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Evaluation of Time in Therapeutic Range on Warfarin Therapy Between Face-to-Face and Telephone Follow-Up in a VA Medical Center

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Abstract

Background: Few studies have evaluated percent time in therapeutic range (TTR) for warfarin managed via face-to-face (FF) to telephone (TELE) visits—all finding no difference between groups. **Objective:** Compare and evaluate TTR for warfarin in patients who received pharmacist-managed care via FF or TELE. **Methods:** Single-center, retrospective study. Eligible participants were ≥18 years old, on indefinite warfarin therapy, followed by clinical pharmacists via FF or TELE from 2010 to 2012. Primary outcome (TTR) calculated via Rosendaal method. Event data included rates of any bleeding, significant bleeding, deep vein thrombosis, pulmonary embolism, cerebrovascular accident, hospitalizations, and death. Clinics were also compared by location. **Results:** Two hundred subjects (90 FF and 110 TELE) were included. Mean TTR was 68.17% and 69.57% in FF and TELE groups, respectively. The FF group had statistically significant higher rates of any bleeding (48.9% vs 30.9%). Rates of significant bleeding in FF versus TELE were not significantly different (6.67% vs 2.73%). The majority followed FF with significant bleeding were at a higher bleeding risk than those followed via TELE. There were low rates of venous thromboembolism (1.1% and 1.8%). **Conclusions:** TTR was ≥65% for most subjects with minimal variability in TTR between clinics. Mean TTR results for each group were greater and above the threshold that has been commonly described in the literature as quality control, suggesting a progression in implementation of telephone-based anticoagulation management.

Keywords

ambulatory care, anticoagulants, anticoagulation, clinical pharmacy, warfarin

Introduction

Warfarin is one of the most widely prescribed anticoagulants in North America. It is currently Food and Drug Administration approved for the prevention and treatment of venous thromboembolism, the prevention of thromboembolic complications with atrial fibrillation, heart valve replacement, and myocardial infarction.[1] Despite being efficacious, warfarin has been shown to be difficult to manage. It has a narrow therapeutic window with respect to international normalized ratio (INR), significant interactions with food and other medications, and has the potential to cause great harm if not monitored and dosed correctly.[2] Despite these setbacks, warfarin has historically been the anticoagulant of choice when long-term or extended anticoagulation therapy is indicated and still is the treatment of choice for patients who are not candidates for the newer anticoagulants. One of the major challenges with warfarin management is maintaining the patient's INR within the predetermined therapeutic range. The majority of patients will have a goal INR range of 2 to 3.[3] When the INR falls below the goal therapeutic range, there is an increased risk of embolism formation. Conversely, when the INR supersedes the goal therapeutic range, there is an increased bleeding risk.[2] Efficacy and safety of warfarin therapy depend on the actual proportion of treatment time spent within the predefined therapeutic range, which can be measured by calculating percent time in therapeutic range (TTR).[4] TTR is a common method used to measure the quality of anticoagulation management. Characteristics of an ideal method to assess quality of oral anticoagulation therapy would include ease of calculation and understanding, standardization to

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allow comparison among individuals, ability to easily identify areas of improvement, and link evidence to outcomes. TTR has been found to possess many of these qualities.[5] Several trials have analyzed oral anticoagulation using this measurement, but each study used a different TTR calculation and defined "good" control differently with a range anywhere from ≥65% to 79%.[5-8] One of the most utilized methods for calculating TTR is the Rosendaal method.[9] This calculation is unique in that it measures length of time between visits to determine a probable duration within the therapeutic range.

In the past 20 years, anticoagulation management has shifted from the traditional physician-based clinic settings to a model implemented by nonphysician providers, including pharmacists.[10] Studies have shown that these clinics dedicated to anticoagulation are associated with improved patient education, improved outcomes, and reduced risk of complications, including hemorrhage and death.[11-15] There have been few studies looking at the difference in TTR in patients followed in pharmacist-managed anticoagulation clinics to specifically compare face-to-face (FF) and telephone (TELE) treatment modalities. The studies did not find a difference in TTR between these 2 groups.[16-17]

Within the Veterans Affairs (VA) health care system, the role and responsibilities of a pharmacist has expanded and continues to change, with one example being the centralization of pharmacist-managed anticoagulation. Successful implementation of telephone clinics in the VA would allow centralization of anticoagulation clinics within the outpatient pharmacy, which has historically been a function of team-based clinical pharmacists. The purpose of this investigation and primary outcome was to determine if any differences exist between TTR in patients followed via FF and TELE follow-up. Secondary outcomes included the rate of hospitalizations for any reason, any bleeding, significant bleeding, deep vein thrombosis (DVT), pulmonary embolism (PE), cerebrovascular accident (CVA), and death from any cause. Currently, there is no specific criterion for FF versus TELE follow-up recommended for clinical use. These results could help determine if there is a need for criteria for anticoagulation follow-up via FF in the clinic or TELE prior to implementing a centralized anticoagulation clinic model within our VA facility.

Methods

Setting

This research was conducted at a VA medical center and its affiliated rural clinics in South Carolina. This institution provides service to over 80 000 veteran patients. Pharmacist-managed anticoagulation clinics exist within 3 main hospital clinics and 7 community-based outpatient clinics (CBOCs). CBOCs are available for veterans residing in rural areas and/or unable to commute to the main hospital. Pharmacists also manage anticoagulation via TELE for home-based primary care (HBPC) patients, a program for veterans whose health circumstances do not allow for frequent travel from home. INR results for FF visits are determined using standard laboratory methodology. INR results for TELE visits are determined using a point-of-care testing device or standard laboratory methodology based on the clinic setting; however, standard laboratory testing is done for most visits. If a point-of-care INR result is >4.0, a venous blood sample is obtained for confirmation testing. TELE and FF visits utilize the same templates and education components. There is a standardized warfarin questionnaire for TELE visits that encompasses the same set of questions that a patient is asked during a FF visit. TELE patients submit their completed questionnaires in a dropbox for the pharmacist to retrieve. TELE patients are contacted by the clinical pharmacist on their scheduled day of follow-up regardless of whether they completed a warfarin questionnaire.

Study Design and Patients

The computerized patient record system was utilized to identify study participants. The facility institutional review board approved the study protocol. Informed consent was not required for retrospective data collection. Adult, outpatient veterans on indefinite warfarin therapy between January 2010 and December 2012 were eligible for this retrospective review. Patients were required to have consistent FF or TELE follow-up visits, defined as regular, scheduled follow-up as indicated in anticoagulation therapy progress notes, with their primary care pharmacist throughout the study period. Subjects were excluded if warfarin therapy was not managed by a VA primary care pharmacist, they were not seen by their primary care pharmacist for 3 months or greater during study period, and they did not have a documented INR value for 3 months or greater during the study period. Some patients received care by both treatment modalities; therefore, assignment to a study group was based on the percentage of total visits that were either FF or TELE. If ≥70% of visits occurred via FF or TELE, the participant was assigned to that respective group.

Data Collection

A standardized, electronic worksheet was used for data collection. Information collected for subjects included demographics, indication for warfarin therapy, annual VA bleeding risk assessments (Table 1), goal INR therapeutic range, INR at each encounter, primary care clinic, visit type (FF or TELE), number of visits per year, food and drug interactions that could have contributed to a nontherapeutic INR, compliance based on reported missed or extra doses,

Table 1. VA Annual Bleeding Risk Assessment.

Assign ONE point for EACH of the following:
- Age greater than or equal to 65 years
- History of CVA
- History of GI bleed

Assign ONE point TOTAL if ANY of the following:
- Recent MI
- Hct <30%
- SCr >1.5 mg/dL
- Diabetes mellitus

Total Points:

Risk Level:

0 = Low bleeding risk

1-2 = Intermediate bleeding risk

≥3 = High bleeding risk

Other medications or conditions that may increase risk of bleeding (yes/no)?
- NSAID use
- Antiplatelet or clopidogrel use
- Alcohol use
- Illicit drug use

and scheduled therapy interruption for a procedure. Percent time in therapeutic range was calculated via the Rosendaal method.[9] The following events were documented if they occurred during the study period: any bleeding (including self-reported), significant bleeding (requiring emergency room treatment or hospital admission), DVT, PE, CVA, hospitalization for any reason, and death. Patient data were obtained from the computerized patient record system, including medical and anticoagulation records, and scanned documents from non-VA hospital admissions or emergency room visits.

TTR was calculated via the Rosendaal method as previously noted using INR measurements recorded at all outpatient anticoagulation visits. The Rosendaal method uses linear interpolation to assign an INR value to each day between successive observed INR values. Goal INR was determined by documented therapeutic goal in anticoagulation records and was incorporated into the equation to determine TTR. All INR measurements, including those obtained on warfarin initiation, were included in this calculation. A TTR was calculated for each patient, and a mean TTR was calculated for each study group and each site of care.

Statistical Analysis

Primary and secondary outcomes were compared across study groups. Assuming an $\alpha = .05$, it was calculated that to achieve 80% power a sample size of 200 patients was needed. All statistical analyses were performed using procedures from SPSS software, version 19. Demographic and nominal data were analyzed using a χ^2 or Fisher's exact test. Percentages were used to describe nominal data in each group. Interval or ratio data were compared using a Student *t* test. A significance level probability of <.05 was used to determine statistical significance.

Results

A total of 200 subjects were included for analysis with 90 FF participants and 110 TELE participants. A summary of subject characteristics including age, gender, race, and anticoagulation parameters is provided in Table 2. Statistically significant differences existed between groups with respect to race and indication for warfarin therapy (CVA). The majority of the study population was male, and more than half of the subjects in each group were ≥65 years of age. Approximately 70% to 75% of individuals in each group had atrial fibrillation as their indication or one of their indications for anticoagulation therapy. No statistically significant differences between study groups were found in the number of subjects whose anticoagulation records reflected interactions contributing to a nontherapeutic INR, self-reported compliance with regard to missed or extra doses, and warfarin interruptions related to procedures.

Twelve primary care clinics were included in this analysis. Approximately 50% of the total subjects were followed by the 3 main hospital clinics. Subjects seen in the main hospital clinics accounted for the majority of the subjects in the FF follow-up group, and subjects seen in the CBOCs accounted for nearly 70% of subjects in the TELE follow-up group (Table 3), potentially allowing for less variability among subjects with regard to anticoagulation management.

Outcome Measures

Overall TTR for FF and TELE follow-up was 68.17% and 69.57%, respectively ($P = .493$). Differences in the rates of hospitalization, DVT, PE, CVA, and death from any cause were not found to be statistically significant (Table 4). A higher rate of any bleeding was found to be statistically significant in the FF group (48.9% vs 30.9%; $P = .0144$). When specifically evaluating the rates of significant bleeding, no significant difference was found between FF and TELE (6.67% vs 2.3%, respectively; $P = .304$). The majority (83.33%) of the individuals that experienced a significant bleed in the FF group were either at an intermediate bleeding risk per VA annual bleeding risk assessment (Table 1) and also receiving antiplatelet therapy or were at a high bleeding risk, whereas the majority (66.67%) of the subjects that experienced a significant bleed in the TELE group were at a low bleeding risk and were not receiving antiplatelet therapy. The mean number of clinic visits per year for FF versus TELE was 17.3 and 15.6, respectively, and this difference was found to be statistically significant ($P = .00165$).

Table 2. Subject Characteristics.

Variable	Face-to-Face (N = 90), n (%)	Telephone (N = 110), n (%)	*P*
Gender			
Male	87 (96.7)	107 (97.3)	.8026
Female	3 (3.3)	3 (2.7)	.8026
Race			
African American	37 (41.1)	18 (16.4)	**.0001**
Caucasian	48 (53.3)	84 (76.4)	**.0006**
Pacific Islander	1 (1.1)	0	.2670
Unknown	4 (4.4)	8 (7.2)	.4009
Age (years)			
<65	37 (41.1)	41 (37.3)	.5823
≥65	53 (58.9)	69 (62.7)	.5823
Indication for warfarin therapy[a]			
Atrial fibrillation	68 (75.6)	79 (71.8)	.5485
CVA	18 (20)	10 (9.1)	**.0271**
DVT and/or PE	24 (26.7)	28 (25.5)	.8493
AVR and/or MVR	4 (4.4)	6 (5.5)	.7414
Goal INR			
2.0-3.0	87 (95.6)	107 (91.8)	.8026
Other[b]	4 (4.4)	9 (8.2)	.2846
Bleeding risk			
Low	6 (6.7)	17 (15.5)	.0524
Intermediate	67 (74.4)	80 (72.7)	.7872
High	14 (15.6)	11 (10)	.2380
Unknown	3 (3.3)	2 (1.8)	.4060
Receiving antiplatelet therapy			
No	58 (64.4)	68 (61.8)	.7039
Yes	32 (35.6)	42 (38.2)	.7039

Abbreviations: CVA, cerebrovascular accident; DVT, deep vein thrombosis; PE, pulmonary embolism; AVR, aortic valve replacement; MVR, mitral valve replacement; INR, international normalized ratio. Bolded values indicate statistical significance.
[a]Indications for warfarin therapy are not mutually exclusive.
[b]Other includes 2.5-3.5, 2.5-3.0, 2.0-2.5, and 1.8-2.2.

Table 3. Clinic Distribution.

Clinic	Face-to-Face (N = 90), n (%)	Telephone (N = 110), n (%)
Main hospital clinics		
A	18 (20)	8 (7.3)
B	23 (25.7)	12 (10.9)
C	21 (23.3)	11 (10)
Community-based outpatient clinics		
D	0	5 (4.5)
E	0	21 (19.1)
F	0	40 (36.4)
G	1 (1.1)	0
H	14 (15.6)	2 (1.8)
I	1 (1.1)	7 (6.4)
J	12 (13.3)	0
Home-based primary care		
K	0	3 (2.7)
L	0	1 (0.9)

Discussion

Two previous studies have compared percent TTR from INR values of study subjects receiving warfarin therapy via face-to-face or telephone pharmacist-managed clinics.[16,17] These previous reports did not find statistically significant differences in percent TTR. One of these studies, by Staresinic and colleagues, utilized the Rosendaal method to determine and compare percent TTR for telephone and face-to-face visits in a VA medical center, similar to this report, but included a lower number of study subjects and excluded data from the first 3 months of anticoagulation therapy. Their study reported a mean percent TTR of 57.8% and 55.1% for face-to-face and telephone management, respectively.[17] Despite the similarities between their study and our analysis, we found our mean percent TTR for each group to be higher and above the threshold that has been commonly described in the literature as quality control (≥65%). To our knowledge, this is the first study performed in a VA medical center reporting

Table 4. Outcome Measures.

Outcome	Face-to-Face (N = 90)	Telephone (N = 110)	*P*
TTR			
Overall	68.2%	69.6%	.493
Main hospital clinics			
A	72.6%	69.7%	.640
B	63.1%	67.5%	.480
C	67.8%	70.6%	.581
Main hospital clinics	69.2%	67.2%	.562
CBOCs	65.9%	70.3%	.150
Event outcomes			
Hospitalization	23.3%	15.5%	.218
Any bleeding	48.9%	30.9%	**.0144**
Significant bleeding	6.67%	2.73%	.304
DVT, PE, CVA	1.1%	1.8%	1.0
Death[a]	1.1%	4.5%	.226

Abbreviations: TTR, time in therapeutic range; CBOC, community-based outpatient clinic; DVT, deep vein thrombosis; PE, pulmonary embolism; CVA, cerebrovascular accident. Bolded values indicate statistical significance.

[a]Causes of death: FF—unknown; TELE—lung cancer, unknown, CVA, hematoma.

mean percent TTR measurements ≥65%, which suggests a progression in implementing telephone-based clinics for anticoagulation.

Our findings do not necessarily highlight a need for developing criteria for either mode of care since significant differences were not found in most of the outcome measures; however, it is important to highlight the rate of any bleeding was significantly higher in the face-to-face group. Those that experienced significant bleeding in the face-to-face group were at a higher bleeding risk than those in the telephone group, which could have been one of the reasons they were seen for follow-up. It is possible that confounding factors related to clinic visit type could have contributed to these findings as well. Patients may be more likely to report any bleeding event in a face-to-face visit, and their degree of reporting could be a result of the provider's approach to inquiring about any bleeding events. Future studies are needed to support the development of criteria based on these findings; however, these results support the facility's desire to explore centralized anticoagulation.

One limitation is that we could not assess patient satisfaction due to the retrospective nature of this study. However, a previous study measured patient satisfaction with a telephone-based approach to anticoagulation managed by a health care team, including a pharmacist, and found that patients were more satisfied with their care, had a greater knowledge of their warfarin therapy, and felt more safe taking warfarin when compared to their clinic experience with a primary care provider.[18] Another limitation is that data from multiple clinics were included in our analysis, with some of the CBOCs only able to manage anticoagulation via telephone. This uneven distribution of subjects among clinics could have introduced confounding variables and selection bias; however, by including all subjects that met inclusion criteria, regardless of their respective clinic, we were able to capture a study population that more truly represents our general population. The CBOCs and HBPC telephone clinics allow the VA medical center to service a greater number of patients throughout the state, and it has been shown that patients living in rural areas or those that cannot reasonably travel to a clinic value telephone management.[19]

Conclusion

No significant differences were found in TTR, rates of significant bleeding events, thromboembolic events, or death from any cause when comparing face-to-face and telephone follow-up of warfarin therapy. This report adds to the available evidence in support of telephone management of warfarin therapy. The results of our primary outcome (TTR) suggest that the implementation and continued delivery of anticoagulation monitoring and follow-up via telephone has potentially improved over the past several years.

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Declaration of Conflicting Interests

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