Can We Predict Daily Adherence to Warfarin?

Results From the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study

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Background: Warfarin is the primary therapy to prevent stroke and venous thromboembolism. Significant periods of nonadherence frequently go unreported by patients and undetected by providers. Currently, no comprehensive screening tool exists to help providers assess the risk of nonadherence at the time of initiation of warfarin therapy.

Methods: This article reports on a prospective cohort study of adults initiating warfarin therapy at two anticoagulation clinics (university- and Veterans Affairs-affiliated). Nonadherence, defined by failure to record a correct daily pill bottle opening, was measured daily by electronic pill cap monitoring. A multivariable logistic regression model was used to develop a point system to predict daily nonadherence to warfarin.

Results: We followed 114 subjects for a median of 141 days. Median nonadherence of the participants was 14.4% (interquartile range [IQR], 5.8-33.8). A point system, based on nine demographic, clinical, and psychosocial factors, distinguished those demonstrating low vs high levels of nonadherence: four points or fewer, median nonadherence 5.8% (IQR, 2.3-14.1); five points, 9.1% (IQR, 5.9-28.6); six points, 14.5% (IQR, 7.1-24.1); seven points, 14.7% (IQR, 7.0-34.7); and eight points or more, 29.3% (IQR, 15.5-41.9). The model produces a c-statistic of 0.66 (95% CI, 0.61-0.71), suggesting modest discriminating ability to predict day-level warfarin nonadherence.

Conclusions: Poor adherence to warfarin is common. A screening tool based on nine demographic, clinical, and psychosocial factors, if further validated in other patient populations, may help to identify groups of patients at lower risk for nonadherence so that intensified efforts at increased monitoring and intervention can be focused on higher-risk patients. *CHEST* 2010; 137(4):883-889

Abbreviations: INR = international normalized ratio; IN-RANGE study = International Normalized Ratio Adherence and Genetics study; IQR = interquartile range; MEMS = medication event monitoring system; PRIME = Program for the Reduction in Medical Errors; SF-36 = Short Form-36

Warfarin serves as the primary therapy to prevent stroke and venous thromboembolism, but adherence to this therapy is poor.^{1,2} Because of the narrow therapeutic range of warfarin, even short periods of subtherapeutic or supratherapeutic anticoagulation may expose patients to recurrent thrombosis or dangerous side effects such as intracranial hemorrhage.³⁻⁵

Periodic monitoring of patients' international normalized ratio (INR) level is a cornerstone of anti-

coagulation therapy.⁶⁻⁸ However, close monitoring, even by specialized anticoagulation clinics, may fail to identify periods of nonadherence until after a thrombotic or hemorrhagic event has occurred.^{9,10} Ideally, provider assessment and patient self-reporting of nonadherence would suffice to supplement INR monitoring, but both have recently been shown to be unreliable.¹¹ Therefore, our objective was to develop a novel clinical prediction rule,^{12,13} based on demographic, clinical, and psychosocial factors, that would

identify at the outset of therapy those subjects at high and low risk for nonadherence to warfarin.

Clinical prediction rules have been developed in other areas of medicine^{14,15} to assist in medical decision making. However, we are not aware of previous efforts to develop a clinical prediction rule in the area of warfarin nonadherence or other high-risk areas of medication nonadherence where even short periods of nonadherence may have important clinical consequences. Such a screening tool for warfarin, if properly validated in other patient populations and settings, could help direct programs of intensified counseling and monitoring for high-risk patients.

MATERIALS AND METHODS

Design and Study Population

Details of the study have been previously reported.¹⁶ Briefly, the INR Adherence and Genetics (IN-RANGE) study, and its component study, Program for the Reduction in Medical Errors (PRIME), was designed as a prospective cohort study in which patients aged 21 years and older with a target INR of 2.0 to 3.0 were recruited within 2 months of initiating anticoagulation therapy. From April 2002 until April 2006, participants were enrolled and followed at two specialized anticoagulation clinics: the Hospital of the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center, both in Philadelphia, Pennsylvania. The institutional review boards of the participating hospitals approved the study, and all participants provided informed, written consent.

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Data Collection

Data on patient demographic and clinical factors at the time of study entry were obtained by trained research personnel through the use of standardized questionnaires. Baseline demographic and clinical factors were collected and consisted of age, gender, race, education level, employment status, marital status, indication for therapy, warfarin use prior to the current indication, medical comorbidities, tobacco smoking status, alcohol consumption, a listing of all medications taken in the week before study enrollment, and participants' health-care utilization and access to health care¹⁷ in the preceding 12 months. At baseline, participants also completed standardized questionnaires on psychosocial factors hypothesized to predict poor adherence: the Short Form-36 (SF-36) mental component subscale, standard version,¹⁸ to rate their quality of life and the Cognitive Capacity Screening Examination to test for the presence of cognitive dysfunction.¹⁹ We included in the model only factors that would be available to the clinician at the time of the initial evaluation.

Outcome

Our primary outcome, warfarin nonadherence, was measured daily using an electronic medication event monitoring system (MEMS) (MEMS caps; AARDEX; Zug, Switzerland). The MEMS cap records the time and date when a participant opens the medication container. Each patient-day observed on warfarin therapy was judged either "adherent" or "nonadherent": an adherent day occurred if exactly one electronic pill cap opening was recorded during a given 24-h period; a nonadherent day occurred if a participant either failed to actuate the MEMS cap container during a 24-h period or did so twice or more (as warfarin was prescribed exclusively as once daily), or an opening occurred when the participant had been specifically instructed to "hold" a dose for high INR.

We fitted a MEMS cap directly on the pill bottle of those participants who accessed their warfarin medication directly from the pill bottle. Participants who used 7-day pillbox reminders to administer all their medications were provided an empty bottle with a MEMS cap attached and then instructed to open and close the MEMS cap bottle each time they took their warfarin, thereby creating an electronic diary of warfarin usage.

Statistical Analysis

Using the patient-day as the unit of analysis, we developed a prognostics model for the probability of nonadherence of a patient on any given day using standard methods. We also implemented, as a sensitivity analysis, a model that ignored the variation in follow-up and considered only patient-level data.

We initially checked for correlation and for missing levels among all potential predictors to arrive at complete, independent factors. For example, we were forced to combine the variables of employment status and age as they were overlapping (older subjects tended to be unemployed). The self-reported household income level was missing too often for analysis. Subjects with missing questionnaire data ($n = 22$) could not be used in the final analysis because we had too little information with which to impute those questionnaire responses.

During our initial stages of model building, we used a multivariable logistic regression model with generalized estimating equations (GENMOD; SAS, Inc.; Cary, NC) and an independence working correlation structure to account for the repeated, dichotomous outcome of daily warfarin adherence in the 114 subjects in the final model.^{20,21} This approach allowed us to assess accurately the statistical significance of each potential risk factor while taking into consideration that we had many repeated observations of the

same patients. Nonadherence to warfarin for a given patient on a given day was the dependent variable in our analysis. As use of the patient-day as the unit of analysis accounted for the variation in the number of days of follow-up by participants, we allowed the number of patient-days on warfarin to vary by patient.²² To provide estimates of variance and confidence bounds, we performed bootstrap resampling (at the patient level) and we reported bias-corrected estimates.^{23,24} We bootstrapped to avoid the risk of bias in variance estimates from less than large samples of data.²⁵ This modeling approach ensures that confidence bounds are not overly narrow.²⁶

Beginning with factors considered for inclusion in the explanatory model,²⁷ we selected prognostic factors based on their ability to improve the *c*-statistic, which was used as a measure of the ability to classify patients correctly.^{28,29} We then assigned points to each factor based on the relative sizes of the regression coefficients (scaled relative to the smallest coefficient and then rounded to the nearest whole number), after which we reassessed model discrimination and calibration (using *c*-statistics and comparisons of observed vs expected percent adherence). We examined the distribution of days of nonadherence across patients to determine whether individual patients were influential to the final estimates. After obtaining a full model of predictive factors, we employed bootstrap resampling to internally validate the model and check whether the final model was an overly optimistic assessment of model predictive capabilities.²⁵

To choose an optimal cut-off for defining those at greatest risk of nonadherence, a range of thresholds was reviewed using clinical criteria and the tradeoff between the number of false positives and false negatives. Owing to the greater cost of false negatives (ie, failing to identify patients at risk for nonadherence), the threshold chosen was prespecified as being relatively low in the point scale, even at a cost of a higher number of false positives (ie, misclassifying some subjects as being at higher risk for nonadherence when they are not at increased risk). After developing our model on the level of patient-days on warfarin therapy, we applied the IN-RANGE point score to our cohort at the patient level to assess how the IN-RANGE model predicts nonadherence over the entire course of a patients' therapy on warfarin. This is the level at which the point score model could be used clinically to screen groups of patients for nonadherence. All statistical analyses were performed using SAS v 9.1 (SAS Institute) and Stata v 10.1 (StataCorp; College Station, TX).

FIGURE 1. Participant enrollment and protocol completion.

RESULTS

The study consists of 114 persons with complete psychosocial evaluation undergoing chronic anticoagulation followed for a median of 141 days (Fig 1). Warfarin nonadherence occurred in 4,793 of

Table 1—Characteristics of 114 Study Participants

Baseline Characteristics	Value
Age, y, mean (range)	55 (23-83)
Sex, male, No. (%)	74 (65)
African-American, No. (%) ^a	62 (54)
Education greater than high school, No. (%)	70 (61)
Employment/age, No. (%)	
Employed	38 (33)
Unemployed	14 (12)
Retired	34 (30)
Disabled, <55 y	18 (16)
Disabled, ≥55 y	10 (9)
Smoking status, No. (%)	
Never	40 (35)
Past	56 (49)
Current	18 (16)
Marital status, No. (%)	
Married	45 (39)
Separated/divorced	29 (25)
Widowed	10 (9)
Never married	30 (26)
Insurance status, No. (%)	
Any VA	43 (38)
Private/Medicare	61 (54)
Medicaid/none	10 (9)
Indication, No. (%)	
Stroke/TIA	3 (3)
Atrial fibrillation	46 (40)
DVT/PE	48 (42)
Dilated cardiomyopathy/LV thrombus	6 (5)
Other	11 (10)
University Hospital site, No. (%)	72 (63)
History, No. (%)	
Prior warfarin use	29 (25)
Cardiac arrhythmia, heart failure, ischemia, other	63 (55)
Hypertension	53 (46)
Diabetes mellitus	38 (33)
Prior stroke	15 (13)
Peptic ulcer disease, gastritis	16 (14)
Abnormal bleeding, abnormal clotting, DVT, PE	27 (25)
Other comorbidities ^b	29 (25)
Number of medications taken at baseline, median (range)	5 (0-20)
SF-36 MCS score, mean (range)	49.0 (23.2-68.6)
General health status, No. (%)	
Very good/excellent	38 (33)
Good	44 (39)
Fair/poor	32 (28)
Cognitive dysfunction, No. (%)	
CCSE score < 20	8 (7)
CCSE score ≥ 20	106 (93)

CCSE = Cognitive Capacity Screening Examination; LV = left ventricle; PE = pulmonary embolism; SF-36 MCS = short form-36 mental component subscale; TIA = transient ischemic attack; VA = Veterans Affairs.

^aRace was self-reported.

^bOther comorbidities: hypothyroidism, hyperthyroidism, cancer, and liver disease.

Table 2—Predictors of Warfarin Nonadherence for 114 Patients

Predictor ^a	β-Coefficient	Points
Education > high school	0.267	+1
Smoking status		
Current	0.496	+2
Past	Ref	0
Never	0.131	0
Employment/age		
Working	1.042	+3
Retired	0.430	+2
Unemployed	Ref	0
Disabled < 55 y	0.883	+3
Disabled ≥ 55 y	1.362	+4
No history of hypertension	0.528	+2
Indication, stroke/TIA	1.443	+4
Prior history of warfarin therapy, present	0.406	+2
Cognitive functioning, impaired (CCSE < 20)	0.962	+3
SF-36 MCS score		
Very low (< 25)	0.848	+3
Low (25-34)	0.566	+2
Below average (35-44)	0.283	+1
Average (45-54)	Ref	0
Above average (55-64)	−0.283	−1
High (65-74)	−0.566	−2
Very high (≥ 75)	−0.848	−3
Baseline general health status		
Fair/poor	0.635	+2
Good	0.246	+1
Very good/excellent	Ref	0

Ref = reference group. See Table 1 for expansion of abbreviations.

^aArea under curve = 0.66 (95% CI 0.61, 0.71); R^2 (regression correlation coefficient) for model = 0.319; regression coefficient constant = −3.236.

22,492 or 21.3% (95% CI, 17.6-25.6) of patient-days observed. An additional 22 subjects who were not included in the analysis because of failure to complete all of the psychosocial questionnaires had a somewhat higher rate of warfarin nonadherence (29% vs 21% of patient-days observed, $P = .08$). When analyzed on the level of the patient (as opposed to the patient-day level), median nonadherence for the 114 subjects in the cohort was 14.4% (interquartile range [IQR], 5.8-33.8) and mean nonadherence was 21.2% (SD ± 19.1%).

Baseline demographic data are presented in Table 1. The mean age of the cohort was 55 years old, and it consisted of two-thirds men and 54% African-Americans. Atrial fibrillation and venous thromboembolism were the main indications for warfarin therapy. Using baseline variables previously shown to be associated with poor adherence to warfarin,²⁷ we developed a predictive model to identify those at highest risk for daily nonadherence to warfarin (Table 2). The model produced a c -statistic of 0.66 (95% CI, 0.61-0.71). A check for overoptimism using bootstrap resampling reaffirmed this c -statistic (shrinkage factor of 0.993,

with 1.0 representing no overoptimism), suggesting that our model might be generalized to other samples of patients.²⁸

Table 3 displays the range of sensitivity, specificity, and positive and negative predictive value cut-offs available based on the IN-RANGE point system for nonadherence performed on a patient-day level analysis. Adoption of a five point threshold to dichotomize between adherent subjects (five points or fewer) vs nonadherent subjects (six or more points) results in a sensitivity of 81.3% (95% CI, 70.1-89.5), specificity of 38.3% (26.0-51.0), positive predictive value of 26.3% (21.5-31.1), and a negative predictive value of 88.3% (83.5-91.9). Selection of higher total point thresholds results in a modest lowering of the negative predictive value but only a slight improvement in the positive predictive value.

By contrast, when the IN-RANGE prediction model is applied to the level of individual participants (as opposed to the patient-days on warfarin), subjects are more easily classified into higher and lower risk strata. For example, subjects with an IN-RANGE point score of 4 points or fewer had a median level of nonadherence of 5.8% (IQR, 2.3-14.1) compared with median nonadherence for the entire cohort of 14.4% (IQR, 5.8-33.8). Subjects scoring higher on the IN-RANGE point score prediction model demonstrated progressively higher median nonadherence rates (Table 4).

DISCUSSION

In what we believe is the first prospective cohort study designed to develop a comprehensive prediction model for warfarin nonadherence using objective electronic recording of daily pill taking, we developed a prognostic model based on a total of nine demographic, clinical, and psychosocial factors. The purpose of this IN-RANGE model is to help providers identify groups of subjects with clinically meaningful differences in nonadherence. In our cohort, we found that subjects with an IN-RANGE point score of 4 or fewer have a median level of nonadherence of 5.8% (IQR, 2.3-14.1), as compared with the overall level of nonadherence of 14.4% (IQR, 5.8-33.8) in the entire cohort and nonadherence of 29.3% (IQR, 15.5-41.9) for those with 8 points or greater. High-scoring subjects, those who are at highest risk for nonadherence, might form a target population for increased monitoring and education, whereas those with lower scores could require less intensive monitoring or counseling.

When the model is applied to predicting nonadherence on the patient-day level of successive, discrete days on warfarin (as compared with the patient level),

Table 3—Range of Sensitivity, Specificity, and Predictive Values for Day-Level Analysis of Warfarin Nonadherence (N = 114 patients)

Score	Cumulative Days, No. (%)		Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)
	Nonadherent	Adherent				
Cumulative points	4,793 (100%)	17,699 (100%)				
≤ 5 points	895 (18.7%)	6,774 (38.3%)	81.3 (70.1-89.5)	38.3 (26.0-51.0)	26.3 (21.5-31.1)	88.3 (83.5-91.9)
≤ 7 points	2,556 (53.3%)	13,458 (76.0%)	46.7 (30.4-63.7)	76.0 (64.4-86.0)	34.5 (26.4-41.9)	84.0 (79.9-87.3)
≤ 8 points	3,566 (74.4%)	15,496 (87.6%)	25.6 (13.2-42.0)	87.6 (78.4-93.8)	35.8 (27.7-43.6)	81.3 (77.2-85.2)

CIs represent bias corrected estimates based on bootstrap resampling.

the model's ability to discriminate is more limited. The modest discrimination on the patient-day level is reflected in the model's *c*-statistic of 0.66 and the relatively low positive predictive values over a range of point scores (see Table 3). As a result, when viewing nonadherence on the patient-day level, there is frequent misclassification of patients with more adherent days as being at higher risk for nonadherence.

The frequent misclassification associated with the model's low positive predictive value would be an important limitation if any planned intervention involved significant risk to the patient or a high cost to the provider. However, if the potential interventions posed minimal or no risk to the patient and were relatively inexpensive (such as more intensified counseling or monitoring), then the low positive predictive value might not be an important limitation. Moreover, given the life-threatening nature and high economic cost to the health system of a stroke, hemorrhage, or recurrent venous thrombosis, the overall cost-benefit ratio might favor adoption of a prediction screening tool, even at the cost of providing counseling or monitoring to a somewhat wider group of patients.^{30,31}

Despite a comprehensive, prospective evaluation of demographic, clinical, and psychosocial variables, we were only able to arrive at a model with modest discrimination ability. This result may point to a larger issue of the difficulty in predicting the behavior of individuals in their daily medication usage, as has been previously observed.³²⁻³⁵ Furthermore, we are not

aware of prior attempts at developing a clinical prediction rule for nonadherence to warfarin or other high-risk medications. Nonetheless, the IN-RANGE prediction model, if adequately validated and refined in other settings with different levels of medication nonadherence, might help providers target important interventions toward a group of patients who at baseline are at increased risk of poor adherence.

The strengths of the IN-RANGE prediction model are the prospective design; the thorough evaluation of candidate demographics, clinical variables, and psychosocial variables; and the electronic recording of warfarin nonadherence. Limitations include, first, the lack of a validation cohort to test our prognostic model in other settings. Our study, performed in an urban, academic-based setting, will need to be replicated in other patient populations and in groups with differing prevalences of nonadherence to ensure generalizability. However, as a check for internal validation, we did perform bootstrap resampling and found there to be no evidence of overoptimism in the estimates of variance. Second, there may be selection bias based on the willingness of subjects to consent to electronic pill cap monitoring, even though we found no significant differences in baseline demographic factors of study subjects who agreed vs those who declined MEMS caps. A third limitation is that the MEMS cap actuation does not guarantee the patient actually consumed the pill upon each occasion of bottle opening. Nevertheless, a close link exists between nonadherence to warfarin and out-of-range INR values using MEMS cap monitoring.¹ Fourth, administration of two questionnaires, the SF-36 mental component subscale and the Cognitive Capacity Screening Exam, might make implementation of the IN-RANGE prediction model cumbersome in some settings, although these questionnaires are freely available and can be completed in minutes. Further work examining other methods of assessing these parameters (eg, shorter versions of the SF-36) would be useful. Fifth, *a priori*, we limited our model to the examination of baseline factors that could be ascertained by clinicians at the time of treatment initiation. Prior research has not identified risk factors for nonadherence that occur after initiating therapy with warfarin.²⁷

Table 4—Patient Level of Nonadherence to Warfarin, by International Normalized Ratio Adherence and Genetics Study Point Score (N = 114 subjects)

Total Points	% Incorrect Warfarin Doses		
	Median	25% Quartile	75% Quartile
≤ 4 points, n = 26	5.8	2.3	14.1
5 points, n = 16	9.1	5.9	28.6
6 points, n = 15	14.5	7.1	24.1
7 points, n = 24	14.7	7.0	34.7
≥ 8 points, n = 33	29.3	15.5	41.9
Summary for cohort, n = 114	14.4	5.8	33.8

In summary, patient adherence to warfarin is poor, with one in five doses taken incorrectly, even in the setting of an anticoagulation clinic. Periodic INR monitoring is crucial but may fail to capture periods of nonadherence until after an adverse event has occurred. A screening tool that provides some incremental benefit in identifying poor adherence over simple INR monitoring or provider and patient assessments could be useful clinically. If further validated in other populations, the IN-RANGE prediction model could be used to help exclude a subgroup of subjects at lowest risk for poor adherence, so that efforts at increased monitoring and intervention can be focused on those at higher risk for nonadherence.

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Dr Localio: contributed to study design, data analysis, and manuscript preparation and revision.

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