Factors That Affect Rate of INR Decline After Warfarin Discontinuation

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ABSTRACT

Background: Despite vast literature on warfarin, optimal strategies for temporarily discontinuing and restarting warfarin have not been established. To improve warfarin discontinuation processes, we investigated known medical and genetic factors that influence stable warfarin dose to determine how well they predict the time until patients become subtherapeutic after discontinuing warfarin.

Methods: This was a retrospective cohort study of patients who temporarily discontinued warfarin before an elective procedure and had at least 2 international normalized ratio (INR) values available during the discontinuation period. Data abstracted included date of discontinuation, warfarin dose, INR values, body surface area, gender, age, indication for warfarin, current medications, eGFR, and presence of bridging therapy with heparin. DNA variants were tested in CYP2C9, VKORC1, and CYP4F2 genes. Subjects were excluded if they received vitamin K, fresh frozen plasma, or prothrombin complexes to reverse anticoagulation. Asymptotic regression models were used to approximate decline in INR during warfarin clearance. Spearman correlations and Kruskal-Wallis tests were used to characterize associations of model estimates with quantitative variables and for group comparisons, respectively.

Results: Other than the expected association with baseline INR, correlations of model parameter estimates with clinical variables were generally weak and not statistically significant. The strongest associations with slope were with serum creatinine and eGFR. There were no significant associations with CYP2C9, VKORC1, or CYP4F2 DNA variants, but there were few subjects combined in the nonwild groups for CYP2C9. Estimated slope showed moderate correlation with observed dose.

Conclusion: Known clinical and genetic predictors of therapeutic dose were not found to be strongly associated with the slope of INR decline after warfarin discontinuation.

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INTRODUCTION

Warfarin is a commonly prescribed anticoagulant used in the prevention and treatment of arterial and venous thrombosis.[1-3] Patients on long-term anticoagulation therapy with warfarin may require temporary discontinuation to attain partial or complete reversal of anticoagulation before undergoing elective surgical and/or nonsurgical procedures.[4-6] Decisions regarding discontinuation are based on the risk of intraoperative and postoperative bleeding weighed against the probability of a thromboembolic event.[7] For patients at low risk for arterial or recurrent venous thromboembolic events, standard practice involves withholding 3 to 5 daily doses of warfarin before the procedure, usually resulting in an international normalized ratio (INR) ≤ 1.5 by the procedure day, providing an acceptably low risk of postoperative bleeding. Warfarin is then typically restarted sometime after the procedure. Patients at high risk for arterial or recurrent venous thromboembolic events (VTE) (eg, mechanical heart valve, VTE event within past 3 months, or arterial embolism in the previous 30 days) receive bridging therapy with unfractionated or low molecular weight heparin that is initiated when INR becomes subtherapeutic (generally < 2.0), and continued postoperatively until a therapeutic INR is achieved.[8-10]

Despite vast literature on warfarin, including its initiation, management, and genetic factors that affect therapeutic dose, optimal strategies for temporarily discontinuing and restarting warfarin have not been adequately assessed.[4,6] Current clinical management on temporary warfarin discontinuation is based on a single case series reported in 1995 using data from 22 patients who achieved therapeutic anticoagulation levels but subsequently

discontinued warfarin therapy.[11] For patients with an INR of 2.0 to 3.0, an exponential, but widely variable rate of decline in INR was noted. By day 5 most patients achieved INR values <1.5. The wide variability in rate of decrease in INR was attributed to age, with a 7% decrease in rate of INR decline for each 10-year increase in age. Age has been recognized as a factor associated with warfarin dosing, with older patients generally requiring a smaller dose compared to younger patients. Thus, older patients reportedly not only require smaller doses, but also take longer to eliminate this drug after discontinuation.

Phenotypic and genetic factors have been identified that systematically influence the therapeutic dose of warfarin.[12-14] In addition to age, these factors include body surface area (BSA), gender, diabetes mellitus, heart valve replacement, medications, and genetic polymorphisms (cytochrome p450 [CYP] 2C9, vitamin K epoxide reductase 1 [VKORC1], and CYP4F2). The influence exerted by these factors on warfarin during discontinuation for patients who were previously stable, and the time to achieve normal or near normal INR value in subjects who temporarily discontinue warfarin is currently unknown. Such knowledge is valuable since improved estimates of time to normal INR following warfarin discontinuation can lower patients' risks for thromboembolic events by reducing the amount of time that patients are without anticoagulants. For high-risk patients, it may be possible to reduce the number of preprocedural days required for successful bridging, thus reducing health care costs, especially those associated with unnecessary utilization of low molecular weight heparin. Furthermore, patients would benefit from an enhanced ability to schedule surgery and procedures with an improved degree of certainty that acceptable INR levels would be attained by the scheduled intervention date.

The goal of this study was to measure the decline in INR over time among subjects who had attained a therapeutic warfarin dose, examine the potential effects of the spectrum of known clinical and genetic factors that influence therapeutic warfarin dose on INR decline, and model when warfarin can be safely discontinued before elective and invasive surgical or medical procedures.

METHODS

The retrospective cohort included patients on a therapeutic dose of warfarin who temporarily discontinued before an elective procedure. Subjects were required to have at least 2 INR values available during the period of discontinuation, although not necessarily on consecutive days. Subjects were excluded if they received vitamin K, fresh frozen plasma, or prothrombin complexes to reverse anticoagulation, or had moderate to severe hepatic insufficiency based on a serum aspartate aminotransferase or alanine aminotransferase more than 2 times the upper limit of normal.

Table 1. Baseline Patient Clinical Characteristics (N=91)

Clinical Characteristic	Number (%)
Male	51 (56%)
Diabetes mellitus	18 (20%)
Liver disease (mild)	2 (2%)
Bridging therapy	49 (54%)
Heart failure	13 (14%)
Indication for warfarin discontinuation	
Surgery	16 (18%)
Endoscopy	7 (8%)
Coronary catheterization	42 (46%)
Other	26 (29%)
Acetaminophen	20 (22%)
Aspirin	46 (51%)
Fluconazole	2 (2%)
Levofloxacin	4 (4%)
Simvastatin	2 (2%)

Table 2. Baseline Quantitative Characteristics

	Patients	Mean	Minimum	Median	Maximum
Age (years)	91	71.2	25	73.9	92
BMI (kg/m^2)	90	29.7	21.4	28.7	50.3
Serum creatinine (mg/dL)	83	1.1	0.6	1.1	4.0
Dose (mg/day)	91	4.7	1.0	4.3	24.3

Abbreviation = BMI, body mass index.

A provisional study cohort of 285 subjects was identified using electronic data. Application of manually abstracted inclusion and exclusion trimmed the final study cohort to 91 subjects. The most limiting factors in cohort development were inadequate data to establish prediscontinuation therapeutic warfarin dose, fewer than 2 INRs during the discontinuation period, and direct clinical intervention to decrease anticoagulation level. The study cohort included 89 subjects with genotype data; genotypes were available both from previous studies[12,15] and from genotyping conducted specifically for this study using samples from Marshfield Clinic's Personalized Medicine Research Project DNA bank.[16] Clinical data were abstracted manually from subjects' electronic medical records, including date of discontinuation, warfarin dose, INR values, gender, age, indication for warfarin therapy, current medications, and the presence of "bridging therapy" with heparin or low molecular weight heparin.

CYP2C9, VKORC1, and Cyp4F2 genetic testing was performed using assays purchased from Applied Biosystems (ABI) (Foster City, California). ABI assays for CYP2C9 were C_25625805_10 and C_27104892_10. The ABI assay for VKORC1 was C_2847860_10. ABI assay C_16179493_10 was used to test the CYP4F2 polymorphism.

Figure. Clearance of Warfarin
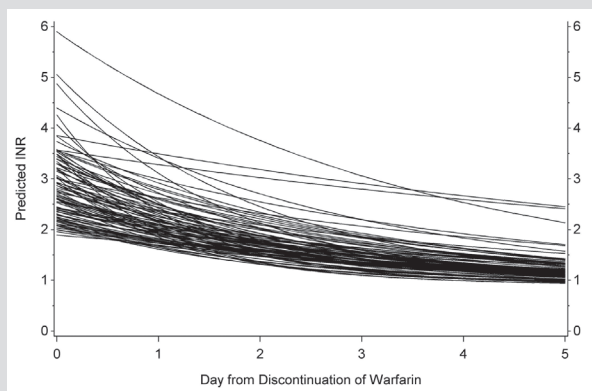
Predicted international normalized ratio (INR) by subject based on a linear model. The model was fit to all subjects using a linear INR scale and shows predicted INR for each subject.

Table 3. Spearman Correlation Coefficients (91 Total Patients)

	Slope r P-value	Day 2 INR r P-value
Intercept	-0.244 0.020	0.654 < 0.001
Slope		0.474 < 0.001

Abbreviations = r, estimated correlation; INR, international normalized ratio.

Statistical Analysis

For subjects meeting the eligibility criteria, INR data were graphically reviewed as a quality assurance measure, and outliers were investigated and updated as necessary. Statistical models were fitted to obtain an estimate of the rate of decline in INR (slope) after discontinuation of warfarin for each subject. In previous work,[17] we used a sigmoidal dose-response curve to model the INR response upon initiating warfarin, and we attempted to fit this model to the discontinuation data. However, due to limitations on the frequency of available INR measures, the full model could be fit on only 30% of the subjects. We developed a linear approximation model as an alternative so data for the entire cohort could be used.[11] This approximation assumes that INR after warfarin discontinuation will show an approximately exponential decline asymptotically over time to a warfarin-free value of about 1.0. Under this assumption, transforming INR by taking the logarithm after subtracting the asymptote results in a linear model. The primary estimates of interest from this model were the intercept (baseline INR, Day 0) and slope (rate of INR decline). To help illustrate the clinical results, we also analyzed model estimates of the expected INR at a specified time after discontinuation, arbitrarily choosing Day 2 as the reference time. The predicted INRs on Day 2 from the full logistic model were quite similar to the results from the linear approxi-

mation for the 29 subjects that could be fit with both models (Spearman correlation = 0.73, $P < 0.001$).

These estimated slopes were summarized to provide information on the overall variability in time to become subtherapeutic. Clinical and genetic factors were evaluated for possible association with the estimated slopes. The Spearman correlation was used to characterize the association with quantitative variables (eg, age), and the Kruskal-Wallis test was used for comparisons among groups (eg, by genotype).

RESULTS

Baseline clinical characteristics for study subjects are summarized in Tables 1 and 2. Subjects ranged in age from 25 to 92 years (mean 71), and 56% were male. Median warfarin dose was 4.3 mg/day, which is consistent with our previous studies (Table 2). One in 5 in the study cohort had diabetes mellitus and 1 in 7 had heart failure. Over 50% of the cohort used aspirin and over 20% used acetaminophen. Antibiotic, antifungal, and statin use at time of discontinuation was infrequent (Table 1). Common invasive procedures were the principal indication for discontinuation; surgery, endoscopy, and coronary catheterization represented over 70% study discontinuations. Bridging therapy was used to manage clinical risks in 54% of patients in the cohort.

The number of INRs modeled per subject ranged from 2 to 10 (median 4). Plots showing the model fit for all subjects using a linear INR scale are shown in the Figure. The model estimates were correlated to varying degrees (Table 3); higher starting INR (intercept) was associated with faster rates of decline in INR (more negative slope), and both higher starting INR and slower decline were associated with higher Day 2 INR.

The correlations of the model parameter estimates with clinical variables tended to be weak and not statistically significant. The strongest associations with slope were shown by age and estimated glomerular filtration rate (GFR) (Table 4). There were no significant associations with the genetic variants in CYP2C9, VKORC1, or CYP4F2 (data not shown); however, there were only 4 subjects combined in the *2/*2, *2/*3, and *3/*3 groups of CYP2C9.

DISCUSSION

Although warfarin is commonly used for the prevention and treatment of a variety of acute and chronic venothromboembolic conditions, there is a paucity of evidence regarding the best way to discontinue warfarin before elective surgical or medical procedures.[8-10] We sought to increase the evidence base for warfarin discontinuation by investigating factors known to affect metabolism and therefore therapeutic dose. These included medications, disease and clinical conditions (eg, liver disease), and genetic factors (CYP2C9, VKORC1, CYP4F2).

Table 4. Spearman Correlation Coefficients

	n	Intercept		Slope		Day 2 INR	
		r	*P*-value	r	*P*-value	r	*P*-value
Male gender	91	0.00	0.987	-0.07	0.500	-0.12	0.258
Body surface area	90	0.02	0.837	-0.07	0.536	-0.06	0.545
Body mass index	90	-0.06	0.565	-0.06	0.558	-0.13	0.221
Age	91	-0.12	0.255	0.19	0.066	0.05	0.640
Serum creatinine	83	0.09	0.424	0.16	0.151	0.24	0.026
Estimated GFR	83	-0.04	0.747	-0.21	0.053	-0.27	0.013

Abbreviations = r, estimated correlation; INR, international normalized ratio; GFR, glomerular filtration rate.

Our principal analysis modeled the decline in INR after warfarin discontinuation using a constrained logistic function based on a published model previously used for warfarin initiation.[17] The model was constrained to the assumption that the INR measurement for subjects free of warfarin is approximately 1.1, since this was the median from our cohort. Imposing this constraint allowed us to fit this initiation model to a higher percentage of the cohort, even though many subjects had limited numbers of INRs in the time period of interest. Given limits on the INRs available, lack of precise INR times and some imprecision in the INR measurement itself, we expected reasonable simplifications to the models to be helpful. Our approach involved perhaps sacrificing a small amount of information in a few subjects with the most INR measurements; however, it allowed us to include many other subjects who had adequate data to fit with a simplified model but not enough for a more complex model.

Contrary to our a priori expectations, our study did not reveal strong correlations between genetic or clinical predictors of therapeutic dose and the slope of INR decline after warfarin discontinuation. We found no genetic or weak associations between clinical factors known to relate to warfarin therapeutic dose and the time needed for INR to decline to subtherapeutic levels.

Genetic factors may well have asymmetric effects on warfarin initiation and maintenance compared to discontinuation among individuals who achieve a stable dose. During initiation, person-level genetic differences matter and contribute to the well-known variability in dose-response patterns during this clinical period. However, eventually these interperson genetic differences and other patient factors are revealed and become reflected in a stable dose. When stable-dose patients discontinue warfarin, the rate of INR decline per unit of time may be expected to be more consistent across individuals precisely because those factors that affect daily warfarin clearance are embedded in daily dose. Variation in rate of INR decline during discontinuation is more likely to be related to changing patient conditions and clinical response than to genetics.

Our results on clinical factor effects generally are consistent with the observations previously reported.[10,11] In both studies, the rate of INR decline was not affected by height, weight (body mass index), or gender. However, advanced age, decompensated heart failure, active malignancy, and extreme elevations in INR were factors that accounted for sustained elevation of INRs >4.0 in patients with supratherapeutic INRs at entry into the study. Our study did not confirm the relatively weak age effect noted by White et al.[11]

Our study has weaknesses that temper our findings and limit comparison of our results with other investigations. The retrospective nature of our study limited both the quantity of INR measures available for analyses and increased the variability of time intervals between INR measures across study subjects. Our preferred approach would have been to model hours from discontinuation; instead, we had to model days from discontinuation. Despite these limitations, our model results generally are consistent with the rate of INR decline as a function of time reported in White et al.[11]

Another limitation was the small number (N = 4) of non-wild CYP2C9 genotypes in the study cohort. Because our study cohort did not include larger numbers of rarer genotypes known to impact warfarin dose, we cannot rule out the possibility of genetic effects on INR decline following discontinuation. Additional studies with larger numbers of rare genotypes will be needed to make this determination. However, as we noted earlier, to the extent that therapeutic warfarin dose has been established, it reflects underlying genetic variation among individuals. Therefore, we hypothesize that the effects of rare genotypes known to affect therapeutic warfarin dose would be similar to those of wild types on rate of INR decline following discontinuation.

CONCLUSION

Contrary to our hypothesis, our study did not identify strong clinical or genetic predictors of therapeutic dose and the slope of INR decline after warfarin discontinuation. Further, we found no evidence to suggest that the current general clinical management guidelines for warfarin discontinuation should be amended. Generally, these include a recommendation to withhold warfarin for 4 to 5 doses (days) for patients with stable INRs in the range of 2.0-3.0 in order to achieve an INR ≤ 1.5 on

procedure day. For elderly patients and patients with INRs > 3.0, more time is generally required to reach a subtherapeutic target INR of < 1.5.[9]

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