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Research Article

ASSESSMENT OF TIME IN THERAPEUTIC RANGE WITH WARFARIN THERAPY IN PHARMACIST VERSUS USUAL CARE GROUP: A RETROSPECTIVE COHORT STUDY

DANIEL MAJERCZYK[1], KIMBERLY RUSCHE[2], PRASHANT SAKHARKAR[1]*

[1]Department of Clinical and Administrative Sciences, Roosevelt University College of Pharmacy, Schaumburg, IL 60173 USA. [2]Union Medical Center, Pharmacy Services, Chicago, IL 60612 USA. Email: psakharkar@roosevelt.edu

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ABSTRACT

Objective: Anticoagulation management with warfarin is a familiar challenge seen in primary care settings. A greater time in the therapeutic range (TTR) has shown improved health benefits in patients treated with warfarin for atrial fibrillation. The aim of this study was to assess the level of anticoagulation control achieved with warfarin therapy measured by TTR.

Methods: Patients attending anticoagulation service at a medical center were included in this retrospective cohort study. Patients with at least two international normalized ratio (INR) values not more than 4 weeks apart were included and placed in a usual care group or a pharmacist care group based on the care received. Anticoagulation control was measured by calculating TTR according to Roosendaal's linear interpolation method. A TTR of >70% was considered high-quality and >60% was considered moderate coagulation control. The data were analyzed for descriptive statistics, associations, and for identifying predictors of TTR. A p value of <0.05 was considered statistically significant.

Results: Mean age of patients was 58±9 years; 57% were male; 48% were White Caucasian, and 43% had a $CHADS_2$ score of ≥3. Patients in the pharmacist group had a high TTR (67.6% vs. 43.4%, p<0.0001) and an INR in a significantly lower sub-therapeutic range than the usual care group (5.6% vs. 14.8%; p<0.0001). Half of the patients in the pharmacist group were able to achieve a TTR threshold of 60% and greater compared to less than one-third among the usual care group. Age and pharmacist care were found to be great predictors of TTR after adjusting for gender, ethnicity, and $CHADS_2$ score (p<0.001).

Conclusion: Our findings confirmed that pharmacist led anticoagulation care positively improved patients' TTR with warfarin.

Keywords: Warfarin, Time in therapeutic range, International normalized ratio, pharmacist, Medication therapy management, Atrial fibrillation.

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common types of arrhythmias. AF is strongly associated with other cardiovascular diseases, such as heart failure, coronary artery disease, valvular heart disease, diabetes mellitus, and hypertension. It is estimated that between 2.7 million and 6.1 million people in the United States have AF and this number is expected to increase with the aging population [1,2]. More than 454,000 hospitalizations occur every year in the United States with AF being the primary diagnosis [3]. AF also results in about 158,000 deaths each year [4]. The death rate from AF as a primary or contributing cause of death has been rising for more than two decades [5]. AF is also associated with thromboembolic events, specifically embolic stroke. The annual risk of embolic stroke is 1.9–18.2% in patients with AF without anticoagulation [6].

Cardiovascular conditions including AF, stroke, thromboembolism, and the presence of a prosthetic valve are common conditions that necessitate warfarin treatment. Even though warfarin anticoagulation in AF prevents thromboembolism, there are still risks associated with subtherapeutic and supratherapeutic anticoagulation since warfarin has a very small window for therapeutic dosing. Anticoagulation management with warfarin is a familiar challenge seen in primary care settings [5-7].

An international normalized ratio (INR) within the therapeutic range has been shown to provide the most benefit for preventing stroke, major hemorrhage, and death [8-10]. The time in the therapeutic range (TTR) is a commonly used quality measure for anticoagulation therapy with warfarin [8,9]. It is evident in the literature that a greater TTR correlates with improved health outcomes for patients treated with warfarin for AF [10,11]. Studies have shown a significant increase in TTR and a reduction in complications with warfarin therapy when patients are managed by the pharmacist. At the clinic where this study was performed, patients on warfarin were broadly managed by physicians and nurses. We hypothesized that the pharmacist role in anticoagulation management would produce a greater percentage of patients within the TTR. The aim of this study was to assess the level of anticoagulation control achieved in patients with warfarin therapy, measured by their TTR.

METHODS

Participants and study design

This was a retrospective cohort study. The study was approved by the Institutional Review Board of Roosevelt University and Union Medical Center, Chicago, for an exempt status. Patients attending anticoagulation service managed by physicians, nurses and pharmacist over a 2-year period were included in this cohort. Patients were considered eligible if they were on warfarin and had at least two INR values not more than 4 weeks apart. Patients with >10% missing data on variables of interest were excluded from the study. Patients were placed in a usual care group if managed by physician alone and in an intervention group if they received pharmacist care.

The sample size was calculated assuming a true mean difference of 8.2% between usual and pharmacist care for the continuous response variable with one instance of usual care per intervention subject. We would require 18 subjects per group to achieve a power of 80% at the alpha level of 0.05. Considering the missing data, a sample size of 20 patients in each group was selected as the size of the study [12].

Interventional protocol

The anticoagulation clinic was managed by the pharmacist and a registered nurse with expertise and knowledge in anticoagulation management. The pharmacist and nurse both interviewed patients during their visits. Patient interactions with the pharmacist at their visits included the following: (1) Assessment of patient's risk factors and comorbidities, (2) confirmation of drug-drug and drug-food interactions, (3) monitoring of prothrombin time (PT) and INR, (4) recommendations to physician(s) for change in warfarin dose if needed, (5) counseling on lifestyle modification – diet, dietary supplement, fermented drinks, etc., smoking and alcohol consumption, and (6) any other information related and relevant to that specific patient. After each recommendation, the patient was probed whether the recommendation was understood by them. If not, the process was repeated. Such interactions lasted on average for 30 min. Beyond this 1-time intervention, none of the subjects in this group were advised thereafter regarding anticoagulation therapy.

Clinical parameters and outcome measures

The following demographic and clinical parameters were elucidated – age, sex, ethnicity, smoking history, alcohol use, INR, bleeding history, and comorbidities (hypertension, diabetes, congestive cardiac failure, stroke, transient ischemic attack, etc.). The primary outcome measures were TTR, supra and subtherapeutic INR levels, and associated risk of bleeding.

Anticoagulation assessment

Anticoagulation therapy was monitored at regular intervals according to the standard of care. Patients' level of anticoagulation control was measured by the number of INR readings within the recommended therapeutic range based on the indication for anticoagulant therapy. TTR was assessed in all subjects for the study's duration. Individual TTR was calculated according to Roosendaal's linear interpolation method [13]. This method adds each patient's time within the therapeutic range by incorporating the frequency of INR measurements and their actual values, assuming that changes between consecutive INR measurements are linear over time, and are divided by the total time of observation [13]. We considered a target INR of 2–3 in this current study based on the CHEST Guideline on Antithrombotic and considered a TTR of >70% as high-quality and >60% as moderate coagulation control [14]. $CHADS_2$ scores were calculated for patients to assess their risk of stroke [14]. An INR of <1.5 and >3.6 was considered subtherapeutic and supratherapeutic, respectively [6].

Statistical analysis

The data were analyzed using IBM SPSS version 25 (IBM, Armonk, NY) [15] for descriptive statistics and associations. Demographic and clinical characteristics were analyzed using the Student's t-test or Mann–Whitney test for continuous variables and the Chi-square and Fisher exact test for categorical variables. The primary endpoint was the effect of the pharmacist care on TTR. Evaluation of the difference in percent INR tests in range and INR variability was determined by the standard deviation of INR measurements. Predictors of INR control were evaluated by performing multiple linear regression analysis with TTR as the dependent variable and relevant clinical and demographic characteristics as the predictors. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

The study cohort included 58 patients who had a total of 17,856 days observed while on anticoagulation therapy, of which 10,382 days (58.1%) were within the therapeutic range. The demographic characteristics of the patients are presented in Table 1. Patients' mean age was 58±9 years, 57% were male, and 48% were White Caucasian. AF (43%), deep vein thrombosis (31%), and pulmonary embolism (19%) were the major indications for anticoagulation therapy in patients. Forty-three percent of patients had a $CHADS_2$ score of ≥3; 33% of patients had ≥3 comorbid conditions, and 40% were on ≥4 medications (Table 1). There were no significant differences observed for demographic characteristics between the two groups (Table 1).

Effect of pharmacist intervention on TTR

Among patients included in this analysis, there were 1019 INR measurements over a 24-month follow-up period. The median number

Table 1: Demographic characteristics of the participant

Characteristics	All	Pharmacist care	Usual care	p-value*
Age in years (Mean±SD)	58±9	60.78±8.2	56.9±9.3	0.124
Male (n, %)	33 (56.9)	11 (33.3)	22 (66.7)	0.778
Ethnicity (n, %)				
White Caucasian	28 (48.3)	8 (47.1)	20 (50)	0.368
African American	13 (22.4)	4 (23.5)	9 (22.5)	
Hispanic	15 (25.9)	4 (23.5)	11 (27.5)	
Other	1 (1.7)	1 (5.9)	0 (0)	
Indication of warfarin therapy				
Atrial fibrillation	29 (42.6)	13 (72.2)	16 (40)	0.060
Deep vein thrombosis	18 (31)	4 (22.2)	14 (35)	
Pulmonary embolism	11 (19)	1 (9.1)	10 (25)	
$CHADS_2$ score (n, %)				
$CHADS_2$ Score 1	11 (19)	6 (10.3)	5 (8.6)	0.220
$CHADS_2$ Score 2	17 (29.3)	6 (10.3)	11 (19)	
$CHADS_2$ Score 3	19 (32.8)	4 (6.9)	15 (25.9)	
$CHADS_2$ Score 4	6 (10.3)	1 (1.7)	5 (8.6)	
$CHADS_2$Score**	2 (1.0–3.0)	2 (1.0–3.0)	2.5 (2.0–3.0)	0.141
Complication (n, %)				
Heart failure	6 (10.3)	2 (33.3)	4 (66.7)	0.971
Hypertension	43 (74.1)	15 (34.9)	28 (65.1)	
Dyslipidemia	40 (65.6)	13 (72.2)	27 (67.5)	
Diabetes mellitus	26 (44.8)	10 (38.5)	16 (61.5)	
Other	33 (56.9)	11 (33.5)	22 (66.7)	
No. of Comorbidities**	2 (1.0–3.0)	2 (1.7–3.0)	2 (1.0–3.0)	0.309
No. of visits**	18 (7.0–25.2)	19.5 (17.7–28.3)	15 (7.0–22.5)	0.039
No. of medications**	3 (1.7–4.0)	3 (1.7–4.0)	3 (1.2–4.0)	0.596
Smoker (n, %)	27 (47.4)	7(38.9)	20 (51.3)	0.410
Alcohol use (n, %)	24 (41.4)	9 (50.0)	15 (37.5)	0.402

*Significance at <0.05; ** Median±IQR (Interquartile Range)

of INR draws per patient was 18 (IQR 8.5–23). Among all measured INR values, the median INR value was 2.4 (IQR 2.1–2.7), and 54% of all measured INR values were in the therapeutic range. The mean and median patient-level TTRs were 46%±22% and 45% (IQR 33–59%), respectively. The mean and median days that individual patients spent within the therapeutic range were 177.3±139 and 143 (IQR 72.1–273.4) (Table 2). Patients with a $CHADS_2$ score of <3 had better INR control compared to a $CHADS_2$ score of ≥3 and were more within the therapeutic range.

The TTR was much higher in the pharmacist group than the usual care group (67.6% vs. 43.4%, p<0.0001); the subtherapeutic range was significantly lower in the pharmacist group than the usual care group (5.6% vs. 14.8%; p<0.0001). However, no significant difference was observed in the supratherapeutic range between these groups. Approximately 6% of the time, patients were at a point of increased thrombotic risk (INR ≤1.5), whereas; <10% of the time they were at increased hemorrhagic risk (INR ≥3.6) in the pharmacist group compared to the usual care group, with 11% and 15%, respectively. Half of the patients in the pharmacist group were able to achieve a moderate coagulation control (TTR threshold of 60% and greater) compared to less than one-third among the usual care group (Table 2). Similarly, 39% of patients were able to achieve high coagulation control (TTR Threshold of 70% and greater) in the pharmacist group compared to 19% in the usual care group. However, these differences were found not to be statistically significant (Table 3).

Effect of intervention on INR variability

The INR variability as determined by the standard deviation of INR results, was slightly higher in the usual care group compared to the pharmacist group (0.74 vs. 0.72); however, this difference was found not to be statistically significant (Table 2).

Predictors of TTR

The multiple regression model produced $R^2 = 0.40$, $F(5, 51) = 6.75$, p<0.001. Age and pharmacist care were found to be good predictors of TTR after adjusting for gender, ethnicity, and $CHADS_2$ score.

DISCUSSION

In this study, the anticoagulation therapy managed by the pharmacist led to significant improvement in patients' days in the therapeutic range. This finding can be attributed to role of the pharmacist in assessing a patient's risk factors and comorbidities, counseling on drug-drug and drug-food interactions, monitoring of PT and INR and recommending change in warfarin dose to the physician(s) if needed, and educating patients on lifestyle modification involving diet, dietary supplement, fermented drinks, etc., smoking and alcohol consumption. Our findings are consistent with the results of other published studies. In a study by Lee *et al*., the TTR for face-to-face with multimodal pharmacist management was found to be significantly greater [16]. Similarly, implementation of an anticoagulation clinic led by the advance practicing pharmacist in a correctional health facility also resulted in good INR control [17]. In another study, patients in pharmacist led education and a follow-up service group were found spending more time in the therapeutic range than their counterpart, a usual care group [18]. A pharmacist-led medication use review service in a community pharmacy was also found to improve anticoagulation therapy in patients on warfarin. A high percentage of patients showed improved INR control in this study [19]. In another study, pharmacist managed warfarin clinic monitoring services were successful in attaining a TTR of >40% and sustaining these values over a 6-month period [20].

Anticoagulation control could be a challenging issue because of warfarin's pharmacokinetic and pharmacodynamic profile and its narrow therapeutic window. Pharmacist intervention could lead to decreased incidence of bleeding and cerebral infarction by improving TTR control among patients on warfarin. In this study, patients' TTR was improved up to 68%, much higher than what was reported in earlier studies. In addition, the subtherapeutic range was found significantly lower in the pharmacist group than the usual care group. Both of these findings clearly affirm the greater role of pharmacists in anticoagulation management. Similarly, less patients (<10%) were found in this study at increased hemorrhagic risk in the pharmacist group compared to the usual care group. These findings are significant, considering 33% of patients were below and 17% above the therapeutic range in one National Assessment of Warfarin Anticoagulation Therapy for Stroke Prevention in AF study [21].

Our results are also consistent with one randomized controlled trial (RCT) where the impact of a community pharmacist's interventions on the quality of anticoagulation in elderly rural patients receiving warfarin was evaluated. The proportion of patients with a TTR ≥ 65% was found significantly higher (86%) in the pharmacist group compared to patients managed by the pharmacist in our study (68%) [22]. This could be due the fact that this was a RCT, where patients were expected to strictly adhere to the study protocol. In another study, a slightly increased TTR (70%) compared to ours (68%) within a clinical pharmacy anticoagulation management service was associated with a lower risk of the composite outcomes of bleeding, thromboembolism, and death in a large AF population receiving warfarin [23].

In a study by Marcatto *et al*., pharmacist managed warfarin therapy was able to improve TTR values in patients with AF and poor quality

Table 2: Anticoagulation control in pharmacist and usual care group

Outcomes	Pharmacist group	Usual care group	p-value*
Days within range	248.2 (184.3–391.0)	90.9 (26.0–191.2)	0.000
Total days	508.5 (403.7–508.5)	185 (97.2–387.5)	0.000
% Days within range	63.1 (44.5–78.9)	46.6 (34.4–64.3)	0.071
Total number of INR tests	20 (18.7–31.2)	14 (7.0–21.0)	0.001
Number of INR tests in range	13.5 (10.7–16.5)	6 (4.0–11.7)	0.000
INR difference above range	0.24 (0.08–0.3)	0.16 (0.02–0.3)	0.438
INR difference above range	0.11 (0.04–0.13)	0.14 (0.08–0.2)	0.145

All values are in median (interquartile range); *Significance at <0.05 on Mann–Whitney test. INR: International normalized ratio

Table 3: Anticoagulation control (TTR) in pharmacist and usual care group

Anticoagulation control	Pharmacist group (n, %)	Usual care group (n, %)	p-value*
Supratherapeutic range	40 (9.7)	61 (10.7)	0.590
Within therapeutic range	280 (67.6)	247 (43.4)	<0.0001
Subtherapeutic range	23 (5.6)	84 (14.8)	<0.0001
TTR threshold of 60%	9 (50)	11 (29.7)	0.095
TTR threshold of 70%	7 (38.9)	7 (18.9)	0.102

*Significance at <0.05 on the Chi-square test. Supratherapeutic range represents INR>3.6; within therapeutic range represents INR (2-3) and subtherapeutic range represents INR<1.5; TTR: Time in therapeutic range. INR: International normalized ratio

of anticoagulation with warfarin [24]. A pharmacist-managed anticoagulation clinic was also found to achieve an adequate TTR in patients with low socio-economic status. Pharmacist intervention in this study was similar to ours and included face-to-face appointments for individual patient education, warfarin-dosing adjustments, and monitoring of drug interactions [25]. All these findings discussed above strongly support the role of pharmacists in anticoagulation management. Patients with a $CHADS_2$ score of <3 on warfarin had better INR control compared to $CHADS_2$ score of ≥3 and were more within the TTR regardless of type of anticoagulation management. This further enumerates the importance of the $CHADS_2$ score in warfarin management and improving patient outcomes. This was an interesting result and consistent with the findings of the study by Odashiro *et al*., where higher $CHADS_2$ score showed lowering of TTR in AF patients on warfarin [26]. We followed patients on warfarin therapy for more than a year. A recent meta-analysis suggested that a follow-up of more than 6 months would be good enough to capture the impact of pharmacist intervention on TTR [27]. In this study, the TTR was increased and improved with pharmacist intervention. However, methods to increase TTR are still desired, such as full implementation of pharmacist services, improved documentation, as well as timely follow-up.

Our study had several limitations. First of all, it was a single center retrospective cohort study. We used TTR control as a surrogate measure to evaluate risk of thrombosis or bleeding. Use of convenience sampling, missing data due to the retrospective nature of this study, and loss to follow-up could have possibly influenced our results. These factors further limited generalization of our results to a larger population.

CONCLUSION

Our study finds that the quality of anticoagulation control in patients was better with pharmacist care where nearly 68% of the patients' days were in the therapeutic range. Our study results confirmed that the pharmacist led anticoagulation care positively impacted patients' TTR. Identifying patients in whom INR control remained poor still poses a challenge, which certainly deserves attention from health-care professionals and policy makers.

AUTHORS' CONTRIBUTIONS

All authors contributed equally in all aspects of this research study. DM and KR contributions include study design, data collection, interpretation of data, and writing of the first draft. PS contributed in study design, data management, data analyses and interpretation, writing of the first draft, and subsequent revisions of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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