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Nonadherence with INR Monitoring and Anticoagulant Complications ☆,☆☆

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ABSTRACT

Introduction: This study tests the hypothesis that nonadherence with INR monitoring is associated with an increased risk for warfarin-related bleeding and thrombosis and describes patient characteristics associated with INR monitoring nonadherence.
Materials and Methods: This was a retrospective, longitudinal, matched cohort study wherein patients were categorized into adherent and nonadherent cohorts; adherent patients were matched 2:1 to nonadherent patients. The primary study endpoint was the first occurrence of bleeding or thromboembolism. Multivariate logistic regression modeling identified patient characteristics associated with INR monitoring adherence or nonadherence.
Results: A total of 4995 and 2544 patients contributed 10729 and 5385 patient-years of warfarin therapy in the adherent and nonadherent groups, respectively. The rate of thromboembolic events during follow up was higher in the nonadherent group than in the adherent group (0.95% vs. 0.62% per patient-year, respectively; $p = 0.019$) and nonadherence to INR monitoring was associated with a moderately higher risk of thromboembolism (adjusted Hazard Ratio = 1.51; 95% confidence interval = 1.04 – 2.20). The difference in bleeding between the two groups was not statistically significant.
Conclusions: Repeatedly missing INR tests is an easily identified clinical parameter that is associated with moderately increased risk for thromboembolism in patients taking chronic warfarin therapy. Clinicians should carefully consider the underlying thromboembolic risk and extent of nonadherence when weighing the benefits of continued warfarin therapy for a given patient.

Introduction

Warfarin is an effective anticoagulant for the prevention and treatment of thrombosis. The international normalized ratio (INR) is used to monitor the anticoagulant effect of warfarin [1]. However, the INR response to warfarin can fluctuate either as a result of interactions with a large number of other drugs, food, herbal agents, or for no apparent reason. In addition warfarin is a narrow therapeutic index drug because of the small difference between beneficial and toxic effects that frequently causes medication-related injury [1,2]. Regular INR monitoring allows warfarin dose adjustments if the monitored INR value is outside the therapeutic range [1].

Adherence describes the extent to which patient's behavior conforms to the requirements of prescribed treatment [3]. Adherence with warfarin therapy requires commitment and cooperation from patients and their caregivers to ensure that the medication is taken correctly and the INR is monitored as instructed by the anticoagulation provider [4]. Nonadherence with various aspects of warfarin therapy, including INR monitoring, are common [5,6].

Available studies evaluating 'warfarin adherence' have focused almost exclusively on pill-taking behavior and not on adherence with INR monitoring. This is important because most anticoagulation providers routinely record the number of times a patient had to be reminded to

Abbreviations: CDS, Chronic Disease Score; CI, Confidence interval; CPAS, Clinical Pharmacy Anticoagulation Service; DVT, Deep vein thrombosis; HR, Hazard ratio; ICD-9, International Classification of Diseases, 9th revision; INR, International Normalized Ratio; KFHP, Kaiser Foundation Health Plan; KPCO, Kaiser Permanente Colorado; LMWH, Low-molecular-weight heparin; PE, Pulmonary embolism; TTR, Time in therapeutic INR range.

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return for INR monitoring. In contrast, common measures of pill-taking behavior such as pill counts, pharmacy dispensing records, self-report surveys, drug assays, biologic markers, and physician reports used in research are not routinely used and have been shown to be largely inaccurate to inform 'real-world' clinical decision making [5,7,8].

While it seems intuitive that habitual nonadherence with INR monitoring would lead to dire clinical consequences, no formal study has definitively associated this behavior with increased risk for bleeding or thrombosis. Additionally, while several small studies have examined patient characteristics associated with warfarin pill-taking nonadherence [4,6–9], similar studies evaluating factors that might predict nonadherence with INR monitoring are not available. The purposes of this study were to assess if nonadherence with INR monitoring is actually associated with an increased risk for bleeding or thromboembolic adverse events, and to describe patient characteristics associated with INR monitoring nonadherence.

Methods

Study Design, Setting, and Patient Population

We conducted a retrospective, matched cohort study at Kaiser Permanente Colorado (KPCO), an integrated health care delivery system that provides services to more than 500,000 members. Anticoagulation services at KPCO are provided by a centralized Clinical Pharmacy Anticoagulation Service (CPAS) [10]. When patients miss INR appointments, they are contacted by the CPAS staff via phone or letter and reminded to return for testing. Approximately 7 days usually elapse between missed INR appointments and reminder contacts. We used KPCO's integrated, electronic medical, pharmacy, and laboratory records system along with the CPAS database (Dawn AC; 4S Systems Ltd, Cumbria, UK) to identify patients, treatments, and outcomes for this study. Approval to conduct this study was obtained from the KPCO Institutional Review Board with waiver of informed consent.

Patients receiving chronic anticoagulation therapy with warfarin between January 2006 and December 2007 for any indication other than venous thromboembolism prevention following orthopedic surgery were eligible for study inclusion. Inclusion criteria required at least 180 consecutive days of Kaiser Foundation Health Plan membership and initiation of warfarin therapy at least 28 days prior to study inclusion and patients could not become pregnant or have blood for INR testing drawn at their residence by mobile phlebotomists at any time during the study period.

Group Assignment and Matching Criterion

For each INR in Dawn AC, the number of times (from zero up to five) patients were reminded to return to the laboratory for missed INR appointments is recorded (hereafter referred to as 'missed INR tests'). We used this information to categorize patients as nonadherent or adherent. Patients who missed two or more INR tests in a row at least once during the study period comprised the nonadherent group. Patients in the nonadherent group could have multiple episodes of nonadherence, however; the first occurrence of nonadherence meeting this definition during the study period was designated as the nonadherent index date. The adherent group was comprised of patients who never missed two INR tests in a row during the study period. Adherent group patients could miss one INR test multiple times during the study period. To ensure that contemporary anticoagulation management practices were applied to both groups, the index date month was used to match nonadherent patients to two adherent patients. No other matching criteria were used to allow a thorough exploration of patient characteristics potentially associated with INR monitoring nonadherence.

Follow-up and Study Endpoints

After group assignment, patients were followed until December 2009 or the occurrence of either the primary study endpoint or plan disenrollment. The primary study endpoint was the first occurrence of a warfarin therapy-related complication; defined as the occurrence of bleeding resulting in hospitalization or emergency department visit regardless of severity or an objectively verified thromboembolic complication.

Bleeding and thromboembolic events were identified through queries of electronic claims and referral records using predefined ICD-9 codes (see Appendix A) and verified through medical record review using a standardized abstraction form. As deep vein thrombosis (DVT) is often managed without hospitalization using low-molecular-weight heparin (LMWH) [11], computerized LMWH dispensing information and medical record review were used to identify and confirm recurrent DVT episodes treated outside of the hospital. Relationship to warfarin therapy for all identified complications was confirmed by two reviewers using the Naranjo scale [12]. Disagreement between reviewers was resolved by a third reviewer.

Secondary study endpoints were: percentage of follow-up INRs below, within, and above the patient-specific therapeutic range, interval between successive follow-up INRs (in days) and the percentage of these intervals exceeding 8 weeks, count of missed INRs during follow-up, and the number of follow-up INRs ≥ 5.0. Additional information including primary indication for anticoagulation, age, sex, targeted INR range, length of warfarin therapy as of index date, and the percent of households with at least some college education and median household income in the patient's residence block based on data from the 2008 US census was collected for each patient. The count of inpatient hospitalizations and comorbid diagnosis history during the 180 days prior to index date was also collected. Comorbid diagnoses included: hypertension, diabetes mellitus, stroke or transient ischemic attack, heart failure, active malignancy (excluding squamous and basal cell carcinoma), thrombophilia, renal dysfunction, hepatic dysfunction, and prior bleeding (specifically–intracranial hemorrhage, gastrointestinal bleeding or epistaxis). A measure of chronic illness burden, the Chronic Disease Score (CDS), was calculated for all patients using information from pharmacy purchases in the six months prior to the index date [13,14].

Data Analysis

Patient characteristics were reported as median and interquartile range for continuous variables and proportions for categorical variables. Differences between nonadherent and adherent group categorical variables were assessed using the McNemar's test and continuous variables were compared using the paired samples t-test or Wilcoxon rank sum test (depending on the distribution of the data).

Kaplan-Meier curves were constructed to estimate the survival functions for bleeding and thromboembolic complications between the groups. Cox proportional hazards modeling was used to estimate hazard ratios and their 95% confidence intervals for bleeding and thromboembolic outcomes while accounting for the possibility of unequal follow-up between the groups. Patients were censored at primary study endpoint, termination of plan membership, or December 31, 2009, whichever came first. A unique 'match' identification number was assigned to each matched set of patients and entered into the model as a cluster variable to account for the correlations within the matched sets and provide unbiased standard error estimates. Models were adjusted for intra-correlations of matched patients and index date and the potential confounding effects of age, sex, chronic disease score, target INR, indication for warfarin use, number of days since warfarin initiation, and prior diagnoses of hypertension, diabetes mellitus, epistaxis, gastrointestinal bleeding, and cancer.