continued)

No	Drugs	Sig	Onset	Severity	Doc	Effect	Mechanism	Management
15	Glutethimide	2	Delayed	Mod	probable	Anticoagulant effect may be decreased	Glutethimide appears to increase the clearance of warfarin by stimulation of hepatic microsomal enzymes.	Monitor INR carefully and adjust doses of warfarin if need.
16	Griseofulvin	2	Delayed	Mod	suspect	Anticoagulant effect may be decreased	Unknown	In patients stabilized on warafrin therapy, monitor INR more frequently when griseofulvin dosage is altered.
17	HMG-CoA reductase inhibitors	2	Delayed	Mod	suspect	Anticoagulant effect may be increased	Inhibition of warfarin hepatic metabolism is suspected.	Monitor INR when start or stopping coadministration of an HMG-CoA reductase inhibitor.
18	Hydantoins: phenytoin	2	Delayed	Mod	suspect	Increase hydantoin serum concentrations with possible toxicity. Increased prothrombin times and increased risk of bleeding.	Several mechanism may be involved.	Monitor patients for signs or symptoms of altered response to hydatoins or warfarin while receiving the combination or when starting of stopping either drug.
19	Levamisole	2	Delayed	Mod	suspect	Anticoagulant effect may be increased	Unknown	Monitor INR when start or stopping coadministration of levamisole. Be prepared to adjust thr warfarin dose as indicated.
20	Macrolide antibiotic: Azithromycin, erythromycin, clarithromycin	1	Delayed	Major	probable	Anticoagulant effect may be increased	Reduce warfarin clearance	Monitor INR frequently when start or stopping macrolide antibiotic,dose adjustment may be necessary for several days following discontinuation.
21	Metronidazole	1	Delayed	Major	establish	Anticoagulant effect may be increased	Inhibit S isomer of warfarin metabolism	Monitor closely, lower dose of warfarin may be required

APPENDIX D. List of drugs that interact with warfarin (Continued)

No	Drugs	Sig	Onset	Severity	Doc	Effect	Mechanism	Management
22	Nalidixic acid	2	Delayed	Mod	suspect	Anticoagulant effect may be increased	Displacement of warfarin from binding sites on plasma proteins. The sustained nature of this interaction indicates another mechanism is also involved.	Monitor INR closely when coadministration of nalidixic acid. A deceased dose of warfarin may be required.
23	NSAIDs: fenoprofen, indomethacin, ibuprofen, ketoprofen,medclofenamate, naproxen,piroxicam, sulindac, tolmetin,diclofenac	2	Delayed	Mod	suspect	NSAID may increase bleeding risk of warfarin. The hypoprothrombinemic effect of warfarin may be increase.	Gastric irretation/decreased platele function contribute.	Monitor patients closely, instruct patients reguarding the early signs and symptoms of bleeding and report to physicain.
24	Penicillins: nafcillin, dicloxacillin,	2	Delayed	Major	suspect	Large IV doses of penicillins can increase the bleeding time. Controversely, nafcillin and dicloxacillin have been associated with warfarin resistance, which may percist at least 3 weeks following discontinuation of the antibiotic.	Warfarin-induced hypoprothrombinemia in conjugation with penicillin-induced inhibition of ADP-mediated platelet aggregation. Possible hepatic enzyme induction for nafcillin and dicloxacillin-induced warfarin resistant.	Monitor for bleeding when giving high dose IV penicillins and warfarin concurrently. In patients receiving nafcillin or dicloxacillin. Carefully monitoring INR on initiation and for at least 3 weeks folloeing discontinuation of the antibiotic.

APPENDIX D. List of drugs that interact with warfarin (Continued)

No	Drugs	Sig	Onset	Severity	Doc	Effect	Mechanism	Management
25	Phenybutazone	1	Delayed	Major	establish	anticoagulant effect may be increased	impair liver metabolism, and cause displacement from plasma protein	Should avoid combination,alternative NSAID agents are safer.
26	Quinine derivatives: Quinidine, quinine	1	Delayed	Major	suspect	Anticoagulant effect may be increased	Quinine derivative may inhibit the hepatically synthesized clotting factors	Monitor closely, lower dose of warfarin may be required
27	Rifamycin: rifabutin, rifampin	2	Delayed	Mod	establish	Anticoagulant effect may be decreased	Increased warfrain clearance, probably because of liver microsomal enzyme induction.	Increase dosage of warafrin will likely required when rifamycins are administered cocommitantly. Monitor INRclosely when rifamycins are discontinued.
28	Salicylates: aspirin, methylsalicylate	1	Delayed	Major	establish	Anticoagulant effect may be increased. The adverse effects of aspirin on gatric mucosa and platelet function may also enhance the possibility of bleeding	Complicated	Monitor closely, adjust dose of warfarin may be required,instruct patients reguarding the early signs and symptoms of bleeding
29	Sulfonamides: sulfamethoxazole, sulfisoxazole, co-trimoxazole,sulfamethizole	1	Delayed	Major	establish	Anticoagulant effect may be increased	Unclear. However co-trimoxazole appears to inhibit S isomer metabolism of warfarin	Monitor closely, lower dose of warfarin may be required
30	Thioamine: methimazole, PTU	1	Delayed	Major	suspect	Anticoagulant effect may be changed	Unknown	Monitor closely, adjust dose of warfarin may be required,instruct patients reguarding the early signs and symptoms of bleeding or subtherapeutic response to warfarin

APPENDIX D. List of drugs that interact with warfarin (Continued)

No	Drugs	Sig	Onset	Severity	Doc	Effect	Mechanism	Management
31	Thyroid hormones: levothyroxine, liothyronine	1	Delayed	Major	probable	Anticoagulant effect may be increased	A more rapid disappearance of vitamin K-dependent clotting factor as a result of thyroid hormone administration has been proposed but not clearly established.	Monitor closely, instruct patients reguarding the early signs and symptoms of bleeding.Dose of warfarin may be decrease during concurrent. Controversely, warfarin dose may need to be increased if discontinuation of thyroid hormone.
32	Vitamin E	1	Delayed	Major	suspect	Anticoagulant effect may be increased	Vitamin E may interfere with vitamin K-dependent clotting factors, thereby adding to the effects of warfarin	Monitor closely, lower dose of warfarin may be required,instruct patients reguarding the early signs and symptoms of bleeding
33	Vitamin K	2	Delayed	Mod	establish	Warfarin action is attenuated or reversed leading to possible thrombus formation. Decreased vitamin K intake may increase the effect of warfarin.	Vitamin K interfere with warfarin mechanism of action.	Warfarin doses may be need to be altered.

Doc=documentation,establish=established, Mod=moderate, No= number, Sig. = Significant, suspect=suspected,

APPENDIX E

APPENDIX E. Outcomes Assessment

Outcomes Assessment

Patient Name_____Age_____Sex_____HN__-_____CNS_____
Date_____

□ **Drug-related problems**
□ Drug-drug interaction □ Drug-disease interaction
□ Drug-food interaction □ Non compliance
□ .....

□ **Major bleeding**.....
□ Decrease in hemoglobin of ≥ 2.0 g/dL
□ Hospitalization.....
□ Blood transfusion
□ .....

□ **Minor bleeding**.....
□ Brusing
□ Bleeding gum
□ Epistaxis
□ Bleeding from minor trauma
□ Decrease of packed cell volume 4 hematocrit unit
□ .....

□ **Thromboembolic event**
□ Cerebrovascular accident (CVA) or stroke.....
CT-scan □ Yes □ No
□ Transient ischemic attack (TIA).....
CT-scan □ Yes □ No
□ Valve thrombosis.....
Echocardiography □ Yes □ No
.....
□ Peripheral or systemic emboli.....
Angiography □ Yes □ No
Surgery □ Yes □ No
□ .....

APPENDIX F

APPENDIX F. Standard interventions by clinical pharmacists of the CVT clinic for initial visit

Standard interventions by clinical pharmacists of the CVT clinic for initial visit

During the initial visit with clinical pharmacists, the following procedures are performed.

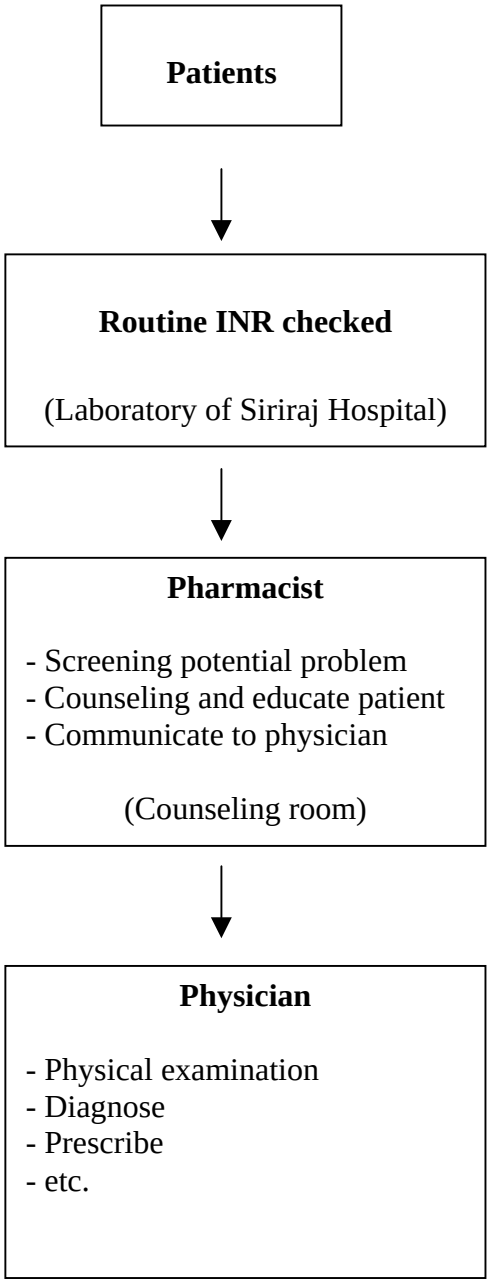
1. Demographic and clinical data will be collected. (APPENDIX C)
2. Patients will be asked 10 questions (APPENDIX A) designed to test their knowledge regarding warfarin therapy. These questions are largely based on the contents of medication counseling and the warfarin booklet produced by the CVT team (APPENDIX B).
3. Patient education on general information about warfarin, dosing regimen, administration technique, signs and symptoms of hemorrhagic or thromboembolic complications, measures to avoid drug interactions, first-aid in the event of bleeding, importance of compliance, modification of lifestyle to decrease risk of complications. Written information of the above issues is given to the patient after the end of the education session.
4. After the education session, the patient will be asked the same 10 questions again to evaluate the post-education score.
5. Screening for drug-related problems such as drug - drug or drug - food interaction (APPENDIX D) that may interfere to warfarin therapy is performed. If such problem has been identified, it will be communicated to the patient' s primary care provider.
6. Patient is given a warfarin card in case of emergency along with warfarin booklet containing INR records.

APPENDIX G

APPENDIX G. Flow of the CVT clinic

Flow of the CVT clinic

Summary the steps of clinic procedures



APPENDIX H

APPENDIX H. Standard interventions by clinical pharmacists of the CVT clinic for follow-up visits

Standard interventions by clinical pharmacists of the CVT clinic for follow-up visits

During the follow-up visit with clinical pharmacists, the following procedures are performed.

1. Assessment of compliance to warfarin therapy
2. Identification of thromboembolic and hemorrhagic complications
3. Detection of drug interactions and suggestion of measures to prevent, avoide or minimize drug interactions
4. Review of patient medication profile since previous visit
5. Suggestion of appropriate dosage adjustment to the primary care provider in case of sub- or supra-therapeutic INRs

BIOGRAPHY

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