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 Rosendaal’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 CHADS₂ score of ≥2. 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 CHADS₂ 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 based on the indication for anticoagulant therapy. TTR was considered statistically significant.

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 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 CHADS2 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 of INR observations per patient was 17.8. The median TTR for the overall study population was 69% (IQR 58%–74%). In the usual care group, the median TTR was 66% (IQR 52%–73%), and in the intervention group, the median TTR was 69% (IQR 57%–74%). The differences in median TTR were statistically significant (p<0.05). The difference in percent INR tests in range and INR variability was considered statistically significant.

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, %) | 28 (48.3) | 8 (47.1) | 20 (50) | 0.778 |
| White Caucasian | 13 (22.4) | 4 (23.5) | 9 (22.5) | 0.778 |
| Hispanic | 15 (25.9) | 4 (23.5) | 11 (27.5) | 0.778 |
| Other | 1 (1.7) | 1 (5.9) | 0 (0) | 0.778 |
| Atrial fibrillation | 29 (42.6) | 13 (72.2) | 16 (40) | 0.060 |
| Deep vein thrombosis | 18 (31) | 4 (22.2) | 14 (35) | 0.060 |
| Pulmonary embolism | 11 (19) | 1 (9.1) | 10 (25) | 0.060 |
| CHADS2 score | 6 (10.3) | 6 (10.3) | 5 (8.6) | 0.220 |
| CHADS2 Score 1 | 17 (29.3) | 6 (10.3) | 11 (19) | 0.220 |
| CHADS2 Score 3 | 19 (32.8) | 4 (6.9) | 15 (25.9) | 0.220 |
| CHADS2 Score 4 | 6 (10.3) | 1 (1.7) | 5 (8.6) | 0.220 |
| CHADS2 Score** | 21 (1.0–3.0) | 2.0 (2.0–3.0) | 2.5 (2.0–3.0) | 0.141 |
| Complication (n, %) | 6 (10.3) | 2 (33.3) | 4 (66.7) | 0.971 |
| Heart failure | 43 (74.1) | 15 (34.9) | 28 (65.1) | 0.971 |
| Hypertension | 40 (65.6) | 13 (72.2) | 27 (67.5) | 0.971 |
| Diabetes mellitus | 26 (44.8) | 10 (38.5) | 16 (61.5) | 0.971 |
| Other | 33 (56.9) | 11 (33.5) | 22 (66.7) | 0.971 |
| No. of Comorbidities** | 21 (1.0–3.0) | 2 (1.7–3.0) | 2 (1.0–3.0) | 0.309 |
| No. of visits** | 19.5 (17.7–28.3) | 15.7 (10.0–22.5) | 0.060 |
| No. of medications** | 3 (1.7–4.0) | 3 (1.7–4.0) | 3 (1.7–4.0) | 0.060 |
| 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)
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 (0.00–0.2)   | 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 score of <3 on warfarin had better INR control compared to CHADS score of ≥3 and were more within the TTR regardless of type of anticoagulation management. This further enumerates the importance of the CHADS score in warfarin management and improving patient outcomes. This was an interesting result and consistent with the findings of the study by Odaširo et al., where higher CHADS score showed lowering of TTR in AP 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, 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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