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CLINICAL RESEARCH STUDY

The Safety of Warfarin Therapy in the Nursing Home Setting

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ABSTRACT

PURPOSE: We examined the preventability of adverse warfarin-related events and potential adverse warfarin-related events ("near misses") in the nursing home setting.

METHODS: We performed a cohort study of all long-term care residents of 25 nursing homes (bed size range, 90-360) in Connecticut during a 12-month observation period. The total number of residents in these facilities ranged from 2946 to 3212 per quarter. There were 490 residents who received warfarin therapy. Possible warfarin-related incidents were detected by quarterly retrospective review of nursing home records by trained nurse abstractors. Each incident was independently classified by 2 physician-reviewers to determine whether it constituted a warfarin-related event, its severity, and its preventability. The primary outcome was an adverse warfarin-related event, defined as an injury associated with the use of warfarin. Potential adverse warfarin-related events were defined as situations in which the international normalized ratio (INR) was noted to be 4.5 or greater, an error in management was noted, but no injury occurred. We also assessed time in specified INR ranges per nursing home resident day on warfarin.

RESULTS: Over the 12-month observation period, 720 adverse warfarin-related events and 253 potential adverse warfarin-related events were identified. Of the adverse warfarin-related events, 625 (87%) were characterized as minor, 82 (11%) were deemed serious, and 13 (2%) were life-threatening or fatal. Overall, 29% of the adverse warfarin-related events were judged to be preventable. Serious, life-threatening, or fatal events occurred at a rate of 2.49 per 100 resident-months; 57% of these more severe events were considered preventable. Errors resulting in preventable events occurred most often at the prescribing and monitoring stages of warfarin management. The percentages of time in the less than 2, 2 to 3, and more than 3 INR ranges were 36.5%, 49.6%, and 13.9%, respectively.

CONCLUSIONS: The use of warfarin in the nursing home setting presents substantial safety concerns for patients. Adverse events associated with warfarin therapy are common and often preventable in the nursing home setting. Prevention strategies should target the prescribing and monitoring stages of warfarin management.

KEYWORDS: Long-term care; Medication safety; Nursing homes; Oral anticoagulants; Warfarin

Concerns relating to the risks of anticoagulation therapy with warfarin are intensified in the long-term care setting, because elderly residents of nursing homes are among the most frail patients in the geriatric population. Given that more than 1.6 million Americans currently reside in nursing homes and the prevalence of medical conditions for which warfarin is indicated increases with advancing age, issues surrounding the management of anticoagulation therapy in

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this population require particular attention.[1-3] Factors such as aging, comorbid conditions, diet, and medications can affect the pharmacodynamics of warfarin, thus making dosing and monitoring more challenging with advancing patient age.[4] As many as 12% of nursing home residents receive warfarin for various reasons, but the quality of anticoagulation care in this setting is suboptimal.[1,2] Although oral direct thrombin inhibitors hold some promise as less-complicated anticoagulants, ximelagatran has been associated with hepatotoxicity and has not received approval by the Food and Drug Administration for use in the United States.[5] For the foreseeable future, warfarin remains the sole oral anticoagulant available for long-term use in the frail elderly.

CLINICAL SIGNIFICANCE

- Adverse events associated with warfarin therapy are common and often preventable in the nursing home setting.
- Specialized anticoagulation services in nursing homes and improved communication protocols between nursing home staff and prescribing physicians may reduce the risk of warfarin-related adverse events.

In prior work examining the scope of adverse drug events in the long-term care setting, we found that warfarin was among the drug types most commonly implicated.[6,7] The purpose of the present study was to carefully assess the safety of anticoagulation therapy with warfarin in the long-term care setting. A particular focus was placed on assessing the preventability of adverse warfarin-related events.

METHODS

Study Setting

This study was conducted in 25 nursing homes located in the state of Connecticut. Data were collected during the period from April 1, 2003, to March 31, 2004. Patients residing in areas of the facilities related to short-term care (eg, subacute care, hospital-level care, or rehabilitation) were not included as potential subjects in the study. The study was approved by the institutional review board of the University of Massachusetts Medical School.

The bed sizes of the participating nursing homes ranged from 90 to 360 beds. Table 1 provides a comparison of the characteristics of the participating nursing homes with facilities in Connecticut, as well as nationally.[8] The total number of residents of these 25 facilities, which comprised the underlying study population, varied from 2946 to 3212 residents over the 1-year study period.

Case-Finding Approach

The study was limited to warfarin-related incidents occurring in the nursing home setting. Incidents were detected through retrospective review of nursing home records in 3-month segments performed by trained nurse abstractors for each eligible resident of the nursing home who was receiving warfarin at any time during that time period. The nurse abstractors searched for possible warfarin-related incidents using a variety of specified triggers, including international normalized ratio (INR) values of 4.5 or greater, evidence of overt bleeding, a hematocrit decrease of 3% or greater from a previous value, an order for vitamin K, a stroke or other thrombotic event, and any emergency department visit or hospitalization.

Outcome Measures

The primary outcome was an adverse warfarin-related event, defined as an injury resulting from the use of warfarin. This definition is consistent with definitions used in previous studies of adverse drug events.[6,7,9-12] Adverse warfarin-related events may have resulted from medication errors (eg, errors in ordering, dispensing, administration, or monitoring) or may have occurred in the absence of any error. We also identified potential adverse warfarin-related events. Potential adverse warfarin-related events were defined as situations in which the INR was noted to be 4.5 or greater and no injury occurred, but an error in warfarin management was identified. Thus, according to this study definition, not all INR values 4.5 or more were considered to be potential adverse warfarin-related events. The 4.5 threshold INR level was chosen for use in this study because various investigations have demonstrated that the risk of intracranial hemorrhage increases dramatically at INRs at or above this point.[13,14]

Warfarin-related incidents were presented to pairs of physician-reviewers (J.H.G., L.R.H., M.J.R., R.B.) who independently classified incidents using structured implicit

Table 1 Comparison of Study Nursing Homes with Facilities in Connecticut and the United States

	Study Nursing Homes n = 25 (%)	Connecticut n = 248 (%)	National n = 18,000 (%)
No. of beds	3411	30,504	1,879,600
Mean (±SD)	136 (±28.7)	123 (±58.6)	104
<50 beds	0 (0)	12 (5)	2100 (12)
50-99 beds	1 (4)	79 (32)	7000 (39)
100-199 beds	23 (92)	137 (55)	7500 (42)
200+ beds	1 (4)	20 (8)	1400 (8)
Ownership			
Profit	16 (64)	196 (79)	12,000 (67)
Nonprofit	8 (32)	50 (20)	4800 (27)
Government	1 (4)	2 (1)	1200 (7)
Certification			
Medicare and Medicaid	25 (100)	241 (97)	14,700 (82)
Affiliation			
Chain	9 (36)	103 (42)	10,800 (60)
Independent	16 (64)	145 (58)	7200 (40)

review according to the following criteria: whether an adverse warfarin-related event or a potential adverse warfarin-related event was present, the severity of the event, whether the event was preventable, and the effects of the event on the patient. This structured implicit review process has been used in prior studies of adverse drug events across a number of clinical settings including the nursing home.[6,7,9,10,12,15-17]

The severity of adverse warfarin-related events was classified according to modification of the criteria of Landefeld and colleagues,[18] as used by White and colleagues.[19] The severity of adverse warfarin-related events was categorized as minor, serious, life-threatening, or fatal. Minor events were those with no medical consequence (eg, bruising). Serious events were those that required specific treatment or a medical evaluation. Life-threatening events included the need for a surgical intervention to stop the bleeding, irreversible sequelae (eg, myocardial infarction or stroke), or any 2 of the following: transfusion of 3 or more units of blood, hypotension, critical anemia, or acute bleeding (<3 days). We also sought to identify all thromboembolic events associated with subtherapeutic INR values (INR < 2).

Adverse warfarin-related events and potential adverse warfarin-related events were considered to be preventable if they were judged to be due to an error and were preventable by any means available. "Preventability" was categorized as preventable, probably preventable, probably not preventable, or definitely not preventable; results were collapsed into the categories of preventable (preventable and probably preventable) and nonpreventable (probably not preventable and definitely not preventable) in the analysis.

The effects of adverse warfarin-related events on nursing home residents were categorized as up to 1 day of symptoms, more days of symptoms, nonpermanent disability, permanent disability, and death. The physician-reviewers categorized an event as causing permanent disability based on evidence that a warfarin-associated injury had caused physical disability or deficits in functioning.[20]

The stages of warfarin management during which an error leading to a preventable event occurred were ordering, dispensing, administration, and monitoring. If an error was deemed to have occurred, the physician reviewers further characterized the error type according to the following categories: wrong dose, wrong drug, missed dose, wrong frequency, extra dose, wrong resident, and known drug interaction. Monitoring stage errors included inadequate laboratory monitoring of warfarin therapy or a delayed response or failure to respond to laboratory evidence of an out-of-range INR value. For a single event, it was often possible to identify errors at more than 1 stage of warfarin therapeutic management or to identify more than 1 error within a single stage of management.

When the 2 physician-reviewers disagreed on the classification of an incident regarding the presence of an adverse warfarin-related event or a potential adverse warfarin-related event, its severity, or its preventability, they met and reached consensus; consensus was reached in all instances in which there was initial disagreement. We compared the initial assessments of the physician-reviewers and calculated interrater reliability using the kappa statistic, with kappa = 0.59 for judgments regarding the presence of an adverse warfarin-related event or a potential adverse warfarin-related event, 0.58 for preventability, and 0.67 for severity. A kappa score of 0.4 to 0.6 reflects "moderate agreement," 0.6 to 0.8 reflects "substantial agreement," and 0.8 to 1.0 is considered "almost perfect."[21]

Statistical Analysis

To determine crude rates of events, the numbers of adverse warfarin-related events and potential adverse warfarin-related events were divided by the total number of nursing home resident-months, which was estimated (with 95% confidence interval [CI])[22] by obtaining census data for all eligible residents on warfarin in the study nursing homes at monthly intervals throughout the course of the study; we accounted for absences from the nursing homes (eg, for hospitalization) and breaks in warfarin use.

We also assessed the time in specified INR ranges (<2, 2-3, >3-<4.5, ≥4.5) per nursing home resident-day on warfarin. INR values for each day were estimated using linear interpolation between values.[23] We excluded any periods from our analyses when a nursing home resident was not taking warfarin or not present in the nursing home (eg, during a hospital stay). We stopped interpolating INR values at the last INR before 1 of these excluded periods and did not restart interpolating until the first INR value following that period. Overall, only 2.8% of total time for all warfarin-treated nursing home residents was excluded from the analysis to determine time in specified INR ranges because of stops and starts of therapy or hospitalizations. Data were available to perform these calculations for 479 (97.8%) of the 490 nursing home residents who were included in the study.

RESULTS

Across the 25 study nursing homes, 490 nursing home residents who were receiving warfarin therapy (mean age, 82.3 ± 10.0 years) yielded 3822.9 resident-months of observation time; 70% were female and 90% were white. The most common indications for warfarin therapy included stroke prevention in atrial fibrillation (58%), treatment/prevention of deep venous thrombosis or pulmonary embolism (26%), and stroke prevention without atrial fibrillation (12%).

Rates of Adverse Warfarin-Related Events and Potential Adverse Warfarin-Related Events

The trained nurse abstractors identified 1501 possible warfarin-related incidents, of which 720 were judged to represent adverse warfarin-related events and 253 were deemed potential adverse warfarin-related events by the physician-reviewers. Of the 720 adverse warfarin-related events, 29%

(n = 207) were judged preventable. All potential adverse warfarin-related events were deemed preventable, by definition.

The overall rate of adverse warfarin-related events and potential adverse warfarin-related events combined (n = 973) was 25.5 per 100 resident-months on warfarin therapy (95% CI, 23.9-27.1 per 100 resident-months). The rate of adverse warfarin-related events (n = 720) was 18.8 per 100 resident-months on warfarin therapy (95% CI, 17.5-20.3 per 100 resident-months), with a rate of 5.4 preventable adverse warfarin-related events per 100 resident-months (95% CI, 4.7-6.2 per 100 resident-months). Potential adverse warfarin-related events occurred at a rate of 6.6 per 100 resident-months on warfarin (95% CI, 5.8-7.5 per 100 resident-months).

Serious, life-threatening, or fatal adverse warfarin-related events occurred at a rate of 2.5 per 100 resident-months on warfarin (95% CI, 2.0-3.0 per 100 resident-months). Preventable serious, life-threatening, or fatal events occurred at a rate of 1.4 per 100 resident-months (95% CI, 1.1-1.8). Of the 95 serious, life-threatening, or fatal adverse warfarin-related events, 57% (n = 54) were deemed preventable, compared with 24% (n = 153) of the 625 minor events (Table 2). Overall, more severe adverse warfarin-related events were significantly more likely to be considered preventable (relative risk = 2.3; 95% CI, 1.9-2.9).

Types and Effects of Adverse Warfarin-Related Events

Ecchymoses, gross hematuria, overt and occult gastrointestinal bleeding, epistaxis, and microhematuria were the most common types of bleeding events (Table 3). Most adverse warfarin-related events lasted more than 1 day (Table 4). Eight events resulted in permanent disability or death. Of 13 life-threatening or fatal events, 11 were considered preventable. Four preventable life-threatening or fatal events occurred in the setting of supertherapeutic INR levels: 2 gastrointestinal bleeds, 1 gluteal bleed, and 1 intracranial bleed. Two gastrointestinal bleeds that were deemed life threatening or fatal were associated with the use of concurrent warfarin, aspirin, and nonsteroidal anti-inflammatory drug therapy. Preventable life-threatening or fatal thromboembolic events included 5 events that occurred in the presence of subtherapeutic INR values, including stroke, systemic embolus, probable mechanical valve thrombosis, pulmonary embolism, and deep venous thrombosis.

Table 3 Types of Bleeding*

Type	No. (%)
Ecchymoses	461 (64)
Gross hematuria	72 (10)
Gastrointestinal (occult)	47 (7)
Epistaxis	44 (6)
Gastrointestinal (overt)	38 (5)
Microhematuria	23 (3)
Vaginal	13 (2)
Hemoptysis	12 (2)
Gingival	9 (1)
Subconjunctival	4 (1)
Ear	3 (<1)
Ocular	2 (<1)
Gluteal	1 (<1)
Intracranial	1 (<1)

*Adverse warfarin-related events could manifest as more than 1 type of bleeding.

Errors Associated with Preventable Adverse Warfarin-Related Events and Potential Adverse Warfarin-Related Events

Among the 207 preventable adverse warfarin-related events and the 253 potential adverse warfarin-related events, errors occurred most commonly at the prescribing (n = 321, 70%) and monitoring (n = 424, 92%) stages of warfarin management. Errors accounting for preventable events were rarely identified at the dispensing (n = 2) or administration (n = 2) stages. A total of 285 (62%) of the preventable events were associated with an error at both the prescribing and monitoring stages of warfarin management. Monitoring errors generally referred to inadequate laboratory monitoring of warfarin therapy or to a delayed response, or a failure to respond to laboratory results (ie, INR values). Among the prescribing errors, the most common were wrong dose (n = 259, 81%) and known drug interaction (n = 80, 25%).

Table 2 Severity and Effects of Adverse Warfarin-Related Events

	No. (%)	
	Total (n = 720)	Preventable (n = 207)
Category of severity		
Fatal	5 (1)	3 (1)
Life threatening	8 (1)	8 (4)
Serious	82 (11)	43 (21)
Minor	625 (87)	153 (74)

Table 4 Effects of Adverse Warfarin-Related Events

	No. (%)	
	Total (n = 720)	Preventable (n = 207)
≤1 d of symptoms	251 (35)	65 (31)
> 1 d of symptoms	460 (64)	135 (65)
Nonpermanent disability	1 (<1)	1 (<1)
Permanent disability and death	8 (1)	6 (3)

Time in Specified International Normalized Ratio Ranges

When all days on warfarin therapy summed across the entire study population were considered, the INR value was <2 in 36.5%, 2 to 3 in 49.6%, more than 3 to less than 4.5 in 11.9%, and 4.5 or more in 2.0%.

DISCUSSION

Residents of nursing homes who are receiving warfarin have adverse warfarin-related events at high rates (18.8 per 100 resident months); approximately 30% of these events may be preventable (ie, associated with an error in management). Of fatal, life-threatening, and serious events, 57% were considered preventable. Errors in warfarin prescribing and monitoring were responsible for nearly all of the preventable events. Consistent with previous studies, this study demonstrates that nursing home residents on warfarin are frequently maintained outside the optimal therapeutic range.

The system of medication management in the nursing home includes the nursing staff within the facility, and the physicians, laboratories, and pharmacy vendors external to the nursing home who interact to provide services to the residents. Although an adverse event in this setting may be directly linked to a "human error," the root cause may be defined as the defect in the system that permitted such an error to occur. In the case of warfarin management for nursing home residents, an important root cause is poor information flow. For example, a frequent occurrence in the care of nursing home residents is a telephone call from the nursing home to a covering physician about a resident with a urinary tract infection, without noting that the resident is taking warfarin.[24] The result may be an order for an antibiotic that interacts with warfarin, without adequate monitoring resulting in a supertherapeutic INR level and increased risk of bleeding.

Although our previous work suggested that there may be underuse of warfarin among apparently ideal candidates who are residents of long-term care facilities,[1] warfarin currently is commonly prescribed in the nursing home setting, with an estimated 200,000 nursing home residents nationwide receiving this therapy at any point in time.[6] Few would argue against the need for a more consistent approach to managing anticoagulant therapy in the nursing home setting. Although more widespread use of specialized clinics for anticoagulation therapy to provide coordinated care has been promoted to improve the effectiveness and safety of warfarin in elderly patients,[25] to date, the benefits of this approach relative to usual care have not been firmly established,[26] and specialized anticoagulation services are rarely used in the nursing home setting.[27]

Leading-edge, high technology-based strategies to alleviate problems in prescribing and monitoring warfarin are currently less amenable to incorporation into most nursing home settings.[28] The information technology infrastructure required to support computerized physician order entry with decision support is almost nonexistent in the majority of US nursing homes. Few long-term care facilities have implemented such systems owing to cost, complexity, and logistic challenges, as well as uncertainty about how effective the systems actually are for reducing drug-related injuries once implemented.

We believe that the findings of this study provide compelling evidence of serious safety concerns around the use of warfarin therapy in the nursing home setting. If our findings are generalized to residents on warfarin in all US nursing homes, there may be approximately 34,000 fatal, life-threatening, or serious adverse warfarin-related events per year, of which the majority may be preventable. Furthermore, "near misses" are common. Many residents of nursing homes on warfarin are subjected to a high risk of bleeding because of high INR levels that are associated with an error in warfarin management. Nursing home residents on warfarin also spend considerable amounts of time in the subtherapeutic range, potentially reducing the benefits of therapy.[29]

Management of warfarin therapy tends to be substantially better in the context of randomized clinical trials compared with usual care situations. For example, in SPORTIF V,[30] among patients assigned to receive warfarin, INR values were within the 2.0 to 3.0 range 68% of the time and less than 2.0 only 20% of the time. In our study, these percentages were 50% and 37%, respectively. It is important to emphasize that a number of the fatal and life-threatening events identified in this study were thromboembolic events occurring when the INR level was subtherapeutic. The risks versus the benefits of therapy must be carefully assessed in any patient initiated on warfarin therapy, particularly in the frail nursing home resident. When such therapy is deemed appropriate, all efforts must be made to provide the full benefits of therapy, while limiting the risks.

Our study has a number of limitations. Foremost among them was our reliance solely on information contained in nursing home records to assess the occurrence of warfarin-related incidents. In randomized controlled trials, comprehensive ascertainment and careful assessment of end points (ie, thromboembolic events and bleeds) are the priority; systematic approaches are used to enhance detection (eg, periodic administration of stroke-symptom questionnaires followed up by direct clinical assessment of the patient). Such approaches were obviously not possible in our study; in our study, we relied on information that could be ascertained solely through retrospective review of nursing home records. Our priority in this study was to assess the safety of warfarin therapy in the nursing home setting by describing how errors in warfarin management contribute to adverse events and "near misses." Our study was not designed to assess the effectiveness of warfarin therapy for the prevention of thromboembolic events.

Intensified educational efforts concerning the safe use of warfarin in the nursing home setting are essential. Even if it is not possible to implement systems-level changes using specialized anticoagulation services or computerized physi-

cian order entry with clinical decision support, efforts to improve the effectiveness of communication between nursing staff and physicians around the use of warfarin therapy should be implemented. Physicians spend little time in the nursing home setting, and therapeutic decision making commonly occurs over the telephone during brief conversations between doctor and nurse. Protocols must be developed and tested to provide accurate information to the prescriber concerning prior INR levels, warfarin dosing information, and interacting medications. If successful, such an approach may serve as a model for improving the safety of other medication categories associated with high rates of preventable adverse drug events and serve to further protect the vulnerable nursing home resident who is at special risk for medication-related problems.

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