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Risk factors for nonadherence to warfarin: results from the IN-RANGE study,^{†,‡}

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SUMMARY

Background—Warfarin is widely used to prevent stroke and venous thromboembolism despite its narrow therapeutic window. Warfarin nonadherence is a substantial problem, but risk factors have not been well elucidated.

Methods—A prospective cohort study of adults initiating warfarin at two anticoagulation clinics (University and VA-affiliated) was performed to determine factors affecting nonadherence to warfarin. Nonadherence, defined by failure to record a correct pill bottle opening each day, was measured daily *via* electronic medication event monitoring systems (MEMS) caps. A multivariable explanatory model using logistic regression for longitudinal data was used to identify risk factors for nonadherence.

Results—One hundred eleven subjects were followed for a median of 137 days. Warfarin nonadherence was common (4787 of 22425 or 21% of patient-days observed). Factors independently associated with higher odds of nonadherence included education beyond high school (odds ratio (OR) 1.8 (95%CI 1.2–2.7)), lower Short Form (SF)-36 mental component score (OR 1.4 (1.1–1.6) for each 10 point decrease); and impaired cognition (≤ 19 points) on the

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Cognitive Capacity Screening Examination (CCSE) (OR 2.9 (1.7–4.8)). Compared to currently employed subjects, unemployed (OR 0.6 (0.3–1.2)) and retired (OR 0.5 (0.3–0.8)) subjects had somewhat improved adherence; disabled subjects over age 55 had worse adherence (OR 1.8 (1.1–3.1)) than younger disabled subjects (OR 0.8 (0.4–1.5)).

Conclusions—Poor adherence to warfarin is common and risk factors are related to education level, employment status, mental health functioning, and cognitive impairment. Within the carefully controlled anticoagulation clinic setting, such patient-specific factors may be the basis of future interventions to improve nonadherence.

Keywords

medication adherence; MEMS; warfarin; anticoagulation

INTRODUCTION

Warfarin is one of the most prescribed medications in the United States and serves as the gold standard therapy to prevent both stroke and venous thromboembolism. ¹ In patients with atrial fibrillation, treatment with warfarin results in a two-thirds reduction in the risk of stroke. ² Warfarin's true efficacy might be even higher as 8–40% of the international normalized ratio (INR) values in primary stroke prevention trials, and up to one-half of INR recordings in ambulatory care outside of research trials, are out of range. ³

Poor adherence is a major contributor to poor anticoagulation control. ⁴ Skipped doses lead to sub-therapeutic anticoagulation periods and a greater risk of stroke or recurrent thromboembolism. Missed doses can also mislead providers into prescribing higher dosages of warfarin that might result in subsequent periods of over-anticoagulation, during which time patients are at increased risk for major hemorrhagic events. ⁵ Extra doses increase the risk of over anticoagulation, which is the major risk factor for bleeding complications.

Prior investigations in warfarin management have focused mainly on a number of clinical factors (e.g., acute illness, drug interactions, dietary changes) ^{6–8} or genetic factors ⁹ that are difficult to anticipate or modify. In contrast, daily adherence to warfarin is both a persistent and potentially modifiable contributor to INR instability and warfarin efficacy. ^{4,10} A number of identifiable psychosocial factors (e.g., depressive symptoms, cognitive functioning, and health related quality of life) ^{11–13} have been associated with medication nonadherence among the medically ill in other disease settings and may serve as a basis to intervene upon subjects more prone to nonadherence.

Research into medication adherence behavior has been limited by difficulties in correctly classifying the outcome as physicians often misidentify patient adherence patterns, whereas patients frequently overstate their medication adherence. ^{14,15} As a result of the dearth of prospective studies measuring daily adherence to warfarin with objective means, relatively little is known about risk factors for poor adherence with daily warfarin use. We therefore sought to determine the demographic, clinical, psychosocial, health utilization, and pill-taking practices related to warfarin nonadherence as measured by prospectively gathered electronic pill cap data, a method considered the most objective measurement of medication adherence. ¹⁶ A better understanding of patient-level and health utilization factors may aid in the developing and targeting of interventions to high risk patients to reduce complications and cardiovascular morbidity due to suboptimal therapy.

METHODS

Design and study population

The Program for the Reduction In Medication Errors (PRIME) component of the INR Adherence and Genetics (IN-RANGE) study was designed as a prospective cohort study enrolling and following patients from April 2002 until April 2006 at two specialized anticoagulation clinics: the Hospital of the University of Pennsylvania (HUP) in Philadelphia and the Philadelphia Veterans Affairs Medical Center (PVAMC). The study population consisted of patients 21 years and older who were recruited for enrollment within 2 months of their initiation of anticoagulation therapy with a target INR of 2.0–3.0. The institutional review boards at the participating hospitals approved the study and all of the participants provided informed written consent to participate.

Data collection

Trained research personnel used standardized questionnaires to obtain baseline information on patient demographic and clinical factors at time of entry into the study, including age, gender, race, education level, employment status, marital status, indication for warfarin, exposure to warfarin prior to the current indication, medical co-morbidities, smoking status, daily alcohol consumption, and all medications taken in the week prior to study entry. Subjects completed additional items derived from the Medical Expenditure Panel Survey to assess their utilization of and access to health care in the prior 12 months with regard to the number of visits to primary care or other physicians, emergency room visits, hospital admissions, and self-reported difficulty in receiving health care or transportation to clinic.¹⁷ At regular follow-up visits, subjects completed standardized questionnaires to determine their method of obtaining warfarin (pharmacy vs. mail order), whether they started or stopped interacting medications, changed the timing of warfarin dosing, performed pill-splitting, used a reminder system, required the assistance of another person to assist with pill-taking, used a pillbox for medications, changed their dietary habits, or experienced a change in their general health status.

We obtained information on psychosocial factors at baseline that were hypothesized *a priori* to be associated with poor adherence through standardized, self-administered questionnaires completed at study entry. The psychosocial factors included measures of quality of life (Short Form (SF)-36 standard version),¹⁸ cognitive dysfunction (Cognitive Capacity Screening Examination (CCSE)),¹⁹ and depressive symptoms (Center for Epidemiologic Studies Depression Scale (CESD)).²⁰ Each of these psychosocial measures has well-established reliability and validity and assesses domains commonly associated with nonadherence to medication among chronic medical patients.

Outcome

The primary outcome for all analyses consisted of participants' warfarin adherence measured daily during the course of the study through the use of electronic medication event monitoring systems (MEMS caps, AARDEX, Zug, Switzerland), a device that captures electronically the date and time of every opening of the medication container. Each day monitored was judged to be either adherent or nonadherent. An adherent day was counted if there was exactly one electronic pill cap opening during a given 24-hour period. Nonadherent days were defined by either failure to actuate a MEMS cap during a 24-hour period or doing so more than once (as warfarin was never prescribed more frequently than once daily). Nonadherent days were also counted when a MEMS cap opening occurred on a day in which the patient was instructed to 'hold' a dose for high INR (and thus should not have opened the bottle at all). Because both skipped doses and extra doses may result in INR instability and undesirable outcomes, and because we found in our prior work that extra

doses are rare compared to skipped doses (accounting for approximately one-seventh of the incorrect doses in that study),⁴ these two types of nonadherent events were not evaluated separately.

Participants who used the pill bottles for daily warfarin administration had the MEMS caps fitted directly onto their pill bottle. Participants who used 7-day pillbox reminder to administer their medications were provided with an empty bottle with a MEMS cap attached and instructed to open and close the MEMS cap bottle each time they took their warfarin from the pillbox reminder.

Statistical analysis

Warfarin nonadherence was the dependent variable in all analyses. We selected patient-days on warfarin as the unit of analysis to maximize statistical power to detect risk factors related to daily use. We performed bivariable and multivariable marginal logistic regressions for longitudinal data using generalized estimating equations with an independence working correlation matrix, as implemented in SAS GENMOD (SAS Institute, Cary, NC, V 9.1, 2006). The working correlation matrix was dictated by the cautions outlined by Pepe and Anderson for longitudinal models with time-varying factors.²¹ The model accounted for the lack of independence of adherence estimates due to repeated measurements within subjects and for the varying contributions of follow-up time per participant.

To develop the statistical model, we initially checked all potential explanatory factors for correlation and for missing levels. In doing so we grouped insurance status into three categories: Veterans Administration, private plus Medicare, and Medicaid or none using the *a priori* assumptions that those eligible for VA coverage differed from all others and that patients relying on Medicaid or self-insuring were poor or otherwise not eligible for other insurance plans. Study site as a variable could not be included in the analysis because the VA as a treatment site was collinear with the VA as an insurer. Therefore, site effects could not be examined separately from insurance status. In addition, because employment status and age were found to be highly collinear, these variables were combined. As income level was missing too often for analysis, we did not consider this factor.

Our starting model included all of the candidate factors that remained after resolving problems of sparse data and collinearity. From this baseline, fully loaded model, we dropped any factors with a *p* value greater than 0.20.²² We then checked for confounding by examining whether there were any changes in the odds ratio (OR) of the remaining factors of approximately 10% or greater after each variable was dropped. Once the final model was in place, we performed a bootstrap analysis of these remaining risk factors to obtain more robust estimates of their confidence intervals.

RESULTS

Information on candidate factors was collected prospectively on 136 subjects who agreed to electronic pill cap monitoring and psychosocial evaluation. A total of 111 of the 136 subjects with complete psychosocial questionnaire data were included in the study (see Figure 1). The study cohort had a mean age of 55 years and consisted of 65% men and 55% African Americans (see Table 1). Sixty-five percent of subjects were recruited from the University-affiliated anticoagulation clinic and the remaining one-third from the VA-affiliated clinic site. Atrial fibrillation and venous thromboembolism were the predominant indications for warfarin therapy. A comparison of the 111 participating study subjects who completed the study protocol with the 148 subjects in the parent IN-RANGE study who either declined using MEMS cap or had an incomplete psychosocial evaluation

demonstrated no significant differences in baseline demographic factors including age, race, education level, or employment status.

The 111 study subjects were followed while undergoing chronic anticoagulation for a median of 137 days (interquartile range 77–273 days). Warfarin nonadherence occurred in 4787 of 22 425 (21%) of patient-days observed. For subjects with at least 50 or more adherence days observed, the fraction of nonadherent days ranged from 0.9 to 79% of total days observed, with an inter-quartile range of 7–34% of days nonadherent. The twenty-five subjects who enrolled in the study but could not be included in the risk factor analysis due to incomplete psychosocial data had a slightly higher rate of warfarin nonadherence which was not statistically significant (26 vs. 21% of patient-days observed, $p = 0.25$). Table 2 presents the bivariable results for the risk factors in the final model and Table 3 displays the multivariable results for those factors which are significantly related to nonadherence to warfarin. In multivariable analysis, we found an increased OR for nonadherence among those with education level beyond high school and those currently employed (compared to those unemployed and retired).

Of the psychosocial factors examined, lower levels of mental health functioning (mental component score of the SF-36) and poor cognitive functioning (CCSE score of 19 points or less) were associated with worse adherence. Measures of physical functioning (physical component SF-36), self-assessed overall general health, sleep quality (Pittsburgh Sleep Quality Index (PSQI)) and depression (CESD) scale, were not associated with adherence in multivariable analyses (data not shown).

Use of the MEMS cap as a diary of daily warfarin usage, which usually occurred in the setting of use of a pillbox to organize all of the subject's medications, accounted for 69% of patient-days observed in the study and was associated with an increased odds of nonadherence. None of the health utilization factors, reported use of other medications, or other pill-taking practices demonstrated a significant association with warfarin nonadherence in multivariable analysis.

Amount of time on warfarin, modeled variously as a linear, linear plus quadratic, and cubic linear functions, had no substantial effect on the results and therefore was not included in the analysis. Lastly, we tested and found unimportant two *a priori* interactions: education level/clinic site as well as cognitive function/use of MEMS caps as a diary. Neither modified the effect of the risk factors for nonadherence. Sample size limitations precluded an expansive exploration of other potential interactions.

DISCUSSION

In our prospective cohort of patients undergoing warfarin therapy, higher education level, current employment, and lower scores on mental health and cognitive functioning were associated with poor adherence to warfarin therapy.

The association between active employment and poor adherence to warfarin is consistent with the finding of Palareti *et al.* who reported active employment as risk factors for INR instability.⁸ Moreover, a link between poor adherence and active employment has also been noted in other disease settings.²³ Although the underlying relationship is not certain, active employment might reflect numerous competing interests which take precedence over consistent pill-taking. The finding of decreased adherence among those with higher educational attainment is consistent with a previous case-control study of dropouts from warfarin clinic.²⁴ Poor adherence by more educated subjects might relate to more independent decision making or, as has been suggested in other settings, to decreased trust in physicians relative to less educated subjects.²⁵

Among the psychosocial variables studied, low cognitive functioning and lower mental health functioning stood out as risk factors for poor adherence to warfarin. Cognitive scores were not associated with warfarin adherence in a prior study that used patient self-report as a means to measure adherence,²⁶ but poor cognition has been related to nonadherence to other medications in elderly patient populations.²⁷ Lower self-assessed mental health status (as scored on the SF-36) has also been associated with worse self-reported adherence in other areas.²⁸ We found no association between adherence to warfarin and depressive symptom scores, in contrast to selected reports in settings such as anti-hypertensive medication use.¹²

Nearly all of the health care access, utilization, and pill-taking practice variables in our study failed to demonstrate close associations with warfarin adherence. However, these factors varied little among our patients, in part because specialized anticoagulation clinics limit this variability in practice. Thus, we cannot exclude these as important factors outside of specialized clinics or in other settings.

The strengths of our investigation are the prospective design; comprehensive examination of demographic, clinical, psychosocial, health utilization, and pill-taking practice variables; and precision of assessment of the outcome of adherence by use of MEMS cap data. Limitations include, first, the large number of variables analyzed, which could have led to false positive findings. However, all variables included were hypothesized *a priori* to be associated with adherence. Second, we may not have detected factors with relatively small effects on adherence. Third, there may be selection bias in terms of the subjects willing to agree to psychosocial evaluation and MEMS cap monitoring, although there were no significant differences in baseline demographic factors compared to those who declined MEMS cap monitoring.

A fourth limitation involved use of MEMS caps to measure adherence. This method raised design challenges as many patients used MEMS caps as a diary while they employed a pillbox reminder system to organize all of their medications. The higher odds of nonadherence associated with this practice may be explained by study subjects' forgetting to activate the MEMS cap after taking their medications directly from their pillbox. Another possibility is that patients who need pillbox reminders have worse overall adherence. Regardless, we accounted for this practice by adjusting for use of MEMS cap as a diary in our multivariable model. We had insufficient sample size to limit the analysis to only visits where MEMS caps were used directly on pill bottles. However, our prior study demonstrated that nonadherence to warfarin was closely linked to out of range INR values both in those who used the MEMS cap as a diary and those who accessed their warfarin directly from the MEMS cap container.⁴

Lastly, although derived from subjects recruited from two different centers, our study findings may not generalize to warfarin management outside of specialized anticoagulation clinics.

In summary, poor adherence to warfarin appears most strongly associated with patient-level factors related to time, memory, and mental health functioning. Within the carefully controlled anticoagulation clinic setting, health utilization variables, and pill-taking practices were not associated with adherence but there was limited variability of these factors in our cohort. These results suggest that in the anticoagulation clinic setting, interventions to improve adherence should focus on memory prompts and evaluation of patient priorities rather than system-level variables.

KEY POINTS

- Warfarin is one of the most prescribed medications in the United States and serves as the gold standard therapy to prevent both stroke and venous thromboembolism
- Poor adherence is a major contributor to poor anticoagulation control. However, relatively little is known about risk factors for poor adherence with daily warfarin use
- In our prospective cohort study of 111 adults monitored *via* electronic MEMS caps, over 20% of doses were taken incorrectly
- Factors independently associated with nonadherence included education beyond high school, current employment, lower mental health functioning, and poor cognition. Other pill-taking practices and indices of health care access and utilization were not closely associated with poor adherence to warfarin
- Within the carefully controlled anticoagulation clinic setting, these patient-specific factors may be the basis of future interventions to improve nonadherence

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Figure 1.
Participant enrollment and protocol completion

Table 1Demographics of patient population ($n = 111$)

Baseline characteristics	Value
Age in years—mean (range)	55 (23–83)
Gender—male—number (%)	72 (65)
African American Race—number (%) [*]	61 (55)
Education level—greater than high school—number (%)	69 (62)
Employment/age—number (%)	
Employed	36 (32)
Unemployed	14 (13)
Retired	33 (30)
Disabled, less than 55 years	18 (16)
Disabled, 55 years or greater	10 (9)
Marital status—number (%)	
Married	42 (38)
Separated/divorced	29 (26)
Widowed	9 (8)
Never married	30 (27)
Insurance status—number (%)	
Any VA	40 (36)
Private/medicare	61 (55)
Medicaid/none	10 (9)
Indication—number (%)	
Atrial fibrillation	44 (40)
DVT/PE	46 (41)
Dilated cardiomyopathy/LV thrombus	6 (5)
Stroke/TIA	3 (3)
Other	12 (11)
University hospital site—number (%)	72 (65)
History—number (%)	
Prior warfarin use	29 (26)
Cardiac—arrhythmia, heart failure, ischemia, other	62 (56)
Hypertension	52 (47)
Diabetes mellitus	37 (33)
Prior stroke/TIA	15 (14)
Primary physician visit in past year—number (%)	94 (85)
Number of other MDs seen in past year—median (range)	2 (0–6)
Number of medications taken at baseline—median (range)	5 (0–20)
Patient uses a self-reminder system—percentage of days observed [†]	78
Another person reminds patient—percentage of days observed [†]	26
Uses MEMS cap as diary—percentage of days observed [†]	69

VA, Veterans Affairs; DVT, deep venous thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack; LV, left ventricle; MEMS, medication event monitor system.

* Race was self-reported.

[†] Time-varying factors: measured repeatedly at follow-up visits.

Table 2

Bivariable analysis of warfarin nonadherence—results for 111 patients*

Variable	OR (95%CI)
Gender—male (vs. female)	0.7 (0.4–1.2)
African American Race (vs. other)	1.2 (0.7–1.9)
Education—greater than high school	1.1 (0.7–1.8)
Employment/age (vs. employed)	—
Unemployed	0.8 (0.3–1.9)
Retired	0.5 (0.3–1.0)
Disabled, less than 55 years	0.9 (0.4–2.0)
Disabled, 55 years or greater	1.2 (0.6–2.4)
History of prior warfarin use (vs. none)	1.3 (0.8–2.0)
History of diabetes mellitus	1.0 (0.6–1.7)
History of hypertension	0.6 (0.4–1.0)
Smoking status (vs. current smoker)	—
Never smoked	0.7 (0.3–1.3)
Past smoker	0.5 (0.3–1.0)
No. of other MDs seen/12 months (1+ vs. 0)	0.8 (0.4–1.6)
No. of hospitalizations/12 months (≥ 2 vs. < 2)	1.1 (0.7–1.8)
Another person reminds patient (vs. none)	1.2 (0.7–2.1)
Cognitive dysfunction (CCSE score 19 or less)	1.5 (0.8–2.8)
SF-36 MCS (per 10 point decrease) [†]	1.4 (1.1–1.6)
General health (vs. very good/excellent)	—
Fair/poor	1.5 (0.9–2.4)
Good	1.3 (0.9–2.0)
Use of MEMS cap as a diary [†]	1.6 (1.0–2.4)

MEMS, medication event monitor system; CCSE, Cognitive Capacity Screening Examination; SF-36 MCS, Short Form-36 mental component score.

* OR, Odds ratio for nonadherence to warfarin on a daily basis, accounting for repeated measures. Bivariable results presented are for factors remaining in the final model (after dropping time-varying and baseline factors with $p > 0.20$).

[†] Factor significant in bivariable analysis.

Table 3

Multivariable analysis of warfarin nonadherence— results for 111 patients*

Variable	Multivariable odds ratio (95%CI) [†]
Education—greater than high school	1.8 (1.2–2.7)
Employment/Age (vs. employed) [‡]	—
Unemployed	0.6 (0.3–1.2)
Retired	0.5 (0.3–0.8)
Disabled less than 55 years	0.8 (0.4–1.5)
Disabled 55 years or greater	1.8 (1.1–3.1)
Cognitive dysfunction (CCSE score 19 or less)	2.9 (1.7–4.8)
SF-36 MCS (per 10 point decrease)	1.4 (1.1–1.6)
Use of MEMS cap as a Diary	1.5 (1.1–2.1)

CCSE, Cognitive Capacity Screening Examination; SF-36 MCS, Short Form-36 mental component score; MEMS, medication event monitor system.

* Multivariable Odds Ratio (OR) is the OR for nonadherence to warfarin on a daily basis, accounting for repeated measures. Multivariable results reflect adjustment for the variables in Table 3 (education, employment, cognitive dysfunction, SF-36 mental component score, use of MEMS caps as a diary) as well as the remaining factors in Table 2 (gender, race, history of prior warfarin use, history of diabetes, history of hypertension, smoking status, number of doctors and hospitalizations in the last 12 months, having another person remind the subject about daily warfarin use, and self-assessed general health status).

[†] All the factors in Table 3 remain statistically significant after bootstrap re-sampling.

[‡] Employment/age category overall $\chi^2 = 27.2$, $p < 0.0001$.