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Research Article

Clinical outcomes of pharmacist-managed care for inpatients with warfarin at Bangkok Metropolitan Administration General Hospital

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ABSTRACT

Previous studies suggested that providing anticoagulation management services by pharmacist improved anticoagulation control in outpatients who uses warfarin. However, few studies evaluated hospitalized patients. Purpose of this study is to assess the impact of additional pharmacist- managed care to usual care in inpatient treating with warfarin.

This study was a quasi- experimental study. Patients in intervention group were monitored by a clinical pharmacist who recommended warfarin dose, screened and managed drug therapeutic problems related to warfarin therapy, suggested monitoring plan and provided patient education. Results of intervention group were compared to historical control (usual care). A total of 92 patients were included (49 cases in control group and 43 patients in intervention group) . Baseline data were not significantly different between two groups. Percentage of patients with international normalized ratio (INR) in target at first followed-up visit in the intervention group was more than those in the control group (60.47% vs. 30.61%, p = 0.015). In control group, one patient had bleeding during admission and 4 patients readmitted due to adverse effect of supratherapeutic warfarin level. On the contrary, there was no adverse event found in the intervention group.

The results of this study suggest that coordination with clinical pharmacists and physicians improved quality of treatment among inpatients receiving warfarin and reduced complications of warfarin use.

1. INTRODUCTION

Warfarin is the most commonly prescribed oral anticoagulant that has been used for more than six decades. Its effectiveness for prevention and treatment of venous and arterial thromboembolism is well established but patients may have serious adverse effects. Thromboembolism and bleeding are the most frequent complications of warfarin therapy [1]. Anticoagulation with warfarin, a narrow therapeutic drug is complicated because of its unpredictable pharmacodynamics, highly inter-individual variability in dose-response, many medications and diet interactions which alter pharmacokinetics of warfarin [1,2]. So, it was not surprising that warfarin has been the most commonly reported medication associated with hospitalization [3].

Results of previous studies suggested that providing anticoagulation management services improved anticoagulation control in outpatient [1]. However, few studies evaluated in hospitalized patients [4-8]. The consequences of these researches concluded that warfarin management by a pharmacist could improve anticoagulation control, significant decrease of patients' length of hospital stay, increased proportion of time spent within therapeutic range, and lower number of patients who received excessive anticoagulation therapy in inpatient setting when compared with usual care. Similarly with a research by Tongsrisomboon P.[9] conducted in Ramathibodi Hospital, more than 1,000-bed university hospital in Thailand, the results revealed that inpatient warfarin monitoring service provided by clinical pharmacist could increase rate of patients who had INR in the target about 50% and could reduce hemorrhagic complications also.

With the different type and size of hospital from previous study, the purpose of this study is to assess the impact of additional pharmacist-managed care to usual care in inpatient treating with warfarin focusing on quality of anticoagulation control at Bangkok Metropolitan Administration (BMA) General Hospital, a 400-bed general hospital with hypothesis that providing pharmacist-managed care for inpatients treating with warfarin can improve anticoagulation control and reduce the complication and hospital stay.

2. MATERIALS AND METHODS

2.1. Material

The materials used in this study include: data collection form, BMA General Hospital Warfarin booklet supported by Berlin Pharmaceutical Industry Co., Ltd. and source of patient's information which were computerized database of BMA General Hospital and outpatient and inpatient chart.

2.2. Method

2.2.1. Definition of intervention

Pharmacist-managed care: This service is performed by a clinical pharmacist which includes laboratory monitoring, providing warfarin dosage adjustment recommendation, screening and reporting potential drug interactions to physician, providing suggestion to prevent or manage problems associated with warfarin therapy, performing patient education and discharge counseling. All recommendations and interventions were provided to physician base on standard drug information such as Micromedex, Drug interaction facts and literature search from Medline by direct verbal communication if the physician was available at ward or by written consultation as a pharmacist note on progress note in patient chart. The physician is free to accept or reject the pharmacist's recommendation.

2.2.2. Study design

This study was a comparative, quasi-experimental study.

2.2.3. Ethical consideration

The study protocol was approved by the Faculty of Dentistry/ Faculty of Pharmacy Mahidol University Institutional Review Board (MU-DT/PY-IRB) and Human Research Ethic Committee of Medical Service Department of Bangkok Metropolitan Administration.

2.2.4. Study population

Patients who were admitted at BMA General Hospital were selected according to inclusion and exclusion criteria as follow:

2.2.4.1. Inclusion criteria

Historical control group

1. Adult patients (> 18 years old) who were admitted in June to November 2013.
2. Received warfarin ≥ 3 doses in hospital and continued use till first followed-up visit.
3. Had INR measures in hospital before discharge and at first followed-up visit.

Intervention group

1. Adult patients (> 18 years old) were admitted in September 2014 to February 2015.
2. Received warfarin ≥ 3 doses in hospital and continued use till first followed-up visit.
3. Had INR measures in hospital before discharge and at first followed-up visit.
4. Patients or caregivers (in case of unconscious) who consented to treatment and signed consent form.

2.2.4.2. Exclusion criteria

Patient who was adjusted warfarin dose after discharged before first followed-up visit.

2.2.4.3 Criteria for termination

a) Patients who did not want to continue the treatment at BMA General Hospital.

b) Patients lost to followed-up after discharge (Delay > 2 weeks after appointment).

c) Patients died from any causes during the study period which was not related to warfarin complication.

d) Patients decided to terminate from the study.

2.2.4.4. Sample size calculation

Sample size estimation was based on Tongsrisomboon P [9] study. Which was conducted to assess the impact of warfarin monitoring service by clinical pharmacists on the quality of anticoagulation control in hospitalized patients at Ramathibodi Hospital. Proportion of patients having coagulation therapy in therapeutic range was significantly higher in the intervention group (62.5% VS 30.0%, P < 0.001) and expected INRs outside therapeutic range in intervention group compared to control group is 100% decrease. Based on significance level $\alpha = 0.05$ and equal sample size from two proportions, required sample size for two arms to achieve an 80% power ($\beta = 0.2$) can be determined by sample size in each group of 36 patients. As estimated plus of 30% for drop out, calculated subjects in each group should be 50 patients.

$$N = \left[\frac{Z\alpha/2\sqrt{2PQ} + Z\beta\sqrt{P1Q1 + P2Q2}}{P1 - P2} \right]^2$$

$$N = \left[\frac{1.96\sqrt{2(0.4625)(0.5375)} + 0.842\sqrt{(0.625)(0.375) + (0.30)(0.70)}}{0.625 - 0.30} \right]^2$$

$$N = 36$$

Where N = Number of patients in each group; Control group and intervention group.

$Z_{\alpha/2}$ = Z value corresponding to the two-tailed alpha ($\alpha = 0.05$); $Z_{\alpha/2} = 1.96$

Z_{β} = Z value corresponding to the beta ($\beta = 0.20$) to achieve 80% power;

Z_{β} = 0.842

P_1 = Proportion of patients with therapeutic INR in intervention group; $P_1 = 0.625$

P_2 = Proportion of patients with therapeutic INR in control group; $P_2 = 0.30$

P = (P1 + P2)/2; P = 0.4625

Q = 1 - P; Q = 0.5375

Q1 = 1 - P1; Q1 = 0.375

Q2 = 1 - P2; Q2 = 0.70

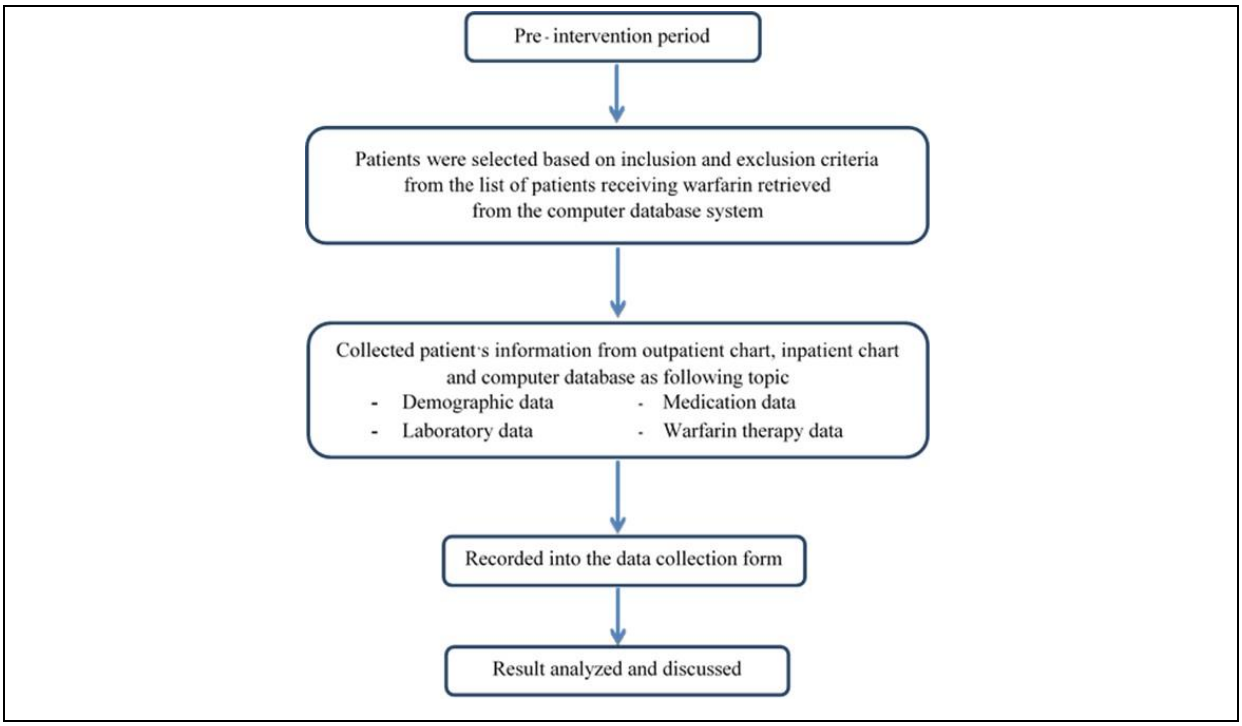

Figure 1. Drescribe study process of pre-intervention period

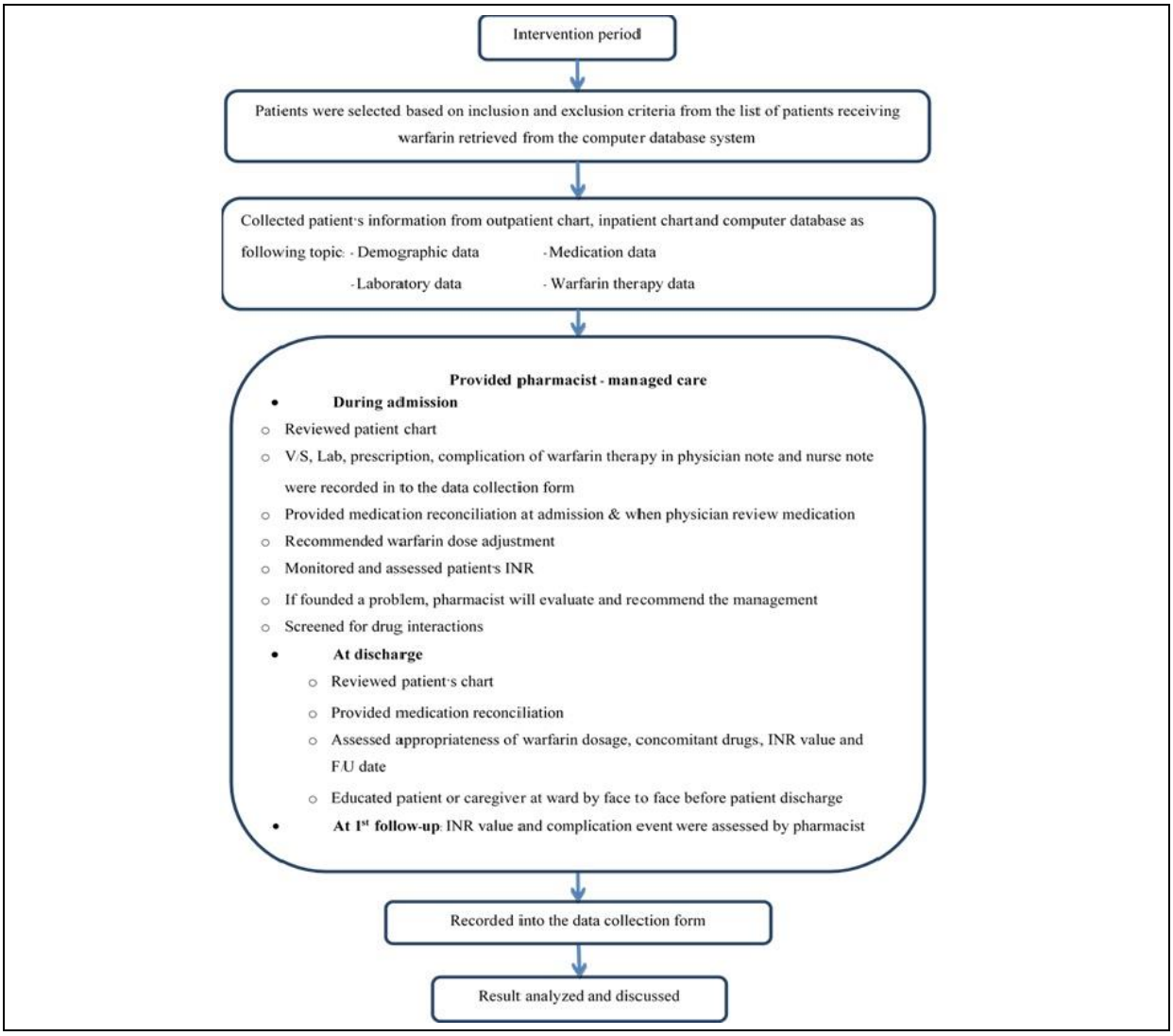

Figure 2. Drescribe study process of intervention period

2.2.5 Study process

This study was divided into 2 periods: pre –intervention period (control group) (Figure 1) and intervention period (intervention group) (Figure 2). Each period covered patients about 6 months.

2.2.6 Study outcome

2.2.6.1 Anticoagulation control

Anticoagulation control is expressed as the percentage of patients achieve therapeutic INR, sub-and supratherapeutic INR at discharge, and at first followed-up visit.

2.2.6.2 Complication events

 Hemorrhagic complications including minor and major bleeding during admission and until first followed-up visit. Major bleeding [10-14] is bleeding which decrease in hemoglobin ≥ 2 g/dL or require blood transfusion ≥ 2 units or fatal or life -threatening bleeding e.g. intracranial bleeding, retroperitoneal bleeding, intraocular bleeding, and major hematoma or bleeding in body cavity e.g. gastrointestinal bleeding, gross hematuria. Minor bleeding is all types of bleeding but not meet the criteria for major bleeding.

 Thromboembolic complications [15,16] are the obstruction of blood vessel with thrombolic material carried via blood stream from the site of origin to occlude in another vessel which includeding cerebrovascular accident (CVA) or stroke, transient ischemic attack (TIA), valve thrombosis, peripheral or systemic embolism during admission and until first followed-up visit.

2.2.6.3 Drug therapy problems (DTPs)-associated with warfarin therapy

2.2.6.4 Pharmacist's interventions and result of interventions

 Pharmacist's interventions are divided in suggestion on time to INR monitoring, dose adjustment and suggestion of safer drugs.

 Result of interventions is referred to physician acceptance. This term is categorized as following:

a) Accepted means physician modifies the treatment based on pharmacist's intervention.

b) Partially accepted means physician modifies some part of the treatment based on pharmacist's intervention.

c) Not accepted means physician did not accept or modify treatment according to pharmacist's intervention.

2.2.7. Data analysis

All statistical analysis was performed by the Statistical Package for Social Science (SPSS) program version 21 and all statistical tests were used p-value of less than 0.05 to detect statistical significant difference. Data from control and intervention group were analyzed as following:

2.2.7.1 Demographic data were presented as descriptive statistics and were compared between control and intervention group as follows:

 Nominal scale such as gender, history of warfarin usage were compared by Chi-square test.

 Interval or ratio scale with normal or non-normal distribution of data such as age, number of INR measurement were compared by using independent t-test or Mann-Whitney U test, respectively.

2.2.7.2 The anticoagulation control

 Average INR at discharge and at the first followed-up visit were compared by using independent t-test or Mann-Whitney U test if the data distributed in non-normal pattern.

 Proportion of patients with therapeutic, subtherapeutic and supratherapeutic INR at discharge and at the first followed-up visit between the control and the intervention groups were compared by using Chi-square test.

2.2.7.3 Complication events

 Number and percentage of hemorrhagic and thromboembolic events during admission and after discharge.

 Proportion of hemorrhagic and thromboembolic complications during admission and after discharge between the historical control and the intervention groups were compared by using Chi-square test.

2.2.7.4 Drug therapy problems (DTPs) associated with warfarin therapy

 Number and percentage of types of DTPs*.

2.2.7.5 Type of pharmacist's interventions and result of interventions

 Number and percentage of types of pharmacist's interventions.

 Number and percentage of types of physician acceptance

* Drug therapy problems (DTPs) in the control group may be under reported due to lack of elaborate identification and incompleteness documentation. Consequently, DTPs was evaluated only in the intervention group.

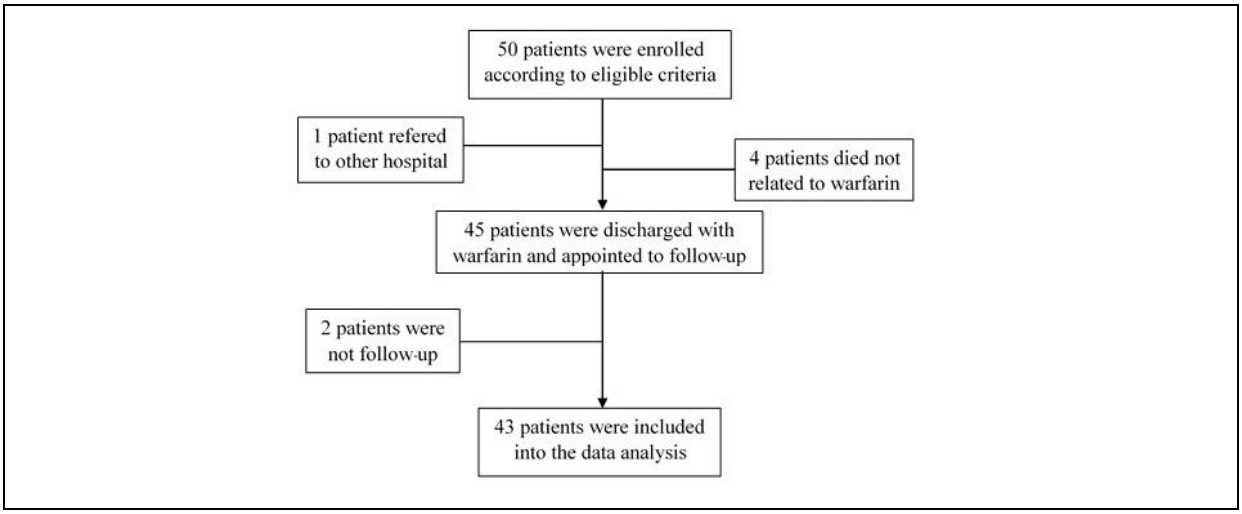

Figure 3. Describe recruitment diagram of patients in the study group

Table 1 Baseline characteristics of participants

Baseline characteristics	Control (n=49)	Study (n=43)	p-value
Gender (%)			
- Male	23(46.9)	12(27.9)	0.061[a]
- Female	26(53.1)	31(72.1)	
Age (years)			
- Average age	61.98 ± 16.154	64.51 ± 15.898	0.305[c]
- Median	65	68	
- Range	[21-95]	[24-87]	
Previous use of warfarin (%)	17 (34.7)	23 (53.5)	0.07[a]
Social history (%)			
- Alcohol drinking	4 (8.16)	2(4.65)	0.496[a]
- Cigarette smoking	1(2.04)	4(9.30)	0.125[a]
- Herbal medicine uses	2(4.08)	5(11.63)	0.173[a]
Underlying disease (%)			
- No underlying disease	3 (6.12)	2 (4.65)	0.655[a]
- 1 underlying disease	5 (10.20)	2 (4.65)	
- 2 underlying diseases	11 (22.45)	8 (18.6)	
- 3 underlying diseases	11 (22.45)	10 (23.26)	
- > 3 underlying diseases	19 (38.78)	21 (48.84)	
Indication for warfarin (%)			
- Atrial fibrillation	22 (44.90)	21 (48.84)	0.611[a]
- Deep vein thrombosis	15 (30.61)	10 (23.25)	
- Stroke	6 (12.24)	3 (6.98)	
- Valvular heart disease	2 (4.08)	1 (2.33)	
- Pulmonary embolism	3 (6.12)	7 (16.27)	
- Raynaud's disease	1 (2.04)	1 (2.33)	
Time to first follow-up visit (days)	11.29± 3.797	10.28± 4.697	0.259[b]
Total INR investigation	240	223	
- Average INR test	4.90±4.403	5.19±5.881	0.955[c]
- Median	4	3	

a = Chi's square, b = Independent t-test, c = Mann-Whitney U test

3. RESULTS

In the study period, 50 patients were recruited. Of those, 7 patients were excluded from the data analysis due to the following reason: 4 patients died from causes which were not related to warfarin therapy during admission, 2 patients were not followed up and 1 patient was referred to other hospital for surgery. Accordingly, 43 patients were included into data analysis in intervention group. In control group, 49 patients were recruited based on inclusion criteria. Eventually, 92 patients were evaluated. Recruitment diagram of intervention group was shown in Figure 3.

3.1. Demographic data

Baseline characteristics of patients are presented in Table 1. All demographic data were comparable between 2 groups.

3.2. Primary outcomes

3.2.1. Anticoagulation control

At discharge, the average INR in control group was 1.79± 0.68 and 1.95± 0.73 (P = 0.29) in the intervention group which were not statically significant different. When followed-up visit, INR in control group was 2.72± 2.39 and 2.62± 1.61 (P = 0. 82) in intervention group which were not statistically significant different. Average and range of INR was shown in Table 2. Distribution of patient's INR at discharge and at first followed-up visit was displayed in Figure 4 and 5 respectively.

The proportion of patients with therapeutic, subtherapeutic and supratherapeutic INR at discharge and at first followed-up visit were shown in Table 3.

There was no statistical significant difference of anticoagulation control between two groups at discharge but some positive trend was observed (28.6% vs 32.6%; p=0.500). On the contrary, proportion of patients with therapeutic INR at first followed-up visit was higher than control group statistical significantly (30.61% vs 60.47%; p=0.015).

Only one patient in control group was found bleeding complication due to warfarin (0. 18 events/100 patient-days) during admission. There was no hemorrhagic adverse event found in intervention group. Proportion of hemorrhagic

Table 2 Average and range of INR in each group

Monitoring time	Control (n=49)	Study (n=43)	p-value
At discharge	1.79± 0.68 [0.97-4.22]	1.96± 0.72 [1.04-3.97]	0.259[a]
At first follow-up visit	2.72± 2.39 [0.79-12.75]	2.59± 1.60 [1.08-10.78]	0.758[a]

[a] Independent sample t-test was used to evaluate the statistical significant difference between group

Table 3 Anticoagulation control of patients in each group

Anticoagulation control	Control group (%) (n=49)	Study group (%) (n=43)	p-value
At discharge			
Therapeutic INR	14 (28.57)	14 (32.56)	0.500[a]
Subtherapeutic INR	33 (67.35)	25 (58.14)	
Supratherapeutic INR	2 (4.08)	4 (9.30)	
At first-follow-up visit			
Therapeutic INR	15 (30.61)	26 (60.47)	0.015[a, *]
Subtherapeutic INR	24 (48.98)	11 (25.58)	
Supratherapeutic INR	10 (20.41)	6 (13.95)	

[a] Chi-square test used to evaluate the statistical significant difference between group
* Statistically significance at $p < 0.05$

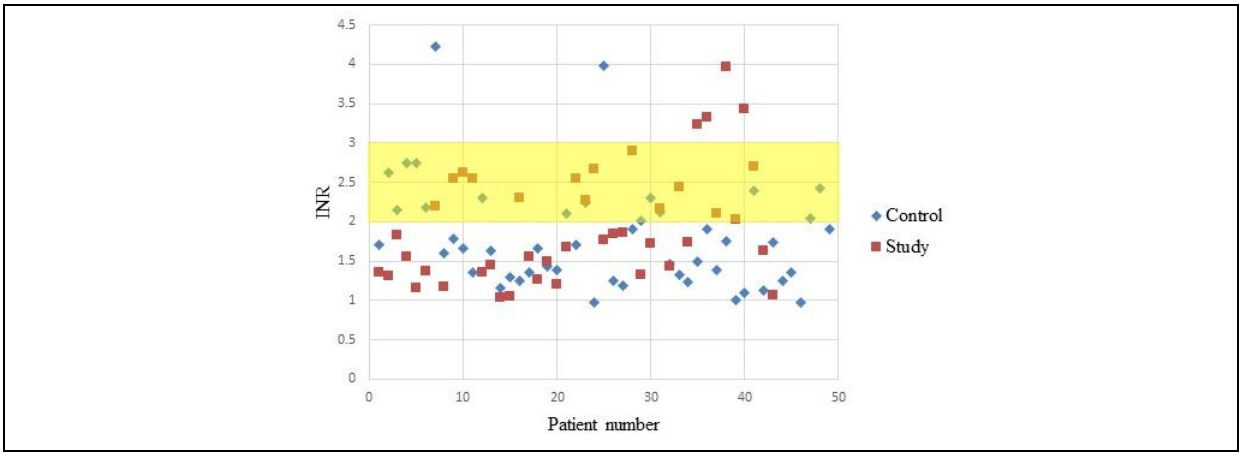

Figure 4. Describe distribution of patient's INR at discharge

complications during admission between two groups was not different.

3.2.2. Complication

After discharge, 4 patients in control group had to readmit due to bleeding or suspected bleeding from supratherapeutic INR. A half of them had major bleeding reported which were intracerebral hemorrhage (ICH) and lower gastrointestinal bleeding (LGIB). Another was admitted for close monitoring without an evidence of hemorrhage. On the other hand, no patient in intervention group was found hemorrhagic complication. There was no patient presented with blood occlusion event in both groups whether during admission or after discharge.

3.3. Secondary outcomes

3.3.1. Drug therapy problems (DTPs)-associated with warfarin therapy

In the study period, pharmacist detected 33 DTPs involved with warfarin therapy. The most common DTP was dosage too low 17 problems (51.52%) followed by dosage too high 10 problems (30.30%) and the last was drug interaction 6 problems (18.18%). Acceptance in each type of DTPs are presented in Table 4.

3.3.2. Pharmacist's intervention

Pharmacist consulted physician for 95 interventions which included recommended dosage adjustment 27 interventions (28.42%),

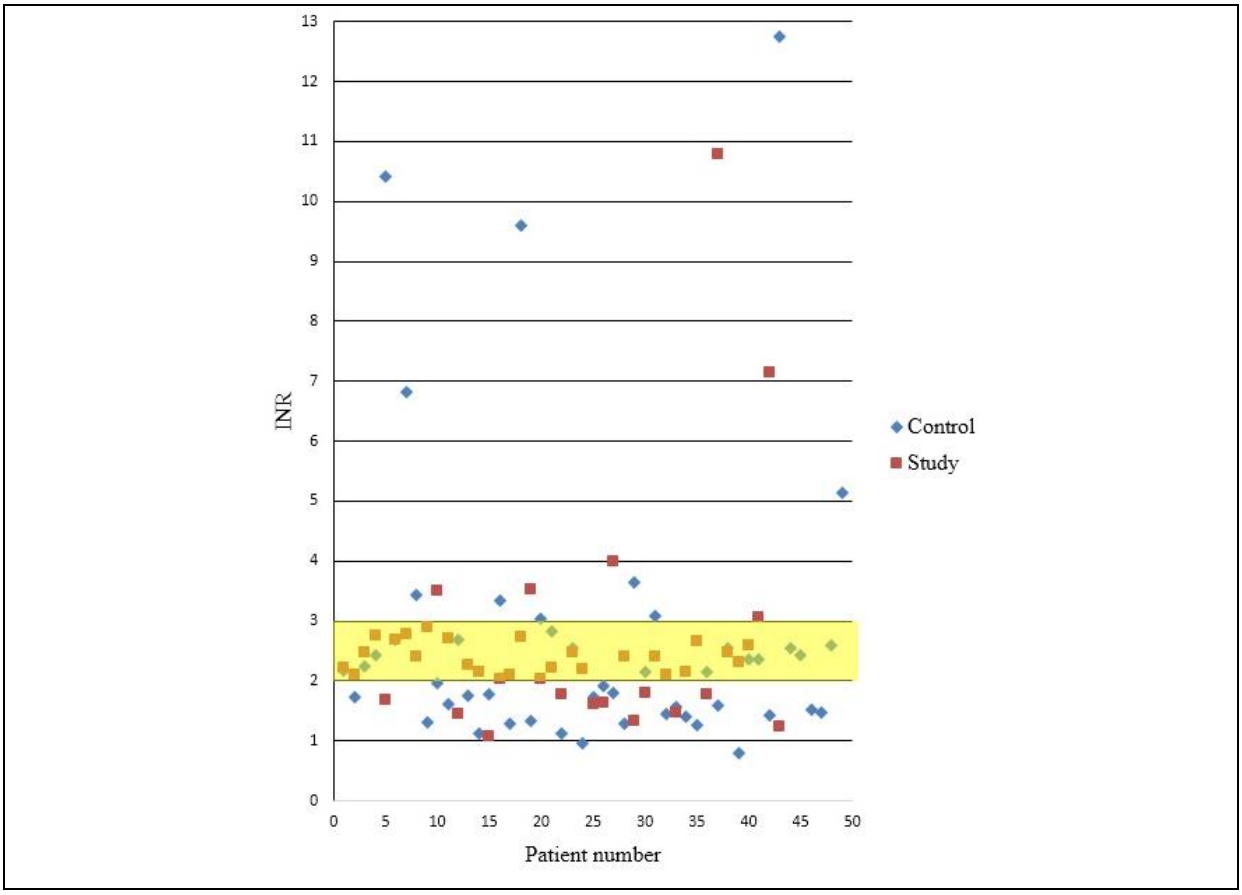

Figure 5. Describe distribution of patient's INR at first-follow-up visit

Table 4 Number and percentage of DTP-associated warfarin therapy

Type of Drug therapy problems	no. (%)	Result of intervention		
		Ac (%)	PAc (%)	NAc (%)
Dosage too low	17 (51.52)	11 (64.71)	4 (23.53)	2 (11.76)
Dosage too high	10 (30.30)	3 (30)	0	7 (70)
Drug interaction	6 (18.18)	1 (16.67)	0	5 (83.33)
Total	33 (100)	15 (45.46)	4 (12.12)	14 (42.42)

Ac is accepted, PAc is partially accepted and NAc is not accepted.

Table 5 Category of pharmacist's intervention

Pharmacist's interventions	Frequency (%)
Dosage adjustment	27 (28.42)
Safer medication suggestion	6 (6.32)
Time to monitor INR recommendation	62 (65.26)
Total	95 (100)

Table 6 Degree of physician acceptance to pharmacist's intervention

Degree of physician acceptance	Frequency	Percentage
Accept	69	71.58
Not accept	20	21.05
Partial accept	6	6.32
Total	95	100

suggested safer drug 6 interventions (6.32%) and recommended appropriate time to monitor INR 62 interventions (65.26%)

Categories of pharmacist's intervention and results of intervention were demonstrated in Table 5 and 6, respectively.

4. DISCUSSION

Baseline characteristic data of patients reflected patients who used warfarin for various indications, but atrial fibrillation was the most common indication in both groups. Factors which influence anticoagulation of warfarin such as gender, age and underlying diseases [17] have been reported. There was no statistical significant difference between two groups. However, the average age in both groups were more than 60 years old, so it can imply that the patients in this study were rather old. Another factor which influences anticoagulation control is history of warfarin usage. Tang et al [18] concluded that longer duration of warfarin therapy was associated with better knowledge and leading to improve in anticoagulation control. In our study, the proportion of patients who used warfarin before admission were not different between two groups.

An INR value in the range of 2.0 to 3.0 was used as the therapeutic INR in this study because of suggestion from many eastern countries studies which concluded that lower intensity INR range could markedly decrease bleeding complication and effectively prevent thromboembolism in patients with mechanical heart valve [19-27]. However, some patients were discharged before their INR reached the defined therapeutic INR. This was due to insufficient beds for patient admission. Physician have to early discharge patients although warfarin level is not reach the steady state. Although, this pattern had an effect on our outcomes, it was used in both two groups. Due to early discharge pattern, the statistical significant difference in percentage of patients with therapeutic INR was not observed at discharge, even if proportion of patients with optimal INR in intervention group was higher than control group. On the contrary, the proportion of patients with therapeutic INR in the intervention group at first followed-up visit was twice as that of the control group (60.47 % vs 30.41%, respectively, $p = 0.015$). Our results conformed to the result of previous studies[5,6,8,28,29]. They concluded that pharmacist's participation in warfarin management can improve anticoagulation control by suggest dose recommendation, identified and prevented or resolved drug therapeutic problems and increased patient's compliance and knowledge about warfarin. These may be the important factors that explain the improvement of anticoagulation control and lower complication. However, in previous studies, the expertise pharmacist had an authority to order warfarin or adjust warfarin dosage and could order INR test independently. Accordingly, they could monitor warfarin suitably. In our study, pharmacist could only provide suggestion in dosage adjustment, request for INR test or offer proper time for monitoring or follow up to the physician. Final decision about treatment plan was depended on physicians' opinion. However, the better outcome in anticoagulation control was still presented. This positive effect may because > 70% of interventions were accepted.

These findings can be concluded that, participation of pharmacist can support the healthcare team to improve the achievement of appropriate anticoagulation control even if studied in different hospital type and size.

One bleeding event was found in the control group and was not found in the intervention group. Although the rate of hemorrhagic complication in the control group was lower than intervention group, there was no statistically significant difference between two groups ($p = 0.346$). Similar to previous study conducted in Thailand [9], our study failed to demonstrate the effect of pharmacist in bleeding complication. This probably due to the small sample size.

After discharge, four patients in the control group had to readmit due to warfarin therapy. After reviewed profiles of patients with bleeding, we found that patients had high risk of bleeding from warfarin because of advance age (> 65 years), hypoalbuminemia and hypertension but the most important reason was inappropriate time to monitor INR. They just had initiate warfarin at last admission and discharge after started warfarin for only 3 and 7 days which their INR might not in optimum therapeutic range, moreover, initiation phase of warfarin associated with higher rate of bleeding than maintenance phase [29] . In general, duration of full action of warfarin after initiation may take at least for one week [1, 2, 30]. Many guidelines recommended for initiation phase that, INR monitoring is usually performed daily, starting after the second or third dose until the INR is in therapeutic range and

maintained for at least 2 consecutive days, then two or three times weekly for 1 to 2 weeks, then less often depend on stability of INR results. But due to early discharge pattern, assessing patient's risk of bleeding before discharge and proper dosing and monitoring in initiation phase is important. For patients who had supratherapeutic INR, we founded that they did not receive appropriate dose adjustment before discharge.

There was no report of thromboembolic complication in our study. Because, rate of this complication is quite low and risk of thrombosis in our study population were various, longer follow up time and larger sample size may be required to detect any differences on these complications.

Thirty-three DTPs associated with warfarin therapy were detected during the study period. Most common problems associated with warfarin therapy in our study were dosage too low, dosage too high, followed by significant drug interaction. Knowledge of pharmacokinetics and pharmacodynamics profiles of warfarin and interacting drugs was therefore necessary to appropriately detect and manage these problems. During the intervention period, 95 interventions were provided to physician. Although, about 70% of all interventions were accepted and may represent the good collaboration between physician and pharmacist, the interventions were highly accepted only in INR monitoring. Less than half of suggestion for prevention or correction problem related to warfarin therapy were accepted (45.46%). This may due to novelty of having pharmacists in inpatient care team. BMA General Hospital never had clinical pharmacist provide pharmaceutical care in hospitalized patient before. Moreover, warfarin clinic in out-patient service was also not established. Trust and collaboration between physician and pharmacist may not be adequate. So, we hope that the result of this study can be the first step of providing a pharmaceutical care to hospitalized patients and can be used to extend the pharmacist activity and produced benefit throughout all inpatients in BMA General Hospital.

There were several limitations in this study. First, this study was a single-center study with lack of randomization, which is the ideal design for an intervention study. Due to the hospital policy, the intervention was aimed to provide pharmacist's service to all patients. Further study with randomization or using propensity score to reduced bias should be performed. Second, all data of the control group were retrospectively collected based on chart review which carried major problem about incompleteness of documentation. Consequently, reliable comparison on certain important parameters may not be made between two groups such as hemorrhagic and thromboembolic complications. Another limitation was only one research pharmacist provided pharmacist-managed care and did not make ward rounds with the physicians because multiple physicians made rounds at difference times and pharmacist performed monitoring service only in official working days and hours. Some labs were not order appropriately before initiation of warfarin and some interventions could not be performed timely such as suggestion for drug with lower interaction profile. Moreover, the practice of early discharge may have some influence on the outcome of our study. This may be a major negative factor leading to suboptimal INR control both at discharge and at first followed-up visit and potentially warfarin complications. Nevertheless, this is a usual practice of the hospital which should occur equally on both groups and often found in Thailand [9,28]. Finally, warfarin treatment plan was depending on physician. The physician can accept or reject suggestions from the pharmacist. This limitation had a strong effect on the result of this study if the physician neglect to pharmacist's advice. Fortunately, more than 70% of recommendation from pharmacist were accepted.

Even much restriction and confounding factors, findings from our study may be valuable for further research and can represent pharmacist impact in inpatients who treated with warfarin in general hospital.

5. CONCLUSION

This study was designed to assess the impact of additional pharmacist-managed care to usual care of inpatient treating with warfarin in general hospital. Results of this study demonstrate that anticoagulation control was significantly better when pharmacist-manage warfarin monitoring service was provided. Potential drug interactions and DTPs were effectively identified by clinical pharmacists. Among these problems, inappropriate dosage regimen was very common. In conclusion, despite several limitations, the results of our study supported the hypothesis that adding pharmacist-managed care to usual care can improve anticoagulation control and reduce complications of warfarin therapy.

6. ACKNOWLEDGEMENTS

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Conflict of interest
There is no conflict of interest in this paper.

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Ethical approval
The study protocol was approved by the Faculty of Dentistry/Faculty of Pharmacy Mahidol University Institutional Review Board (MU-DT/PY-IRB) and Human Research Ethic Committee of Medical Service Department of Bangkok Metropolitan Administration.

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REFERENCES

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133 (6 Suppl):160S-98S.
2. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141 (2_suppl):e44S-e88S.
3. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365 (21):2002-12.
4. Biscup-Horn PJ, Streiff MB, Ulbrich TR, Nesbit TW, Shermock KM. Impact of an inpatient anticoagulation management service on clinical outcomes. Ann Pharmacother. 2008;42 (6):777-82.
5. Dager WE, Branch JM, King JH, White RH, Quan RS, Musallam NA, et al. Optimization of inpatient warfarin therapy: impact of daily consultation by a pharmacist-managed anticoagulation service. Ann Pharmacother. 2000;34 (5):567-72.
6. Boddy C. Pharmacist involvement with warfarin dosing for inpatients. Pharm World Sci. 2001;23 (1):31-5.
7. Damaske DL, Baird RW. Development and implementation of a pharmacist-managed inpatient warfarin protocol. Proc (Bayl Univ Med Cent). 2005;18 (4):397-400.
8. Wong YM, Quek YN, Tay JC, Chadachan V, Lee HK. Efficacy and safety of a pharmacist-managed inpatient anticoagulation service for warfarin initiation and titration. J Clin Pharm Ther. 2011;36 (5):585-91.
9. Tongsrisomboon P. Inpatient warfarin monitoring service at Ramathibodi Hospital [MS. dissertation]. Bangkok: Mahidol university; 2009.
10. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141 (2 Suppl):e152S-84S.
11. Aspinall SL, DeSanzo BE, Trilli LE, Good CB. Bleeding Risk Index in an anticoagulation clinic. Assessment by indication and implications for care. J Gen Intern Med. 2005;20 (11):1008-13.
12. Eikelboom JW, Hirsh J. Bleeding and management of bleeding. Eur Heart J Suppl. 2006;8 (Suppl G):G38-G45.
13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123 (23):2736-47.
14. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138 (5):1093-100.
15. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89 (2):635-41.
16. You JH, Chan FW, Wong RS, Cheng G. Is INR between 2.0 and 3.0 the optimal level for Chinese patients on warfarin therapy for moderate-intensity anticoagulation? Br J Clin Pharmacol. 2005;59 (5):582-7.
17. White PJ. Patient Factors That Influence Warfarin Dose Response. J Pharm Pract. 2010;23 (3):194-204.
18. Tang EO, Lai CS, Lee KK, Wong RS, Cheng G, Chan TY. Relationship between patients' warfarin knowledge and anticoagulation control. Ann Pharmacother. 2003;37 (1):34-9.
19. Yoon IK, Lee KE, Lee JK, Chang BC, Gwak HS. Adequate intensity of warfarin therapy for Korean patients with mechanical cardiac valves. J Heart Valve Dis. 2013;22 (1):102-9.
20. Zhou XM, Zhuang W, Hu JG, Li JM, Yu JF, Jiang L. Low-dose anticoagulation in Chinese patients with mechanical heart valves. Asian Cardiovasc Thorac Ann. 2005;13 (4):341-4.
21. Cheung CM, Tsoi TH, Huang CY. The lowest effective intensity of prophylactic anticoagulation for patients with atrial fibrillation. Cerebrovasc Dis. 2005;20 (2):114-9.
22. Matsuyama K, Matsumoto M, Sugita T, Nishizawa J, Yoshida K, Tokuda Y, et al. Anticoagulant therapy in Japanese patients with mechanical mitral valves. Circ J. 2002;66 (7):668-70.
23. Haibo Z, Jinzhong L, Yan L, Xu M. Low-intensity international normalized ratio (INR) oral anticoagulant therapy in Chinese patients with mechanical heart valve prostheses. Cell Biochem Biophys. 2012;62 (1):147-51.
24. Akhtar RP, Abid AR, Zafar H, Khan JS. Aniticoagulation in patients following prosthetic heart valve replacement. Ann Thorac Cardiovasc Surg. 2009;15 (1):10-7.
25. Lee LH. Thrombotic and haemorrhagic complications in patients with mechanical heart valve prostheses attending the Singapore General Hospital

Anticoagulation Clinic. Ann Acad Med Singapore. 2000;29 (1):71-4.
26. Tientadakul P, Sangtawesin W, Opartkiattikul N, Luenee P, Sakiyalak P. Retrospective evaluation for optimal oral anticoagulant intensity after mechanical heart valve replacement at Siriraj Hospital. Thai Heart J. 1994;7:97-102.
27. Ploylearmsaeng S. Optimal maintenance dose of warfarin therapy in outpatients with mechanicalprosthetic heart valve replacement at Rajvithi hospital [MS. dissertation]. Bangkok: Chulalongkorn University; 1998.
28. Khamkongkhun S. Impact of warfarin-monitoring service by a clinical pharmacist in patients undergoing cardiovascular and thoracic surgery [MS. dissertation]. Bangkok: Faculty of Graduate Studies, Mahidol University; 2007.
29. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133 (6 Suppl):257S-98S.
30. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation. 2003;107 (12):1692-711.