ORIGINAL

Hospital pharmacist intervention improves the quality indicator of warfarin control : A retrospective cohort study

Taesong An*[1], Eiji Kose[2], Akihiko Kikkawa[1], and Hiroyuki Hayashi[2]

[1]*Department of Pharmacy, Yokosuka Kyousai Hospital, 1-16 Yonegahamadohri, Yokosuka-shi, Kanagawa 238-8588, Japan and* [2]*Department of Pharmacotherapy, School of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi-shi, Chiba 274-8555, Japan*

Abstract

Background/Aims **Our previous study showed that time in therapeutic range (TTR) control of warfarin therapy was negatively affected in non-valvular atrial fibrillation (NVAF) patients with heart failure. This study assesses the effect of intervention by hospital pharmacists on TTR control in Japanese NVAF patients with heart failure.** ***Method*** **This retrospective cohort study included NVAF patients with heart failure admitted and discharged from the cardiovascular internal medicine ward between March 2011 and July 2013. Participants were classified into two groups according to the instructions by hospital pharmacists and physicians (Intervention group) and by physicians only (Usual care group). The primary outcome was TTR. Secondary outcomes were major bleeding and minor bleeding.** ***Results*** **In total, 57 participants (35 males, 22 females ; mean age : 69.7 years) were classified into the Intervention (n = 25) and Usual care (n = 32) groups. TTR within-therapeutic range was significantly higher and within sub-therapeutic range was significantly lower in the Intervention than the Usual care group. Major bleeding and minor bleeding were not significantly different between the two groups.** ***Conclusion*** **The intervention of hospital pharmacists with anticoagulation therapy can lead to proper use of warfarin, which can be useful when physicians prescribe warfarin. J. Med. Invest. 64 : 266-271, August, 2017**

Keywords **:** *warfarin, non-valvular atrial fibrillation, heart failure, time in therapeutic range*

INTRODUCTION

Epidemiological studies by the Japanese Circulation Society have shown that approximately 800,000 patients have atrial fibrillation (AF). It has also been reported that the number of such patients will surpass one million in 2030 (1). Cardiogenic cerebral embolism with AF greatly decreases patients' prognosis or quality of life compared with lacunar infarction and atherothrombotic brain infarction. The prognosis of cardiogenic cerebral embolism due to AF is very poor, with an approximate 50% chance of survival one year after diagnosis, as shown by the Hisayama Study (2). Thus, it is very important to prevent complications in patients with AF. Thrombi formed in the atrium are rich in fibrin (as in the case of venous thrombi), and anticoagulant therapy is shown to be beneficial. Warfarin (WF) therapy is recommended in the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS Joint Working Group 2013) (3) for non-valvular AF (NVAF) patients with a risk of embolism. The efficacy of WF therapy depends on the target treatment level during the therapy ; i.e., time in therapeutic range (TTR). Also, the international normalized ratio (INR) should be controlled to attain target treatment levels during WF therapy. This means that TTR markedly affects the efficacy of WF therapy ; i.e., TTR is a quality indicator of WF control. Morgan *et al*. reported that TTR and the incidence of cerebral infarction strongly correlate ; i.e., the incidence of cerebral infarction is low when TTR control is good (4). When TTR is low, a lesser therapeutic effect of WF is expected, which increases the risk of complications (5). When TTR is < 65%, the therapeutic efficacy of WF cannot be achieved (6). Obtaining good TTR control can be difficult because WF has a narrow therapeutic window and has many interactions with food and drugs. In a previous study, we reported that the factors that affect TTR control are associated with heart failure (7). Therefore, careful monitoring of NVAF patients with heart failure is needed to achieve good TTR control. However, it is difficult for physicians alone to sufficiently explain the above considerations to patients ; therefore, hospital pharmacists are required to manage TTR control.

The aim of this study was to assess TTR control of patients with NVAF receiving WF therapy.

METHOD

1. *Subjects*

The inclusion criteria were as follows : [1] patients admitted to the Cardiovascular Medicine Department of Yokosuka Kyousai Hospital for ablation of arrhythmias between March 2011 and July 2013 and who started WF therapy ; [2] duration of WF of ≥1 year ; [3] Prothrombin time-INR (PT-INR) measured at least once every 1–2 months (7) ; and [4] NVAF patients with heart failure. The exclusion criteria were patients with missing data and those who had NVAF without heart failure. Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013) (3) recommended a target PT-INR of 2.0–3.0 in NVAF patients aged < 70 years and a target of 1.6–2.6 in those aged ≥70 years. However, a previous report showed that a target PT-INR of 1.6–2.6 in those aged < 70 years is effective (3). Thus, we set the target PT-INR at 1.6–2.6 in the current study. PT-INR targets in the present study are identified for the Japanese population. In addition, all patients in the study gave their informed consent.

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Address correspondence and reprint requests to Taesong An, Department of Pharmacy, Yokosuka Kyousai Hospital, Yonegahamadohri, Yokosuka-shi, Kanagawa 238-8588, Japan and Fax : +81-46-825-2103.

2. *Study design*

A retrospective cohort study was conducted using data from medical records of the subjects. The follow-up period of subjects is 1 year. We defined patients who received instruction by hospital pharmacists in addition to instruction by physicians as the Intervention group and who were instructed by physicians only as the Usual care group. We compared background and laboratory data between the two groups. Hospital pharmacists' interventions in Yokosuka Kyousai Hospital included the following : {1} confirmation of drugs or drug interactions presented at admission ; {2} monitoring of bleeding and PT-INR ; {3} proposing to physicians to change the dose of WF when appropriate ; {4} lifestyle precautions ; {5} declaration at the visit of medical institutions ; {6} confirmation of interaction of WF and supplements or foods such as fermented soybeans, green juice, and chlorella. Hospital pharmacists are veteran pharmacists with a minimum of 10 years working experience in clinical practice and instructed patients with the brochure regarding the essential consideration of WF. Hospital pharmacists randomly intervened with patients at admission. None of the patients had complicated cases that pharmacists were able to instruct on. All patients were able to communicate. On the other hand, physicians' interventions included orally instructing only the efficacy and effect of WF at admission without using brochures on the consideration of WF. Most physicians did not provide the patients with lifestyle guidance.

3. *Clinical parameters*

We examined the following parameters to elucidate any differences between the Intervention and Usual care groups. Information regarding participant characteristics, including sex, age, weight, body mass index (kg/m^2), complications (e.g., hypertension, type 2 diabetes, stroke, transient ischemic attacks, and dyslipidemia), smoking history, average WF dose, bleeding after WF administration, bleeding history, congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attacks ($CHADS_2$) score, number of PT-INR measurements, and coefficient of variation (CV)-INR were collected via medical records.

Laboratory data, including systolic blood pressure (SBP), diastolic blood pressure (DBP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), total cholesterol (T-Cho), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), total protein (TP), albumin (Alb), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), and brain natriuretic peptide (BNP) were collected via medical records.

In the present study, eGFR was calculated based on the Modification of Diet in Renal Disease (MDRD) equation as shown below. MDRD equation based on Scr measured using the enzymatic method was published in 1999 (8). In consideration of racial differences, The Japan Society of Nephrology announced the MDRD formula suitable for the Japanese population in 2009.

$$\text{Male} : 194 \times (\text{Scr})^{-1.094} \times (\text{Age})^{-0.287}$$

$$\text{Female} : 194 \times (\text{Scr})^{-1.094} \times (\text{Age})^{-0.287} \times 0.739$$

4. *Outcome measures*

The primary outcome was TTR. PT-INR was measured every 1–2 months in the present study ; TTR was calculated using the Rosendaal method, which calculates the ratio of the period during PT-INR within the target treatment region from the entire measurement period of PT-INR (9). In addition, the time the steady state of WF is reached is estimated in 2–3 weeks from the level of prothrombin, which has a very long half-life (i.e., 3–4 days). Therefore, we calculated TTR using PT-INR after 5 days of WF administration.

Secondary outcomes were major bleeding and minor bleeding. The present study used the bleeding criteria set by the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) (10-11) to define bleeding after WF administration. Accordingly, major bleeding was defined as a reduction in the Hb level of at least 2.0 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in Hb of at least 5.0 g/dL, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.

5. *Sample size calculation*

A sample size calculation was performed using Power and Sample Size Calculation software (version 3.0, 2009, Dupont & Plummer, Department of Biostatistics, Vanderbilt University). We planned a study using continuous response variables from independent usual care and intervention subjects with one instance of usual care per intervention subject. In a previous study (12), the response within each group was normally distributed with standard deviation (SD) of 8.5. If the true difference between the intervention and usual care means is 8.2, we would require 18 subjects per group to be able to reject the null hypothesis that the population means of the Intervention and Usual care groups are equal with probability (i.e., power) of 0.8. The type I error associated with this test is 0.05.

6. *Statistical Analysis*

Results are presented as mean ± SD or median (interquartile range). We performed normality testing to compare the data volume between Intervention and Usual care groups. When data were normally distributed, the Student's t-test was used to test for significant differences between groups ; the Mann–Whitney U test was used when data were not normally distributed. We used the χ^2 test or the Fisher's exact test to compare categorical data. The significance level was set at $p < 0.05$. Statistical analyses were performed using JMP® (Version 12, SAS Institute Inc., Cary, NC, USA).

7. *Ethical approval*

This study was approved by the Yokosuka Kyousai Hospital Ethics Committee, as well as by the School of Pharmacy, Nihon University Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

1. *Subjects*

During the 2-year research period, 100 patients were hospitalized in the Cardiovascular Medicine Department of Yokosuka Kyousai Hospital for ablation of arrhythmias. Of these, 38 patients did not have heart failure and 5 had missing data ; data of the remaining 57 patients were analyzed.

2. *Patients' background data at baseline*

Baseline background data for all patients are shown in Table 1. There were no significant differences between the groups on all parameters.

3. *Baseline clinical laboratory data*

Baseline clinical laboratory data are shown in Table 2. AST and

ALT were significantly higher in the Intervention group than in the Usual care group (AST : 29.0 [23.0–41.0] IU/L vs. 26.0 [20.0–29.0] IU/L, p=0.0335 ; ALT : 27.0 [23.0–34.0] IU/L vs. 21.0 [15.0–27.0] IU/L, p = 0.0062). There were no significant differences between the groups on all other parameters.

4. *Main outcome measures*

TTR was significantly higher in the Intervention group than in the Usual care group (73.8% [61.4–93.4] vs. 59.8% [44.2–77.4], p = 0.0169). The sub-therapeutic range was significantly lower in the Intervention group than in the Usual care group (3.8% [0.3–22.4] vs. 22.2% [7.2–34.8], p = 0.0023). However, no significant differences between groups were observed for the supra-therapeutic range. Major bleeding occurred in fewer patients in the Intervention group (2/25 patients ; 8.0%) than in the Usual care group (4/32 patients ; 12.5%) ; however, there were no significant differences between groups. Incidence of minor bleeding was almost identical in both groups (~28%).

DISCUSSION

The most important finding of the present study was that intervention by hospital pharmacists led to a significant improvement in the anticoagulation control compared with the usual care. This finding is attributable to the fact that hospital pharmacists carefully instructed patients, placing attention on efficacy, side effects, and interactions with foods. Such findings are consistent with results in previously published studies (13-15). However, we previously reported that TTR control of WF therapy was negatively affected in NVAF patients with heart failure (7). There have been few reports regarding TTR control of NVAF patients with heart failure. Therefore, the findings obtained in the present study have novelty. If TTR control among NVAF patients with heart failure improves through intervention of hospital pharmacists, this could lead to a decreased incidence of cerebral infarction or complications such as bleeding.

The absorption of drugs administered to patients with heart failure may be poor owing to certain factors such as decreased blood flow or edema in the gastrointestinal tract. In general, in left heart failure patients, drugs to be excreted in the urine are retained in the blood by decreased urinary excretion due to decreased renal blood flow rate ; hepatic metabolism is also delayed due to decreased hepatic blood flow rate, and the blood drug concentration increases. Alternatively, in right heart failure patients, blood drug concentration remains constant because they maintain equilibrium with tissue compartment. In addition, we must consider that renal and liver clearance is decreased when renal blood and hepatic blood flows are decreased. Therefore, we believe that WF levels in the blood may vary owing to hemodynamic fluctuations. Indeed, our previous research revealed that heart failure was associated with poor TTR control (7). Improving TTR control requires intervention by hospital pharmacists rather than leaving TTR management up to a sole physician.

In the present study, TTR improved approximately 14% ; TTR of the Intervention and Usual care groups were approximately 74% and 60%, respectively. Samsa *et al*. reported that TTR improved by 5% through patient self-management (16). The value obtained in the present study is much higher than that of Samsa *et al*. ; thus, we feel that intervention of hospital pharmacists is extremely useful in TTR control. In addition, approximately 40% of patients in the Intervention group vs. 21% in the Usual care group had TTR of approximately 80% or more, which indicates extremely good TTR control. In other words, pharmacotherapy collaboration of physicians and hospital pharmacists may be one factor that contributes to the success of anticoagulant therapy, since TTR control of the Intervention group was approximately two-fold higher than that of the Usual care group. On the other hand, when TTR is low, we cannot expect therapeutic efficacy of WF, which increases the risk of complications (5). A previous report showed that when TTR was < 65%, the therapeutic effect of WF could not be achieved (5). In the

Table 1 : Baseline participant background data

Characteristic	Intervention group (n = 25)	Usual care group (n = 32)	p value
Male *n*, (%)	12 (48)	23 (71.9)	0.0662 [c]
Age (y)	70 [64–76.5]	72 [66.3–76.8]	0.5514 [b]
Body weight (kg)	61.3 ± 8.9	62.6± 11.7	0.6623 [a]
Body mass index (kg/m^2)	24.4 ± 2.8	23.5± 3.2	0.2825 [a]
Complications *n*, (%)			
Hypertension	19 (76)	18 (56.3)	0.1211 [c]
Type 2 diabetes	2 (8)	10 (31.3)	0.3385 [d]
Stroke	5 (20)	4 (12.5)	0.5828 [d]
Transient ischemic attacks	0 (0)	1 (3.1)	0.3725 [d]
Dyslipidemia	12 (48)	9 (28.1)	0.1227 [c]
Smoking history *n*, (%)	8 (32)	17 (53.1)	0.1551 [c]
Average WF dose (mg)	3.1 [2.5–3.8]	2.8 [2.2–4.3]	0.5571 [b]
Bleeding after WF administration *n*, (%)	9 (36)	13 (40.6)	0.7219 [c]
Bleeding history *n*, (%)	1 (4)	4 (12.5)	0.2603 [d]
$CHADS_2$ score (points)	3 [2–3]	2 [2–3]	0.6079 [b]
No. of measurements of PT-INR (times)	9 [7–10]	8.5 [7.0–9.8]	0.4332 [b]
CV-INR	0.25 ± 0.09	0.24± 0.08	0.5832 [a]

Values are mean ± SD or median (interquartile range) where appropriate.
Abbreviation : Prothrombin time international normalized ratio : PT-INR, coefficient of variation-INR : CV-INR
[a] t-test, [b] Mann–Whitney U test, [c] χ^2 test, [d] Fisher's exact test

Table 2 : Baseline laboratory data

Characteristic	Intervention group (n = 25)	Usual care group (n = 32)	*p* value
SBP (mmHg)	126 [104–133.5]	121.5 [112–141.5]	0.3979 [b]
DBP (mmHg)	74.8 ± 12.3	75.6 ± 14.2	0.8250 [a]
AST (IU/L)	29 [23–41]	26 [20–29]	0.0335 [b]
ALT (IU/L)	27 [23–34]	21 [15–27]	0.0062 [b]
BUN (mg/dL)	15 [13–20]	16 [14–20]	0.5948 [b]
Scr (mg/dL)	0.81 [0.74–0.94]	0.82 [0.62–1.07]	0.8218 [b]
eGFR (mL/min/1.73 m^2)	62.0 ± 14.4	70.0 ± 21.4	0.3285 [a]
T-Cho (mg/dL)	177.6 ± 38.9	157.7 ± 34.5	0.0687 [a]
TG (mg/dL)	87 [57.5–128]	87 [62.5–126]	1.0000 [b]
HDL-C (mg/dL)	54 [45.3–64.8]	47 [39.3–60]	0.2436 [b]
LDL-C (mg/dL)	102.5 ± 28.0	92.0 ± 22.9	0.1428 [a]
CRP (mg/dL)	0.18 [0.06–0.62]	0.27 [0.09–0.77]	0.4507 [b]
TP (g/dL)	6.9 ± 0.6	6.9 ± 0.6	0.7150 [a]
Alb (g/dL)	3.9 ± 0.5	3.8 ± 0.4	0.2049 [b]
RBC ($\times 10^6/\mu L$)	4.4 ± 0.5	4.2 ± 0.7	0.1555 [b]
Hb (g/dL)	13.8 ± 1.4	13.2 ± 2.1	0.1962 [b]
Hct (%)	41.9 ± 3.6	40.1 ± 6.1	0.2013 [b]
BNP (pg/mL)	184.2 [88.5–287.4]	175.4 [77.9–350.9]	0.8400 [b]

Values are mean ± SD or median (interquartile range) where appropriate.
[a] *t*-test, [b] Mann–Whitney *U* test

Table 3 : Anticoagulation control (TTR) in Intervention and Usual care groups.

Outcomes	Intervention group (n = 25)	Usual care group (n = 32)	*p* value
Supra-therapeutic range (%)	13.9 [0.5–24.2]	4.4 [0–15.9]	0.2012
Within-therapeutic range (%)	73.8 [61.4–93.4]	59.8 [44.2–77.4]	0.0169
Sub-therapeutic range (%)	3.8 [0.3–22.4]	22.2 [7.2–34.8]	0.0023

Values are median (interquartile range) where appropriate. Supra-therapeutic range represents PT-INR > 2.6 and sub-therapeutic range represents PT-INR < 1.6. Within-therapeutic range represents 1.6 < PT-INR < 2.6.
The Mann–Whitney *U* test was used to compare the Intervention group with the Usual care group.
Abbreviation : Time in therapeutic range : TTR, Prothrombin time international normalized ratio : PT-INR

Table 4 : Effect of Intervention versus Usual care groups on major bleeding and minor bleeding

Outcomes	Intervention group (n = 25)	Usual care group (n = 32)	*p* value
Major bleeding			
No. of patients with event *n*, (%)	2 (8)	4 (12.5)	0.8268 [a]
Total of person-years of follow-up	51.5	47.6	
No. of events per 100 person-years	3.9	8.4	

Outcomes	Intervention group (n = 25)	Usual care group (n = 32)	*p* value
Minor bleeding			
No. of patients with event *n*, (%)	7 (28)	9 (28.1)	0.9323 [b]
Total of person-years of follow-up	51.5	47.6	
No. of events per 100 person-years	13.6	18.9	

[a] Fisher's exact test, [b] χ^2 test

current study, TTR in the Usual care group was approximately 60%. We therefore suggest that WF may not have reached its full therapeutic potential. Although the reason for the low TTR in the Usual care group is unknown, it is likely attributable to the following explanation : the sub-therapeutic range was 22.9% in the Usual care group and significantly exceeded 3.8% in the Intervention group. In other words, poor adherence may be due to insufficient understanding regarding complex considerations, complications, medications, or interactions with food or supplements. Thus, in order to properly maintain TTR, these instructions should be based on the patient's background (i.e., dietary habits) ; further, when patients purchase medications at other medical institutions or pharmacies, they should be given instruction regarding interactions with WF.

Although major bleeding after WF occurred in both groups (< 13% of patients), this complication was not fatal due to appropriate treatment. Minor bleeding occurred in equal proportions (less than a third) of patients in the two groups. Overall, there were no significant differences between the two groups in major and minor bleedings. However, while not significantly different, the Intervention group had a higher value than the Usual care group in the supra-therapeutic range, leading us to conclude that more bleeding events occurred in the Intervention group than in the Usual care group. Actuality, major bleeding occurrences were higher in the Usual care group than in the Intervention group. This was due to one patient who showed a high value in the supra-therapeutic range (64.1%) in the Intervention group, which superficially inflated the value.

Collaborated anticoagulation care has been accepted as the model of care in many advanced countries (17). Physicians set the diagnoses and disease treatment goals and indicate the specific management of anticoagulant therapy to pharmacists in the Kooteni Medical Center located in the United States of Northern Idaho. In other words, pharmacists administrate WF or heparin according to the protocol established for each drug and instruct the necessary clinical laboratory tests or create medical records, and conduct the management of anticoagulation therapy (18). It is unknown whether the same procedure will be adopted in Japan in the future. However, in recent years, pharmacists have been required to participate in multidisciplinary medical teams and to engage in proactive pharmacotherapy. Pharmacists should attempt to improve patient outcomes by assessing the management of pharmacotherapy, taking advantage of pharmacists' expertise regarding the anticoagulation therapy of WF.

Several key strengths should be highlighted. First, a recent meta-analysis suggested that a follow-up time of ≥6 months would be required to capture all dimensions of pharmacist-managed WF therapy effects on clinical outcomes (13). Our study met that criteria, demonstrating a significant effect on TTR and non-significant effects on lesser complications. Second, our study overcame the limitations of previous local studies (19-20) (i.e., short follow-up period, lack of control group). Third, there have been few reports focusing on NVAF patients with heart failure. Thus, we believe that the patients in this study provided a realistic representation of patients receiving WF therapy in advanced countries.

This study had several limitations. First, the study followed a single-center retrospective cohort design. Multi-center prospective cohort studies should be conducted based on the results of this study. Second, the severity of heart failure in subjects was unknown. Pharmacokinetics of WF may fluctuate because the amount of circulating plasma can differ depending on the severity of heart failure. However, since BNP in both groups did not significantly differ, it is less likely that it affected the results of this study. Third, the presence or absence of the onset of cerebral infarction was not confirmed because the observation period was as short as 1 year in the present study. We should set the incidence of thrombosis as the primary outcome. However, thrombosis takes a long time to develop. A large clinical trial is required to evaluate thrombosis as the primary outcome. Thus, the present study evaluated TTR control as the surrogate outcome. Fourth, a previous study showed that other factors cause fluctuation of patient plasma prothrombin time, such as being carriers of WF susceptibility genes (e.g., cytochrome P450 2C9 and vitamin K epoxide reductase complex subunit 1, intake of vitamin-K-containing foods, medication adherence, or drug interactions (21). However, we were unable to investigate these factors due to the retrospective nature of this study. Therefore, there is a possibility that these factors influenced the results of this study.

In conclusion, the present study revealed that TTR control among NVAF patients with heart failure improved through intervention of hospital pharmacists in addition to instruction by physicians. Therefore, intervention of hospital pharmacists in anticoagulation therapy can lead to the proper use of WF, which can be useful when physicians prescribe WF. Further study is needed to clarify whether the intervention of pharmacists prevent the incidence of thrombosis based on the results of the present study.

CONFLICT OF INTEREST

None of authors has any conflict of interest to declare.

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