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Assessment of oral anticoagulation control at pharmacist-managed clinics: A retrospective cohort study

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In chronic kidney disease (CKD) patients, the ratio of warfarin enantiomers is changed and becomes unstable due to a reduction of cytochrome P450 (CYP) 2C9 activity of, which contributes to the development of hemorrhagic complications. The aim of this study was to investigate the influence of interventions by clinical pharmacists in addition to guidance by physicians on time in therapeutic range (TTR) control of warfarin therapy for CKD patients with non-valvular atrial fibrillation (NVAF). This retrospective cohort study included NVAF patients with CKD admitted and discharged from a cardiovascular internal medicine ward between March 2011 and July 2013 in Yokosuka Kyousai Hospital. Participants were classified into two groups according to the instructions by clinical 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. In total, 39 participants (28 males, 11 females; mean age: 72.1 years) were classified into the intervention (n = 16) and usual care (n = 23) groups. TTR in the intervention group was significantly higher than in the usual care group. Major bleeding and minor bleeding were not significantly different between the two groups. The intervention of clinical pharmacists with anticoagulation therapy can lead to a proper use of warfarin prescribed by physicians.

1. Introduction

In Japan, the number of patients with atrial fibrillation (AF) has increased with the aging population and poor lifestyle choices. Epidemiological studies by the Japanese Circulation Society have illustrated that approximately 0.8 million patients in the country have AF. It has also been reported that the number of patients with AF will surpass 1 million in 2030 (Inoue et al. 2009). Meanwhile, the prevalence of chronic kidney disease (CKD) is also increasing steadily (Japan Nephrology Society 2012). According to estimates, the number of patients with CKD in Japan is approximately 13,300,000, representing 13% of the adult population (Japan Nephrology Society 2012). Various diseases including diabetes mellitus, hypertension, obesity, and smoking are known risk factors for CKD, and the incidence of CKD is expected to further increase in the future. Regarding the association between CKD and AF, 15% of patients with CKD have AF (Nakajima et al. 2016). Conversely, one-third of patients with AF have CKD. These diseases are closely associated; hence, the prevalence of CKD-associated AF will increase in the future. Furthermore, both are independent risk factors for cerebral infarction. The prognosis of cardiogenic cerebral embolism due to AF is extremely poor, with a survival rate of approximately 50% one year after diagnosis, as determined in the Hisayama Study (Kubo et al. 2006). Functional prognosis is also poor, and anticoagulation therapy for prevention is important (Nakajima et al. 2016). The protective efficacy of warfarin (WF) against cardiogenic cerebral embolism has been established for patients with nonvalvular AF (NVAF). A previous study reported that WF can prevent cardiogenic cerebral embolism in approximately 68% of patients (Atrial Fibrillation Investigators 1994). Therefore, WF is recommended in the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013) (JCS Joint Working Group 2013) for treating patients with NVAF who carry a risk of embolism. The efficacy of WF depends on the target treatment level during treatment, i.e., time in therapeutic range (TTR). In addition, the international normalized ratio (INR) should be controlled to attain the target treatment level during WF therapy. Therefore, TTR markedly affects the efficacy of WF therapy. Morgan et al. (2009) reported that TTR and the incidence of cerebral infarction are strongly correlated, i.e., the incidence of cerebral infarction is low when TTR control is good. When TTR is short, we cannot expect WF to be therapeutically efficacious, which increases the risk of complications such as bleeding (Wallentin et al. 2010). WF has a narrow therapeutic window and multiple interactions with food and drugs. Moreover, in patients with CKD, the concentration of WF enantiomers becomes unstable due to reduction in CYP2C9 activity, leading to hemorrhagic complications (Nakajima et al. 2016). Taken together, when patients with CKD receive WF, education regarding prothrombin time (PT)-INR control, bleeding monitoring, and other issues is important, and it is conceivable that not only physicians alone but also pharmacists should instruct the patients in detail.This study aimed to investigate the influence of intervention by a pharmacist in addition to guidance by doctors on TTR on outcomes for patients with CKD and NVAF.

2. Investigations and results

2.1. 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, 58 patients did not have CKD and 3 had missing data; data of the remaining 39 patients (intervention group: 16, usual care group: 23) were analyzed.

2.2. 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.

Table 1: Baseline background

Characteristic	Intervention group (n=16)	Usual care group (n=23)	*p* value
Male *n*, (%)	9 (56)	19 (82)	0.0693
Age (y)	71.8±2.2	72.3±1.8	0.8765
Body weight (kg)	57.9 [51.2-67.8]	63.0 [52.5-66.1]	0.5542
Complications *n*, (%)			
Hypertension	11 (69)	14 (61)	0.2570
Type 2 diabetes	2 (13)	6 (26)	0.2898
Dyslipidemia	4 (25)	4 (17)	0.5650
Heart failure	10 (63)	14 (61)	0.9180
Myocardial infarction	4 (25)	5 (22)	0.8126
Stroke	1 (6)	1 (4)	0.7927
Anemia	2 (13)	7 (30)	0.1783
Smoking history *n*, (%)	7 (44)	16 (70)	0.1139
$CHADS_2$ score (points)	2.1±1.3	2.1±1.1	0.9217
Average INR	2.0±0.3	2.0±0.4	0.8548
Average WF dose (mg)	2.5 [2.0-3.7]	2.4 [1.9-3.3]	0.9090
No. of measurements of PT-INR (times)	7 [6-9]	7 [6-9]	0.9306
%INR (%)	71.6±15.1	56.9±20.5	0.0194
CV-INR	0.19±0.09	0.22±0.10	0.2513

Values are mean ± standard deviation or median (interquartile range) where appropriate.

Table 2: Baseline laboratory data

Characteristic	Intervention group (n=16)	Usual care group (n=23)	*p* value
SBP (mmHg)	120.0 [103.5-126.8]	128.0 [118.0-136.0]	0.1879
DBP (mmHg)	65.8±9.6	72.3 ±13.4	0.1055
AST (IU/L)	31.5 [23.5-39.0]	23.0 [21.0-26.0]	0.0046
ALT (IU/L)	25.5 [19.5-36.5]	17.0 [13.0-23.0]	0.0039
γ-GTP (IU/L)	20 [20-79]	36.0 [21.3-52.5]	0.9867
BUN (mg/dL)	18.0 [16.5-25.5]	21.0[17.0-26.0]	0.4899
Scr (mg/dL)	1.02 [0.86-1.25]	1.19 [1.00-1.32]	0.0892
eGFR (mL/min/1.73m^2)	51.0 [42.6-55.9]	44.9 [35.9-52.9]	0.1843
T-Cho (mg/dL)	163.8±50.3	170.5±41.4	0.7315
TG (mg/dL)	134.0 [84.5-195.5]	113.0 [85.0-142.0]	0.4091
HDL-C (mg/dL)	61.0 [44.5-66.0]	54.0 [37.5-65.0]	0.2549
LDL-C (mg/dL)	99.3±36.4	92.4 ±32.2	0.5883
CRP (mg/dL)	0.12 [0.04-0.25]	0.12 [0.04-0.66]	0.9302
TP (g/dL)	7.0±0.6	7.1±0.5	0.6185
Alb (g/dL)	4.1 [3.6-4.2]	4.1 [3.9-4.2]	0.8663
RBC(×10^6/μL)	4.2±0.2	4.2±0.2	0.7700
Hb (g/dL)	13.2 [12.3-14.1]	12.5 [11.4-14.0]	0.6474
Hct (%)	40.2 [36.9-42.2]	39.0 [34.1-44.0]	0.8930
BNP (pg/mL)	117.8 [59.2-234.1]	183.4 [65.4-402.0]	0.1157

Vames are mean ± Standard deviation or median (interquartile range) where appropriate.

2.3. Baseline clinical laboratory data

Baseline clinical laboratory data are shown in Table 2. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly higher in the intervention group than in the usual care group (AST: 31.5 [23.5–39.0] IU/L vs. 23.0 [21.0–26.0] IU/L, p = 0.0046; ALT: 25.5 [19.5–36.5] IU/L vs. 17.0 [13.0–23.0] IU/L, p = 0.0039). There were no significant differences between the groups on all other parameters.

2.4. Main outcome measures

TTR was significantly higher in the intervention group than in the usual care group (76.8 ± 15.6 % vs. 55.9 ± 25.1 %, p = 0.054). However, no significant differences between the groups were observed for the supra-therapeutic range and the sub-therapeutic range. The incidence of major bleeding was almost identical in both groups (~18%). Minor bleeding occurred in fewer patients in the Usual care group (10 / 23 patients; 43.5%) than in the intervention group (5 / 16 patients; 31.3 %); however, there were no significant differences between the groups.

3. Discussion

The most important finding of the present study was that the intervention by hospital pharmacists led to a significant improvement in anticoagulation control compared with usual care. This finding

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

Outcomes	intervention group (n=16)	Usual care group (n=23)	*p* value
Supra-therapeutic range (%)	0.5 [0.0-12.3]	4.7 [0.0-38.7]	0.2766
Within therapeutic range (%)	76.8±15.6	55.9±25.1	0.0054
Sub-therapeutic range (%)	14.3 [2.9-32.2]	15.5 [2.3-59.9]	0.5481

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.

Table 4: Effect of intervention versus usual care on major bleeding and minor bleeding

Outcomes	Intervention group (n=16)	Usual care group (n=23)	*p* value
Major bleeding			
No. of event with event (%)	3 (18.8)	4 (17.4)	0.9135
Total of person-years of follow-up	15.9	24.4	
No. of event per 100 person-years	18.9	16.4	

Outcomes	Intervention group (n=16)	Usual care group (n=23)	*p* value
Minor bleeding			
No. of event with event (%)	5 (31.3)	10 (43.5)	0.4376
Total of person-years of follow-up	13.8	23.7	
No. of event per 100 person-years	36.2	42.2	

is attributable to the fact that hospital pharmacists carefully instructed patients, stressing efficacy, side effects, and interactions with foods. Such findings are consistent with the results of previously published studies (Saokaew et al. 2010; Witt et al. 2005; Young et al. 2011). However, there have been few reports regarding TTR control in patients with NVAF and CKD. Therefore, the findings obtained in the present study are novel. If TTR control among patients with NVAF and CKD improves through the intervention of hospital pharmacists, the incidence of cerebral infarction or complications such as bleeding could be reduced. When renal function declines, the amount of plasma protein changes depending on the disease type, and the affinity of WF for plasma protein also changes. As plasma protein levels decrease in conjunction with decline in renal function, levels of the free form of WF, as an acidic drug, may increase. Therefore, aggravation of CKD may increase free blood levels of WF and affect PT-INR control. Furthermore, a previous report illustrated that when renal function decreases, the activity of CYP 2C9, which metabolizes WF, also decreases (Samsa et al. 2000). In clinical practice, decreased renal function is associated with major bleeding in patients receiving WF (Limdi et al. 2009). Moreover, long-term WF treatment suppresses the expression of vitamin K-dependent protein matrix gamma-carboxyglutamic acid protein, which leads to arteriosclerosis and consequently deterioration of renal function (Wieloch et al. 2013). As evidenced by these findings, it is conceivable that not only physicians alone but also the pharmacists should intervene to control TTR in patients with CKD and NVAF.In the present study, TTR improved by approximately 21%; TTR of the intervention and usual care groups were approximately 76.8 % and 55.9 %, respectively. Samsa et al. (2000) reported that TTR was improved by 5% through patient self-management. The superior improvement observed in this study illustrates that intervention by hospital pharmacists is extremely useful regarding TTR control. In addition, sub-analysis of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events revealed that a 10% improvement in TTR was associated with a 0.4% decreased risk of stroke and systemic embolism (Nieuwlaat et al. 2012). Taken together, these results indicated that collaborative efforts on pharmacotherapy by pharmacists and doctors lead to high-quality anticoagulation therapy.By contrast, when TTR is low, we cannot expect WF to be therapeutically efficacious, which increases the risk of complications (Wallentin et al. 2010). A previous report revealed that when TTR was <65%, a therapeutic effect could not be achieved for WF (Connolly et al. 2008). In the current study, TTR in the usual care group was approximately 56.2%. We therefore suggest that the full therapeutic potential of WF has not been achieved. Although the reason for the low TTR in the usual care group is unknown, it must be noted that approximately 20% of patients in the usual care group had extremely short TTRs (<30%), and each patient had complications such as heart failure, hypertension, and diabetes. Pharmacotherapy of these diseases tends to require polypharmacy, and increased drug interactions, changes in clinical condition, decreased adherence, and other variables may affect TTR control.Major bleeding after WF therapy occurred in 18.8% of patients in the intervention group, versus 17.4 % for the usual care group. This complications were not fatal due to appropriate treatment. Minor bleeding was identified in 31.3 % of patients in the intervention group and 43.5% of those in the usual care group. Overall, there were no significant differences between the two groups regarding major and minor bleeding rates, given that the bleeding rates were low. When renal function declines, WF increases bleeding risk. Therefore, we should manage PT-INR carefully in patients with NVAF and CKD. Moreover, a previous report demonstrated that

long-term WF use decreases renal function (Wieloch et al. 2013). It may be necessary to examine in detail the optimal range of INR for patients with CKD.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, as approximately 75% of the subjects in this study are CKD stage 3a, there are not many severe patients. Third, 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 (Olesen et al. 2012). 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 CKD 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.

4. Experimental

4.1. Study design

A retrospective cohort study was conducted using data from medical records of the subjects. The follow-up period of subjects was one 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 ten 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. By contrast, 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.

4.2. 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 (Kose et al. 2015); and (4) NVAF patients with CKD. The exclusion criteria were patients with missing data and those who had NVAF without CKD. Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013) (JCS Joint Working Group 2013) 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 (JCS Joint Working Group 2013). 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.

4.3. 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, body weight, complications (e.g., hypertension, type 2 diabetes, dyslipidemia, heart failure, myocardial infarction, stroke, anemia), smoking history, congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attacks ($CHADS_2$) score, average PT-INR, average WF dose, 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), AST, ALT, γ-glutamyltransferase (γ-GTP), 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 (Levey et al. 1999.). In consideration of racial differences, The Japan Society of Nephrology announced the MDRD formula suitable for the Japanese population in 2009.

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

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

4.4. 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 (Rosendaal et al. 1993). 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) (Young et al. 2011; Stemer et al 2011) 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 comprised 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 four units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.

4.5. 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 (Saokaew et al. 2012.), 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.

4.6. 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).

4.7. 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.

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Conflict of interest**:** The authors declare no conflict of interest.

References

Atrial Fibrillation Investigators (1994) Risk factors for stroke and efficacy of antithrombotic
therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 154: 1449 – 1457.

Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S; ACTIVE W Investigators (2008) Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 118: 2029–2037.

Inoue H, Fujiki A, Origasa H, Ogawa S, Okumura K, Kubota I, Aizawa Y, Yamashita T, Atarashi H, Horie M, Ohe T, Doi Y, Shimizu A, Chishaki A, Saikawa T, Yano K, Kitabatake A, Mitamura H, Kodama I, Kamakura S (2009) Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 137: 102 – 107.

Japan Nephrology Society (2012) Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. Nihon Jinzo Gakkai Shi, Japan.

JCS Joint Working Group (2013) Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). 78: 1997 - 2021.

Kose E, Arai S, An T, Kikkawa A, Aoyama T, Matsumoto Y, Hayashi H (2015) Analysis of factors affecting time in therapeutic range control after warfarin administration. Pharmazie 70: 494–498.

Kubo M, Kiyohara Y, Ninomiya T, Tanizaki Y, Yonemoto K, Doi Y, Hata J, Oishi Y, Shikata K, Iida M (2006) Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. Neurology 66: 1539 - 1544.

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 130: 461–470.

Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, Acton RT, Allon M (2000) Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol 20: 912-921.

Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM (2009) Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. Thromb Res 124: 37–41.

Nakajima M, Watanabe M, Ando Y (2016) Anticoagulant therapy for stroke prevention in CKD patients. Jpn J Stroke 38: 449-454.

Nieuwlaat R, Connolly BJ, Hubers LM, Cuddy SM, Eikelboom JW, Yusuf S, Connolly SJ; ACTIVEInvestigators (2012) Quality of individual INR control and the risk of stroke and bleeding events in atrial fibrillation patients: a nested case control analysis of the ACTIVE W study. Thromb Res 129: 715-719.

Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C (2012) Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 367: 625-635.

Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E (1993) A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 69: 236–239.

Samsa GP, Matchar DB (2000) Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. J Thrombosis Thrombolysis 9: 283-292.

Saokaew S, Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A, Napawan Jeanpeerapong (2010) Effectiveness of pharmacist-participated warfarin therapy management: a systematic review and meta-analysis. J Thromb Haemost 8: 2418–2427.

Saokaew S, Sapoo U, Nathisuwan S, Chaiyakunapruk N, Permsuwan U. Anticoagulation control of pharmacist-managed collaborative care versus usual care in Thailand. Int J Clin Pharm 34: 105–112, 2012.

Stemer G, Lemmens-Gruber R (2011) Clinical pharmacy activities in chronic kidney disease and end-stage renal disease patients: a systematic literature review. BMC Nephrology 10: 12-35.

Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ; RE-LY investigators (2010) Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trail. Lancet 376: 975–983.

Wieloch M, Jönsson KM, Själander A, Lip GYH, Eriksson N, Svensson PJ (2013) Estimated glomerular filtration rate is associated with major bleeding complications but not thromboembolic events, in anticoagulated patients taking warfarin. Thrombosis Res 131: 481-486.

Witt DM, FCCP, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ (2005) Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. Chest 127: 1515–1522.

Young S, Bishop L, Twells L, Dillon C, awboldt J, O'Shea P (2011) Com-parison of pharmacist managed anticoagulation with usual medical care in a family medicine clinic. BMC Family Practice 12: 88-94.