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The Quality of Warfarin Prescribing and Monitoring in Veterans Affairs Nursing Homes

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Abstract

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OBJECTIVES—To describe the quality of warfarin prescribing and monitoring in Veterans Affairs (VA) nursing homes and to assess the factors associated with maintaining a therapeutic International Normalized Ratio (INR).

DESIGN—Retrospective cohort.

SETTING—Five VA nursing homes.

PARTICIPANTS—All Veterans who received warfarin between January 1 and June 30, 2008 at the nursing homes.

MEASUREMENTS—Using medical records, we estimated the percentage of person-time spent in the target INR range, the proportion of patients with INRs in the therapeutic range on ≥ 50% of their person-days and the frequency of INR monitoring. We used multivariable logistic regression to identify factors associated with maintaining a therapeutic INR ≥ 50% of the time.

RESULTS—Over six months, 160 patients received 10,380 person-days of warfarin. INRs were in the therapeutic range for a majority (55%) of the person-days, and 99% of the INR tests were repeated within four weeks of the previous result. On an individual level, 49% of patients had INRs in the target range for ≥ 50% of their person-days. Achieving this outcome was more likely in patients with prevalent warfarin use versus new use (Adjusted odds ratio [AOR]=2.86; 95% confidence interval [CI]=1.06, 7.72). Conversely, patients with a history of a stroke (AOR=0.38; 95% CI=0.18, 0.80) were less likely to have therapeutic INRs for ≥ 50% of their days.

CONCLUSION—Warfarin appears to be effectively prescribed and monitored in VA nursing home patients. Future studies should focus on increasing time in therapeutic range among patients with poor INR control.

Keywords

warfarin; healthcare quality assurance; nursing homes

INTRODUCTION

As many as 17% of nursing home patients are prescribed warfarin for indications such as atrial fibrillation, deep venous thrombosis and mechanical valve replacement.[1,2] However, there is a disproportionate association between warfarin use and medication-related problems, with as many as 80% of potential adverse drug events (ADEs), or near misses, involving this medication alone in the nursing home setting.[3] Few studies have focused on the quality of warfarin prescribing and monitoring in nursing homes, and none have been conducted in Veterans Affairs (VA) nursing homes.[1,2,4] The existing studies indicate that there is room to improve the prescribing of warfarin as measured by the proportion of days the International Normalized Ratio (INR) is in the therapeutic range.[1,2,4] Time in therapeutic range is strongly associated with clinical outcomes, such as the incidence of thromboembolic events among patients with atrial fibrillation.[5–8]

Despite the importance of time in therapeutic range, the patient-specific factors associated with maintaining a therapeutic INR in nursing home patients remain unclear. It is also relevant to study this issue in VA nursing homes because of access to and availability of computerized provider order entry, in-house providers (i.e., physicians, advanced practitioners and pharmacists), on-site pharmacies and on-site laboratory services. Therefore, the objectives of this study are to describe the quality of warfarin prescribing and monitoring in Veterans at five VA nursing homes and to assess the factors associated with maintaining a therapeutic INR in this patient population.

METHODS

Study Setting

We identified Veterans who received warfarin at one of five VA nursing homes located throughout the United States (West Haven, CT; Pittsburgh, PA; Durham, NC; Lake City, FL, and Phoenix, AZ). These sites were selected because they vary in size, and previous nursing home studies have shown that facility size is an important factor in the quality of prescribing.[9–11] The number of licensed beds at these five sites ranged from 32 to 300.

Study Sample and Data Collection

The cohort included all Veterans who received at least one dose of warfarin between January 1, 2008 and June 30, 2008 at one of the five participating nursing homes, regardless of the duration of therapy or type of stay (e.g., long-term care, hospice, rehabilitation). The study was approved by the Institutional Review Boards for these homes. A pharmacist at each site retrospectively identified the study sample using a search of Veterans Health Information Systems and Technology Architecture (VistA). VistA connects computer workstations at VA facilities with software applications that are accessed by end users through a graphical user interface known as the Computerized Patient Record System (CPRS).

For all patients meeting the eligibility criteria, pharmacists collected the following baseline data using the electronic medical record (i.e., CPRS): date of birth, sex, race, height, type of stay, indication for warfarin, and duration of warfarin therapy prior to the study period. We recorded potential risk factors for bleeding in patients on warfarin as defined in the Bleeding Risk Index (i.e., history of stroke, history of gastrointestinal bleed, recent myocardial infarction, presence of diabetes mellitus, hematocrit <30% or serum creatinine >1.5mg/dl).[12] We also collected data on the presence of disease states (e.g., congestive heart failure, hypo- or hyperthyroidism, active cancer, malnutrition) that may increase the risk of bleeding or a thromboembolic (TE) event, either directly or through an interaction with warfarin that leads to an increase or decrease in the INR (i.e., drug-disease interactions). Throughout the study period, we recorded all weights, INR values, warfarin doses administered and the concurrent use of other medications with the potential to interact with warfarin based on the "highly probable" and "probable" interactions in the review by Holbrook et al.[13] Drug-drug interactions were classified as "new" if they were not present at baseline. In addition, data were collected on all bleeding events, TE events and INRs ≥4.5 without bleeding.

Primary and Secondary Outcome Measures

The primary outcome was the quality of warfarin prescribing, which we operationally defined in two ways: 1) the percentage of time in the therapeutic range for the entire cohort and 2) the proportion of patients with INRs in the therapeutic range on ≥ 50% of their person-days. We chose this second measure because maintaining a therapeutic INR ≥ 50% of the time was the minimum threshold required to achieve a benefit from warfarin therapy among patients with atrial fibrillation.[5] In addition, it would be more clinically useful to identify factors associated with attaining this threshold, which indicates stability over time, rather than having a therapeutic INR on any given day. The secondary outcome was the quality of warfarin monitoring, which we operationally defined as the proportion of repeat INRs drawn within four weeks of the previous INR.[14,15]

Clinical Outcome Measures

We described potential complications of warfarin therapy, including bleeding, TE events and INRs ≥ 4.5 without bleeding. The threshold of ≥4.5 was selected because it has been used in a study of the safety of warfarin use in non-government nursing home patients,[1] and

the risk of an intracranial hemorrhage increases dramatically at INRs above 4.[16] Bleeding was categorized as major and minor, with major bleeding as defined by the International Society on Thrombosis and Haemostasis.[17] A major bleeding event includes fatal bleeding, symptomatic bleeding in a critical organ or area (e.g., intracranial, intraspinal, intraocular resulting in visual changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), bleeding causing a decrease in the hemoglobin of 2gm/dL or more, and bleeding leading to a transfusion of 2 or more units of whole blood or red blood cells. All other bleeding events were considered to be minor. The probability that warfarin caused a major bleeding event was assessed by a pair of pharmacist-physician investigators (JTH and SMH) using the Naranjo algorithm.[18] These same investigators used the Therapeutic Failure Questionnaire to ascertain whether a TE event probably was a result of a warfarin therapeutic failure.[19]

Statistical Analyses

Patient characteristics were summarized at baseline. To describe the quality of warfarin prescribing and monitoring, we examined all INR values obtained for study patients. Among patients with at least two INR assessments, the average percentage of person-days the INR was in the therapeutic range was estimated using the linear interpolation method of Rosendaal et al., in which the change in two consecutive INRs is assumed to be linear over the time interval.[20] The therapeutic range was defined using the goal set for each patient according to the indication for warfarin (e.g., INR goal of 2–3 for atrial fibrillation). The average percentage of person-days that the INR was sub- and supra-therapeutic was calculated using the same method. To assess provider response to an out-of-range INR value, we evaluated the average daily dose of warfarin during the seven days before and after the result. For INR values that were subtherapeutic (according to the INR goal for each patient), we reviewed the data to see if the warfarin dose increased, and for INRs that were supratherapeutic, we ascertained whether the dose was held and/or decreased. For the clinical outcome measures, point estimates and 95% exact Poisson confidence intervals (CIs) were calculated.

Multivariable logistic regression models were used to identify risk factors associated with patients having a therapeutic INR ≥ 50% of the time. Potential independent variables included: sex; height; weight; body mass index; type of patient stay; indication for warfarin; duration of warfarin therapy; risk factors for bleeding or a TE event, and the concurrent use of other medications (at baseline and newly prescribed) that may interact with warfarin. First, we examined the univariable associations between each predictor variable and the outcome of having a therapeutic INR ≥ 50% of the time using Chi square tests (Fishers exact for small cell sizes) or one-way analysis of variance as appropriate. Those predictor variables that were suggestive of a univariable association with the outcome (i.e., $p \geq 0.15$) were included in a multivariable model that adjusted for site, age and race. The small number of sites precluded formal assessment of site-level characteristics. The Hosmer and Lemeshow goodness-of-fit test was used to check the overall model fit.[21] SAS software (Cary, NC) version 9.2 was used to conduct all analyses.

RESULTS

Over a six month period, 160 patients in the five participating nursing homes received 10,380 person-days of warfarin therapy. During the study, the daily prevalence of warfarin use ranged from 9.6% to 12.4%, and the mean daily dose of warfarin was 5.0mg (S.D. 2.6). Table 1 shows characteristics of the population at baseline (i.e., the first day of warfarin use during the study period). The mean age of these patients was 71.0 (S.D. 11.7) years, and a majority was white men. Most patients were admitted for rehabilitation (43%) or long-term care (33%), and 85% were receiving warfarin prior to baseline. The most common

indications for warfarin were atrial fibrillation (62%), deep vein thrombosis or pulmonary embolism (35%), or stroke (11%); thus, the INR goal was 2.0–3.0 in 94% of the patients. About 89% of the patients received at least one medication that potentially interacts with warfarin at baseline. The most frequently prescribed interacting drugs at baseline were omeprazole (in 51% of patients), simvastatin (in 45%), aspirin (in 34%), citalopram (in 18%) and levothyroxine (in 13%). During the study period, 46% of patients received a newly prescribed medication with the potential to interact with warfarin.

Quality of Warfarin Prescribing

Overall, INRs were in the therapeutic range for a majority (55%) of the person-days, and more person-time was spent in the subtherapeutic (35%) than supratherapeutic range (11%) (Table 2). INRs were <1.6 or ≥ 4.5 on only 13% of the person-days. On an individual level, about 49% of patients had INRs in the therapeutic range for ≥ 50% of their person-days.

For INRs that were < 1.6, the average daily dose of warfarin for the seven days that followed increased in 75% (159/212) of such occurrences. When the INR was ≥ 1.6, but not in the patient-specific therapeutic range, providers increased the warfarin dose 53% (160/300) of the time. For INRs that were above the goal range, but <4.5, providers held or decreased the dose of warfarin 93% (156/168) of the time.

Quality of INR Monitoring

A total of 1597 INR values were obtained in 156 patients. Four patients with short stays did not have INRs measured, but they were monitored prior to admission. In a four week period, patients had an average of 5.2 (S.D. 2.7) INRs obtained. Among those patients with at least two INR values (N=142 patients), the mean number of days between INRs was 6.7 (S.D. 6.2), and 99% of INRs were repeated within four weeks of the previous INR.

Multivariable Factors Associated with Patients Having Therapeutic INRs on ≥ 50% of Their Person-Days

The adjusted odds of having INRs in the therapeutic range for 50% or more of their person-days was 2.86 (95% CI=1.06, 7.72) for patients receiving warfarin prior to baseline versus those who initiated warfarin therapy during the study period (Table 3). Conversely, patients with a history of a stroke (OR=0.38; 95% CI=0.18, 0.80) were less likely to have therapeutic INRs on ≥ 50% of their person-days.

Bleeds, Thromboembolic Events and INRs ≥ 4.5

During the course of the study, 39 minor bleeds occurred in 26 patients (0.38 per 100 person-days of warfarin, 95% CI 0.27–0.52). There was one major bleed (0.01 per 100 person-days of warfarin, 95% CI 0.002–0.05) and no therapeutic failures (i.e., TE event). The patient with a major bleed had a large hematoma, and the hemoglobin dropped 2.2 gm/dL. Warfarin was temporarily held, and the dose was decreased. A total of 24 INRs ≥ 4.5 without bleeding occurred in 15 patients (0.23 per 100 person-days of warfarin, 95% CI 0.15–0.35). In each instance, warfarin was held temporarily, and the dose also was decreased in 33%.

DISCUSSION

Few published studies describe warfarin prescribing and monitoring in nursing home patients, and to our knowledge, this is the first to assess the quality of warfarin use in VA nursing homes. A common measure of prescribing quality is time in therapeutic range. In our study, 55% of the person-days were spent in the therapeutic range while on warfarin. This compares well with other studies of nursing home patients, where a therapeutic INR

was maintained 49.6%–54.1% of the time.[1,2,4] Although time in target range is associated with clinical outcomes,[8,22,23] the threshold required to achieve the benefit is not clear. In a study of patients with atrial fibrillation, a decrease in TE events and intracranial hemorrhage was observed only when the time in therapeutic range was at least 50%, and the benefit rose sharply as the time in range increased.[5] Another study reported that the risk of stroke was reduced when patients with atrial fibrillation spent > 70% of the time at an INR goal range of 2.0–3.0, and overall survival improved when the INR was in this range >40% of the time.[6] In our study, 49% of the patients were in the therapeutic range at least 50% of the time; no comparable data are available from other studies of nursing home residents. Regarding the days out of target range, patients in our study spent a higher proportion of time in the subtherapeutic versus the supratherapeutic range, and a relatively small proportion of that time was at critically low or high INR values (i.e., < 1.6 or ≥ 4.5). This is also consistent with other studies of nursing home residents.[1,2,4] It is possible that providers are more concerned about safety in a patient population that typically is elderly with other risk factors for major bleeding. Providers responded to INRs that were out of range, especially when the value was elevated (e.g., ≥ 4.5). All sites had a policy for reporting critically elevated INRs to the ordering provider as soon as the results were generated by the laboratory. In addition, a recent observational study suggests that responding too frequently to INRs that are slightly sub-or supratherapeutic may result in a reduction in person-time spent in the therapeutic range while on warfarin.[24] Therefore, while the quality of prescribing was good, there appears to be room for improvement in maintaining a therapeutic INR for a longer duration of time in both VA and non-VA settings.

Other studies suggest that time in therapeutic range can be increased with more frequent monitoring.[8,25] In our study, we found that INRs were checked frequently, with an average of 5.2 INR measurements obtained per patient in a four week period. This is more often than the average of 3.4 INR measurements reported in another study of nursing home patients.[2] Guidelines from the American College of Chest Physicians recommend monitoring the INR at an interval of no longer than every four weeks in patients on a stable dose of warfarin,[14] and a multidisciplinary panel agreed with this frequency of monitoring for nursing home patients on chronic warfarin therapy.[15] In our study, only 1% of the INRs were not obtained within four weeks of the previous INR.

Defining the optimal testing frequency is difficult given the number of factors that can influence anticoagulation control. In the nursing home setting, these factors can include fluctuations in the status of comorbid conditions (e.g., heart failure) and changes in potentially interacting medications, nutritional state and the quality of warfarin dose management.[24] There could be a point where increased monitoring does not result in more time in the goal range. This makes sense intuitively because the full antithrombotic effect of warfarin requires a reduction in prothrombin, which has a half-life of approximately 60–72 hours.[14] In our study, increased monitoring did not seem to improve the amount of time in the target range when compared with other studies.

In order to improve time in therapeutic range, it would be useful to know what factors are associated with consistently maintaining a therapeutic INR (i.e., spending ≥ 50% of the time in the target INR range) among nursing home patients. In our study, we found that patients on warfarin prior to the study period (i.e., prevalent users) were more likely to be in the therapeutic range than were patients who initiated treatment during the study period (i.e., new users). This is expected because it takes time to achieve a stable dose response in patients who are just starting warfarin. Conversely, Veterans with a history of a stroke were less likely to spend ≥ 50% of their time in the therapeutic range. In some patients with a history of a stroke, providers may have been more conservative in their dosing due to concerns about falls and an increased risk of bleeding. However, as mentioned previously, if

the patient has atrial fibrillation, then maintaining an INR of 2–3 is important to decrease the risk of both stroke and hemorrhage.[5,6,23]

Although there were no TE events related to a failure, or error in the management, of warfarin therapy and only one major bleed, this study was not designed to assess outcomes. In a study of long-term care residents by Gurwitz et al., fatal, life-threatening or serious warfarin-related adverse events occurred at a rate of 2.5 per 100 person-months on warfarin.[1] Patients were older (mean age of 82.3 years), and Gurwitz et al. classified any event that required treatment or medical evaluation as serious.[1] It is likely that some of these bleeding events would have been categorized as minor according to our definition, and a standardized definition of a major bleeding would help when comparing rates in future studies.[26] With regard to INRs ≥ 4.5 without bleeding, our event rate of 0.23 per 100 person-days of warfarin is comparable to that reported by Gurwitz et al. (i.e., 6.6 per 100 person-months or 0.22 per 100 person-days).[1] However, they only included events where an error in warfarin management occurred and classified these incidents as potential ADEs.

Although we conducted a comprehensive and detailed chart review to assess the quality of warfarin prescribing and monitoring in VA nursing home patients, there are limitations. First, we relied on retrospective chart reviews to detect potential adverse events, and we could have missed some bleeds, especially those that were minor. Second, our primary outcome measures were based on the use of linear interpolation to estimate the time in therapeutic range between two consecutive INR values, so the results could be influenced by non-linearity between test results. However, only 11% (18/160) of the patients did not have at least 2 INR values, and the average time between INRs was less than one week. Third, we were unable to assess the influence of provider characteristics on the quality of warfarin dose management, because multiple providers were involved in the care of the same patient. Finally, there may be other unmeasured, potentially confounding factors associated with maintaining INR control in nursing home patients that were not included in this analysis.

CONCLUSION

Overall, warfarin appears to be effectively and safely prescribed and monitored in this study of five VA nursing homes as reflected by the time in therapeutic range, at least monthly monitoring of the INR and the small number of adverse events. Patients on chronic warfarin therapy and those without a history of stroke were more likely to maintain INR control. Future studies should focus on interventions to further increase the time in therapeutic range among patients with poor INR control.

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Table 1

Characteristics of Patients Receiving Warfarin in VA Nursing Homes

Characteristic	N (%) (n=160)
Site	
A	68 (43)
B	5 (3)
C	23 (14)
D	39 (24)
E	25 (16)
Age (years)	
<65	56 (35)
65–74	33 (21)
>74	71 (44)
Male	156 (98)
Race	
White	114 (71)
Black	33 (21)
Other/Unknown	13 (8)
Body Mass Index (BMI) (n=155)	
Underweight (BMI < 18.5)	4 (3)
Normal weight (BMI 18.5–24.9)	39 (25)
Overweight (BMI 25.0–29.9)	44 (28)
Obese (BMI ≥ 30)	68 (44)
Type of Stay	
Long-term care	53 (33)
Rehabilitation	69 (43)
Respite	14 (9)
Hospice	5 (3)
Other	18 (11)
Unknown	1 (1)
Indication for Warfarin*	
Atrial fibrillation	99 (62)
Deep vein thrombosis/pulmonary embolism	56 (35)
Stroke	17 (11)
Mechanical aortic or mitral valve	5 (3)
Cardiomyopathy	3 (2)
Hypercoagulable state	3 (2)
Bioprosthetic valve	3 (2)
Other	16 (10)
Risk Factors for Bleeding	
History of stroke/transient ischemic attack	61 (38)

Characteristic	N (%) (n=160)
History of gastrointestinal bleed	10 (6)
Recent myocardial infarction	5 (3)
Presence of diabetes	80 (50)
Presence of hematocrit < 30%	68 (43)
Presence of serum creatinine > 1.5mg/dl	75 (47)
Presence of Conditions That May Influence INR	
Congestive heart failure	74 (46)
Thyroid dysfunction	29 (18)
Malnutrition	14 (9)
Receiving chemotherapy or radiation	10 (6)
Acute or chronic liver failure	6 (4)
Other	4 (3)
Number of Warfarin-Interacting Medications at Baseline	
None	18 (11)
1	26 (16)
2	41 (26)
3	32 (20)
≥ 4	43 (27)

INR=International Normalized Ratio

* Total is > 100% because patients may have more than 1 indication for warfarin. Of the 17 patients with stroke as an indication for warfarin, five did not have a concomitant indication.

Table 2

Time in Specified International Normalized Ratio (INR) Ranges*

INR Range	Person-Days in INR Range N (%) (n=9118 person-days of warfarin)+
Therapeutic	4983 (55)
Subtherapeutic	3177 (35)
INRs < 1.6	1128 (12)
Supratherapeutic	958 (11)
INRs ≥ 4.5	96 (1)

* The therapeutic, sub- and supratherapeutic INR ranges were patient specific with 94% having an INR goal of 2–3. In these patients, an INR < 2 was subtherapeutic, and an INR >3 was supratherapeutic.

+ 9118 person-days of warfarin were used for these analyses instead of 10,380 because INR values could not be assigned to those days that were before the first INR or after the last INR in the study period. The total is > 100% due to rounding.

Table 3

Multivariable Factors Associated with Patients Having ≥ 50% Person-Days in the Therapeutic Range*

Variable	Adjusted OR (95% CI)	p-value
Site		0.42
A	Reference	
B	3.69 (0.37, 37.22)	
C	0.50 (0.17, 1.51)	
D	1.35 (0.58, 3.13)	
E	0.86 (0.31, 2.39)	
Age (years)		0.55
<65	Reference	
65–74	1.12 (0.44, 2.90)	
>74	1.52 (0.70, 3.33)	
Race		0.91
White	Reference	
Black	1.20 (0.49, 2.93)	
Missing	0.93 (0.27, 3.27)	
Warfarin Initiated Prior to Baseline		
No	Reference	0.04
Yes	2.86 (1.06, 7.72)	
History of Stroke/Transient Ischemic Attack		0.01
No	Reference	
Yes	0.38 (0.18, 0.80)	

* p=0.63 for the Hosmer and Lemeshow goodness-of-fit test.