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Factors Affecting Time to Maintenance Dose in Patients Initiating Warfarin

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Abstract

Purpose—Patients starting warfarin often experience lengthy dose-titration periods, when they are at high risk for bleeding and thromboembolism. However, relatively little is known about why some patients take longer than others to reach maintenance dose. Thus, we sought to identify social, clinical, and genetic factors associated with prolonged time to maintenance dose (TTM).

Methods—We conducted a time-to-event analysis, using a prospective cohort of patients initiating warfarin (N = 390). Additionally, we examined whether changes in post-initiation factors were associated with TTM. Finally, we performed a secondary analysis in a subcohort (N = 156) assessing the effect of adherence on TTM.

Results—No genetic or post-initiation factors were significantly associated with TTM. However, previous use of warfarin (HR = 0.64; 95% CI 0.46, 0.88), current smoking status (HR = 0.61; 95% CI 0.39, 0.96), fewer than 4 doctor's visits in the previous year (HR = 0.63 vs 4–12 visits; 95% CI 0.46, 0.88), and worse general health status (HR = 0.63; 95% CI 0.47, 0.84) were significantly associated with longer TTM. Use of illegal injectable drugs (HR = 2.51; 95% CI 1.17, 5.39) was associated with shorter TTM. On secondary analysis, the hazard ratio for better adherence and TTM was 1.70 (95% CI 0.88, 3.27).

Conclusions—TTM was associated with pre-existing behavioral factors, health care utilization, and health quality but not clinical comorbidities or genetic factors in patients initiating warfarin. Future studies are needed to determine whether warfarin patients with prolonged TTM would have better outcomes on alternative agents.

Keywords

warfarin; pharmacogenetics; survival analysis; treatment effectiveness; race

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Conflicts of Interest:

S.E.K. has consulted for several pharmaceutical companies, including Pfizer Inc and Janssen Pharmaceuticals, all unrelated to warfarin. None of the other authors have any other potential conflicts to report.

Prior Presentations:

Preliminary results of this study were presented at the 2012 ICPE in Barcelona, Spain.

Introduction

Patients initiating warfarin often experience lengthy dose-titration periods of weeks to months, during which time they are at particularly high risk of both bleeding and thromboembolic complications from improper anticoagulation levels.[1,2] Additionally, during the dose-titration phase, patients may have their international normalized ratio (INR) monitored as frequently as 1–2 times per week, while INR monitoring during the maintenance phase of therapy is generally only once every 1–2 months. As a result of this substantial increase in monitoring burden, patients with a long time to maintenance dose (TTM) may have increased medical costs, reduced quality of life,[3] greater dissatisfaction, and higher rates of warfarin discontinuation.[4,5] Furthermore, given the recent availability of alternative oral anticoagulants—including dabigatran, rivaroxiban, and apixaban—a better understanding of the causes of prolonged TTM in warfarin therapy is of increasing importance, because it could potentially help identify patient subsets who might be better treated with less burdensome alternative agents.

In contrast to the large amount of research that has been done on the genetic and clinical factors relating to warfarin maintenance dose requirement,[6] relatively little is understood about the factors that lead to a longer TTM. Previous research on the association between genetic variants and TTM has been mixed,[7–11] with few studies conducted in prospective cohorts. Given the multifactorial nature of warfarin response, however, it seems implausible that genetic variants are the only important factors associated with TTM. Indeed, a variety of non-genetic factors, including social and clinical factors, have been associated with several other endpoints that may be related to prolonged TTM, including poor warfarin adherence,[12,13] time in therapeutic INR range,[14,15] and risk of bleeding events.[16–19] However, such factors have not, to our knowledge, been rigorously studied in the specific context of TTM.

We sought to examine the association between social, clinical, and genetic factors and TTM for patients initiating warfarin. Additionally, we aimed to identify whether changes in factors after warfarin initiation could lead to increased TTM. Identifying such factors could help identify patient subsets that might be better treated with warfarin versus one of the newer anticoagulants. To accomplish these aims, we conducted a time-to-event analysis of the INR Adherence and Genetics (IN-RANGE) cohort, a large prospective cohort of adults initiating warfarin.[12,20]

Methods

IN-RANGE cohort

The IN-RANGE cohort of warfarin patients has been used to study the clinical and genetic predictors of warfarin maintenance dose and adherence.[12,20–27] Participants were recruited from specialty anticoagulation clinics at the Hospital of the University of Pennsylvania (HUP), the Philadelphia Veterans Affairs Medical Center (PVAMC), and Hershey Medical Center. Institutional review board approval was obtained at all three sites, and all study participants provided written informed consent. Exclusion criteria included being under 21 years old, being unwilling or unable to provide consent, having an abnormal INR prior to

starting warfarin or heparin therapy, or the presence of antiphospholipid antibodies. Participants were enrolled between April 2002 and February 2006. All participants were initiating a new course of warfarin upon enrollment; some participants may have had previous courses of warfarin. All participants in the original IN-RANGE cohort (N = 390) were eligible for inclusion in the current study.

Primary outcome

The primary outcome was the time from warfarin initiation to the first maintenance dose-defining visit, in days. Having a longer TTM is generally worse for patients because of increases in bleeding and thrombosis risk as well as patient burden. Patients were considered to have achieved maintenance dose if they had three consecutive INRs within the target therapeutic range, with no constraint on the amount of time between INRs. This definition was prespecified prior to cohort enrollment. TTM was a secondary outcome of the original IN-RANGE study; however, *a priori* power calculations demonstrated adequate power to detect clinically meaningful hazard ratios (Supplementary Table 1).

Exposures

A total of 38 pre-existing, or 'baseline,' variables were considered for analysis. These included social, clinical, and genetic factors, which were all assessed at the time of recruitment (Supplementary Table 2). Genetic factors studied were the *VKORC1* −1639G>A variant (rs9923231), the *CYP2C9**2 and *CYP2C9**3 variants (rs1799853 and rs1057910, respectively), and the *APOE* ε2 and ε4 alleles (based on the rs7412 and rs429358 variants, respectively). As described previously,[23] DNA was extracted from buccal swab preparations and analyzed using PCR amplification by collaborators who were blinded to patient characteristics and outcomes. All non-genetic factors were ascertained via self-report, making the data comparable to that available to clinicians managing warfarin patients.

Additionally, several 'post-initiation' factors were studied, including changes in the use of interacting medications, quantitative and qualitative changes in diet, changes in weight, and changes in alcohol consumption since starting warfarin. Changes in interacting medications were defined as starting or stopping an interacting medication after warfarin initiation; the list of potentially interacting medications is shown in Supplementary Table 3. Finally, warfarin adherence, measured by medication event monitoring system (MEMS) caps,[12] was considered in a secondary analysis because adherence data were only available in 40% of the cohort (N = 156).

Primary Analysis

Cox regression models, stratified by clinical site, were used for all analyses. Variable selection for the primary model of baseline factors was performed using a combination forward-backward algorithm, described in the Supplementary Appendix. The variables included in the final model were age, race, previous use of warfarin, current smoking status, illegal injectable drug use, number of doctor's visits in the previous year, general health status, history of arrhythmia, and having a variant in *VKORC1*. Complete-case analysis was used because only 32 individuals (9% of cohort) were missing data on any of these variables.

Because of their known effect on maintenance dose, genetic factors were analyzed separately, adjusted for final model variables. Genetic factors were specified as binary variables, indicating whether at least one variant was present, in order to avoid data sparseness when assessing prespecified interactions between genotype and race. For the same reason, *CYP2C9**2 and *3 variants were combined into a single binary variable. The effects of post-initiation factors, adjusted for final model variables, were also analyzed separately. All post-initiation factors were specified as time-dependent variables, with their value representing the total number of changes that an individual had experienced by a given date. Additionally, because of their time-dependent specification, models for post-initiation factors were adjusted for visit number to help prevent confounding by varying frequency of INR monitoring. Finally, because this study used the same cohort for variable selection and model estimation, there was concern about model overfitting and sensitivity to outliers. Thus, all reported point estimates, confidence intervals, and P-values in the primary analysis were estimated using 1,000 bootstrap replications (see Supplementary Appendix).[28]

Secondary Analyses

Warfarin adherence was analyzed using the subcohort of patients with available MEMS cap data (N = 156), adjusting for final model variables. Adherence was specified as a time-dependent binary variable, indicating whether an individual had been ≥80% adherent over the past three visits. Age was excluded from adjusted adherence models to reduce the potential bias from adjustment of near-instruments,[29,30] because it is known to be a strong predictor of warfarin adherence[20,24] while not being associated with the outcome. Use of illegal injectable drugs was also excluded because of unstable estimates from data sparseness in the subcohort. Finally, we performed a secondary analysis examining whether individuals with high (≥49 mg/wk) or low (≤21 mg/wk) maintenance dose had increased TTM. As in the primary analysis, point estimates, confidence intervals, and P-values for all secondary analyses were based on 1,000 bootstrap replications.

Sensitivity Analyses

We conducted a sensitivity analysis using inverse probability of censoring weights to determine the potential impact of informative censoring on our results (see Supplementary Appendix).[31,32] A sensitivity analysis was also performed treating visit number, rather than days, as the unit of time for the primary analysis, in order to look at the impact of potentially variable visit frequencies on our results. Additionally, we performed a sensitivity analysis where standard, non-bootstrapped model-based estimates were calculated. Finally, the individual effects of *CYP2C9**2 and *CYP2C9**3 as well as using an additive specification (i.e. 0, 1, or 2) for all genetic variants were assessed in a sensitivity analysis. All analyses were performed using R 3.0.2.

Results

There were 390 subjects in the cohort, whose characteristics are shown in Table 1. Median TTM was 45 days (IQR 15, 135), with 288 subjects (74%) achieving maintenance dose by the end of the study. Median number of visits required to achieve maintenance dose was 7 (IQR 4, 13). Genotype frequencies by race are shown in Supplementary Table 4.

The results for the final model are shown in Table 2. Note that because this is a time-to-event analysis, hazard ratios below 1 indicate that a factor is associated with longer TTM and is worse for patients, on average. Complete data on all variables in the final model were available in 358 subjects (91%), with 267 (75%) achieving maintenance dose by the end of the study. Previous use of warfarin (HR = 0.64 vs no previous use of warfarin; 95% CI 0.46, 0.88), current smoking status (HR = 0.61 vs current non-smoking status; 95% CI 0.39, 0.96), having fewer than 4 doctor's visits in the previous year (HR = 0.63 vs 4–12 visits; 95% CI 0.46, 0.88), and having fair/poor general health status (HR = 0.63 vs excellent/very good/good general health; 95% CI 0.47, 0.84) were significantly associated with longer TTM. In contrast, use of illegal injectable drugs (HR = 2.51 vs no reported drug use; 95% CI 1.17, 5.39) was associated with shorter TTM. There was evidence to suggest that the proportional hazards assumption may be violated for our primary analysis ($P = 0.01$), but inspection of survival curves for individual covariates indicated that this should not have a qualitative effect on our results. The effects of genetic factors alone, stratified by race, are shown in Table 3. No genetic variant was significantly associated with TTM either before or after adjustment for covariates (All $P_{main\ effect} > 0.06$), and no significant interactions between genetic variants and race were observed (All $P_{interaction} > 0.4$). As shown in Table 4, no post-initiation factor was statistically significant either before or after adjustment for covariates (All $P > 0.2$).

In secondary analyses, better adherence showed a significant univariable association with shorter TTM (HR = 1.95; 95% CI 1.06, 3.59), but this association was not significant after adjustment for covariates (HR = 1.70; 95% CI 0.88, 3.27), as shown in Table 5. By contrast, final maintenance dose was not significantly associated with TTM in either unadjusted [high dose HR = 1.03 (95% CI 0.79, 1.34); low dose HR = 1.13 (95% CI 0.78, 1.64); overall $P = 0.81$] or adjusted [high dose HR = 1.10 (95% CI 0.78, 1.54); low dose HR = 1.11 (95% CI 0.73, 1.69); overall $P = 0.79$] analyses.

In sensitivity analyses, use of inverse probability of censoring weights did not appreciably change the results from those shown in Table 2, with a 3.3% mean change in hazard ratio estimates (Supplementary Table 5). Additionally, use of visit number, rather than days, as the unit of time did not substantially change the results, with a 6.8% mean change in hazard ratio estimates (data not shown). Our results were also not substantially changed when standard, non-bootstrapped estimates were used, with a 1.1% mean change in hazard ratio estimates (data not shown). Finally, use of an additive specification for genetic variants and having separate variables for the *CYP2C9**2 and *CYP2C9**3 variants did not substantially change the results, with small quantitative changes toward the null (data not shown).

Discussion

In this study, we examined the social, clinical, and genetic factors associated with TTM, using the IN-RANGE prospective cohort of adults initiating warfarin therapy. We found that previous use of warfarin, current smoking status, having fewer than 4 doctor's visits in the previous year, and worse general health status were all associated with longer TTM, while use of illegal injectable drugs was associated with shorter TTM. To our knowledge, this

study is the first systematic examination of all of these factors for the clinically-relevant outcome of TTM in patients initiating warfarin.

Primary Analysis

Most of the literature on factors associated with TTM has focused on the effects of genetic variants, and our findings for genetic variants are largely consistent with these previous studies. None of the genetic variants studied were significantly associated with TTM. Like other prospective studies,[10,11] we failed to observe an association between *CYP2C9**2 or *3 and TTM in either African Americans or Caucasians. While evidence suggests that *CYP2C9**5, *6, *8, and *11 may be more important than *CYP2C9**2 and *3 for determining warfarin maintenance dose in African Americans due to their higher prevalence,[33] significant associations between these variants and TTM have not been previously observed.[10]

Similarly, *VKORC1* was not significantly associated with TTM in either African Americans or Caucasians, which is consistent with the overall literature.[7–11] Our hazard ratio in African Americans, however, was similar to that observed by Limdi et al,[10] although statistical significance was not achieved in either study. Our study was sufficiently powered to detect clinically meaningful hazard ratios, and even when adjusting for multiple variables we had more than 26 events per degree of freedom in our model, well more than the generally recommended 10 events per degree of freedom.[34,35] Thus, if there is indeed a real effect, it seems likely to be of small magnitude. Finally, our results did not confirm a previous finding of an association between *APOE* and TTM in African Americans.[7] However, this previous study excluded individuals who did not reach maintenance dose and had limited adjustment for confounders; thus, the discrepancy could potentially be attributable to differences in study design.

By contrast, non-genetic factors—including behavioral factors (e.g. smoking status), healthcare utilization (e.g. number of doctor's visits in the previous year), and health quality (e.g. self-reported general health status)—appeared to be more important than genetic factors for determining TTM (Table 2). Worse general health status has been previously shown to be associated with worse warfarin adherence,[24] and current smoking status has been associated with increased warfarin dose requirement[36,37] as well as decreased time in therapeutic range,[15] so it is unsurprising that these factors were found to be associated with longer TTM. Furthermore, fewer than 4 doctor's visits in the previous year might be a marker for reduced health care access or health literacy, so it could conceivably be related to longer TTM through the effect of these factors on medication adherence and INR monitoring burden.

More surprising was the finding that previous use of warfarin was associated with longer, rather than shorter, TTM. Previous warfarin users did not differ from new warfarin users in terms of their warfarin indication or comorbidities (data not shown); however, they did appear to have their INRs checked less frequently, with 32% of previous warfarin users being seen at least once per week on average compared to 45% for new warfarin users, although this difference was not statistically significant (Supplementary Table 6). One can

hypothesize that physicians may have monitored patients with prior warfarin experience less frequently, thus leading to a longer TTM.

Similarly, the finding that patients who reported using illegal injectable drugs tended to have a shorter TTM was counterintuitive. While it is possible that physicians were intentionally monitoring these patients more closely, confirmatory evidence will be needed before concluding that the observed association was not primarily due to chance. Changes in post-initiation factors were also surprisingly not associated with TTM, suggesting that most of these changes typically do not occur early enough in the course of therapy to have a substantial impact on TTM. However, changes in post-initiation factors could still be important determinants of anticoagulation control in patients on long-term warfarin therapy after maintenance dose has been achieved. Finally, it is also worth noting that most traditional clinical and demographic factors were not associated with TTM, including all clinical comorbidities examined and use of interacting medications at baseline.

Secondary Analyses

Better adherence was not significantly associated with shorter TTM after adjustment for covariates. However, given that the point estimate for adherence was comparable to significant factors in the primary analysis, it seems plausible that there could be a real effect. Because of their shorter half-lives and inability to monitor, there is some concern that nonadherent patients on alternative oral anticoagulants might be expected to have worse outcomes than nonadherent warfarin patients.[38] Future studies are needed to clarify the effect of adherence on TTM and the effects of adherence on outcomes with alternative oral anticoagulants.

Limitations

There are several potential limitations of this study: 1) While one strength of our study is that we included all available follow-up time in our analyses, there is still the possibility of bias due to informative censoring. We attempted to assess the impact of informative censoring by performing a sensitivity analysis incorporating inverse probability of censoring weights. Because the results were not appreciably changed, we can be more confident that informative censoring is not substantially biasing our results. 2) We were limited to the variables available in this cohort, which may have led to missing some important predictors of TTM as well as residual confounding of factors we did study. 3) This study used the same dataset for variable selection and effect estimation, potentially leading to problems with overfitting. As a result, we bootstrapped all point estimates and confidence intervals in both primary and secondary analyses. Bootstrapped results were not substantially different from standard estimates; however, these results will still need independent validation. 4) Finally, these data are from specialty anticoagulation clinics, potentially reducing their generalizability to warfarin patients in other clinical settings.

Conclusions

In conclusion, TTM was associated with baseline behavioral factors, health care utilization, and health quality in patients initiating warfarin, while traditional clinical comorbidities and genetic factors appeared less important. The observed associations could plausibly be related

to differences in warfarin adherence, anticoagulation control, and visit frequency that occur after warfarin initiation. Future studies will be needed to address whether warfarin patients with prolonged TTM will have better outcomes on alternative oral anticoagulants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Time to maintenance dose in warfarin patients was primarily associated with baseline behavioral factors, health care utilization, and health quality, while traditional clinical comorbidities and genetic factors appeared less important.
- Observed associations may be related to differences in warfarin adherence, anticoagulation control, and INR monitoring frequency after warfarin initiation.
- Previous warfarin users should not be expected to achieve maintenance dose more quickly and should not be monitored less frequently.
- Future studies are needed to determine whether warfarin patients with prolonged TTM would have better outcomes on alternative oral anticoagulants.

Table 1

Characteristics of the IN-RANGE clinical cohort (N = 390).

Characteristic	N (%) or Mean (SD)
Age (years)	59.2 (15.0)
Female gender	119 (31)
Race:	
African American	174 (45)
Caucasian	206 (53)
Other	10 (3)
Body Mass Index:	
< 25	122 (32)
25–30	125 (32)
> 30	140 (36)
Warfarin indication:	
Atrial fibrillation/flutter	188 (48)
DVT/PE	116 (30)
DCM/LV thrombosis	26 (7)
Stroke/TIA	22 (6)
Other	38 (10)
Target INR 2–3	389 (99.7)
Maintenance dose (mg/wk)	39.9 (22.0)
Previous use of warfarin	96 (25)
History of hypertension	192 (49)
History of diabetes	107 (27)
History of PUD	36 (9)
History of CHF	78 (20)
> 1 Interacting medications	210 (54)
Smoking status:	
Never smoked	141 (36)
Past smoker	185 (47)
Current smoker	64 (16)
CYP2C9 genotype:	
*1*1	283 (76)
*1*2	59 (16)
*1*3	26 (7)
*2*3	3 (1)
VKORC1 −1639G>A genotype:	
GG	209 (56)
GA	149 (40)
AA	15 (4)
Insurance status:	
Private	215 (56)

Characteristic	N (%) or Mean (SD)
Any VA	107 (28)
Medicaid	16 (4)
Medicare only	17 (4)
None	29 (8)
Employment status:	
Working	128 (33)
Unemployed	34 (9)
Retired	143 (37)
Disabled	81 (21)
Income per household member:	
< $15,000/year	109 (33)
$15,000–$20,000/year	99 (30)
> $20,000/year	122 (37)
AC clinic site:	
HUP	184 (47)
PVAMC	137 (35)
Hershey	69 (18)

Abbreviations:anticoagulation (AC), *congestive heart failure* (CHF), *deep vein thrombosis* (DVT), *dilated cardiomyopathy* (DCM), *Hospital of the University of Pennsylvania* (HUP), *left ventricular* (LV), *peptic ulcer disease* (PUD), *Philadelphia Veterans Administration Medical Center* (PVAMC), *pulmonary embolism* (PE), *and transient ischemic attack* (TIA).

Table 2

Unadjusted and adjusted hazard ratios for time to maintenance dose for variables included in the final model.

Baseline Factor[a] (N = 358)[b]	N (%) or Mean (SD)	N (%) Reaching Maintenance Dose[c]	Unadjusted[d] Hazard Ratio[e]	Unadjusted[d] P-value[f]	Adjusted[d] Hazard Ratio[e]	Adjusted[d] P-value[f]
Age (years)	59 (15)	—	1.01 (1.00, 1.01)	0.24	1.01 (1.00, 1.02)	0.15
Race						
African American	159 (44)	111 (70)	0.85 (0.65, 1.11)	0.24	1.02 (0.73, 1.42)	0.90
Caucasian or other	199 (56)	156 (78)	—		—	
Previous use of warfarin						
Yes	89 (25)	61 (69)	0.69 (0.52, 0.93)	0.015*	0.64 (0.46, 0.88)	0.007*
No	269 (75)	206 (77)	—		—	
Current smoking status						
Yes	61 (17)	37 (61)	0.72 (0.47, 1.09)	0.12	0.61 (0.39, 0.96)	0.031*
No	297 (83)	230 (77)	—		—	
Self-reported illegal injectable drug use						
Yes	17 (5)	14 (82)	1.65 (0.73, 3.73)	0.23	2.51 (1.17, 5.39)	0.018*
No	341 (95)	253 (74)	—		—	
No. doctor's visits in previous year:						
< 4	95 (27)	64 (67)	0.71 (0.52, 0.96)	0.085	0.63 (0.46, 0.88)	0.024*
4 – 12	174 (49)	146 (84)	—		—	
> 12	89 (25)	57 (64)	0.86 (0.62, 1.20)		0.88 (0.61, 1.28)	
General health						
Fair/poor	114 (32)	77 (68)	0.66 (0.50, 0.88)	0.005*	0.63 (0.47, 0.84)	0.002*
Excellent/very good/good	244 (68)	190 (78)	—		—	
History of arrhythmia						
Yes	189 (53)	139 (74)	0.90 (0.70, 1.16)	0.43	0.79 (0.59, 1.05)	0.10
No	169 (47)	128 (76)	—		—	
No. variants in *VKORC1*						
≥1	159 (44)	119 (75)	1.23 (0.95, 1.59)	0.11	1.33 (0.99, 1.78)	0.061
0	199 (56)	148 (74)	—		—	

[a] All non-genetic factors are based on self-report.

[b] Both unadjusted and adjusted results are from the same complete-case dataset to improve comparability.

[c] Individuals who failed to reach maintenance dose by the end of the study were considered censored.

[d] All models are stratified by anticoagulation clinic site.

[e] Hazard ratios and confidence intervals are based on the mean and variance from 1,000 bootstrap replications. Hazard ratios less than 1 indicate longer time to maintenance dose; hazard ratios greater than 1 indicate shorter time to maintenance dose.

[f] All P-values are based on the Wald test using the mean and variance of estimates from 1,000 bootstrap replications. Categorical variables were tested jointly.

[*] $P < 0.05$

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Table 3

Unadjusted and adjusted hazard ratios for time to maintenance dose for genetic factors, stratified by race.

Gene/allele (N = 358)[a]	African American	No. of variants	N (%)	N (%) Reaching Maintenance Dose[b]	Unadjusted[c]		Adjusted[c,f]	
					Hazard Ratio[d]	$P_{interaction}$[e]	Hazard Ratio[d]	$P_{interaction}$[e]
VKORC1	No	≥1	127 (64)	97 (76)	1.09 (0.81, 1.46)	0.42	1.31 (0.93, 1.85)	0.85
		0	72 (36)	59 (82)	—		—	
	Yes	≥1	32 (20)	22 (69)	1.41 (0.78, 2.54)		1.40 (0.71, 2.77)	
		0	127 (80)	89 (70)	—		—	
CYP2C9	No	≥1	72 (38)	58 (81)	0.97 (0.69, 1.36)	0.99	1.05 (0.73, 1.52)	0.49
		0	120 (62)	93 (78)	—		—	
	Yes	≥1	12 (8)	8 (67)	0.96 (0.53, 1.73)		0.68 (0.35, 1.35)	
		0	143 (92)	99 (69)	—		—	
APOE ε2	No	≥1	28 (14)	20 (71)	1.08 (0.68, 1.73)	0.93	0.91 (0.52, 1.58)	0.46
		0	168 (86)	134 (80)	—		—	
	Yes	≥1	36 (23)	25 (69)	1.11 (0.62, 2.01)		1.21 (0.61, 2.40)	
		0	121 (77)	85 (70)	—		—	
APOE ε4	No	≥1	45 (23)	37 (82)	1.01 (0.71, 1.44)	0.93	0.97 (0.67, 1.42)	0.92
		0	151 (77)	117 (77)	—		—	
	Yes	≥1	60 (38)	43 (72)	1.03 (0.57, 1.86)		1.00 (0.51, 1.98)	
		0	97 (62)	67 (69)	—		—	

[a] Both unadjusted and adjusted results are from the same complete-case dataset to improve comparability.

[b] Individuals who failed to reach maintenance dose by the end of the study were considered censored.

[c] All models are stratified by anticoagulation clinic site.

[d] Hazard ratios and confidence intervals are based on the mean and variance from 1,000 bootstrap replications. Hazard ratios less than 1 indicate longer time to maintenance dose; hazard ratios greater than 1 indicate shorter time to maintenance dose.

[e] P-values for interactions are based on the Wald test using the mean and variance of interaction terms from 1,000 bootstrap replications.

[f] Adjusted for all baseline factors shown in Table 2.

[*] $P < 0.05$

Table 4

Unadjusted and adjusted hazard ratios for time to maintenance dose for post-initiation factors.

			Unadjusted		Adjusted[g]	
Post-Initiation Factor[a] (N = 358)[b]	**N (%) ≥1 change[c]**	**Median time to first change[d]**	**Hazard Ratio[e]**	**P-value[f]**	**Hazard Ratio[e]**	**P-value[f]**
Change in interacting medication	48 (13)	47 (28, 83)	0.93 (0.70, 1.24)	0.62	1.01 (0.76, 1.34)	0.95
Change in diet:						
Qualitative	105 (29)	14 (7, 34)	0.97 (0.80, 1.17)	0.73	1.00 (0.82, 1.23)	>0.99
Quantitative	155 (43)	14 (7, 36)	0.91 (0.78, 1.07)	0.24	0.98 (0.84, 1.15)	0.82
Change in weight	180 (50)	17 (7, 35)	0.93 (0.82, 1.06)	0.26	0.97 (0.83, 1.13)	0.70
Change in alcohol use	35 (10)	50 (29, 86)	0.86 (0.60, 1.23)	0.42	0.96 (0.68, 1.34)	0.80

[a] Post-initiation factors are specified as ordinal time-dependent covariates, with their value equaling the total number of changes in the post-initiation factor reported by a given date.

[b] Both unadjusted and adjusted results are from the same complete-case dataset to improve comparability.

[c] Number (%) of individuals to report at least one change in the given post-initiation factor over the course of follow-up.

[d] Median time (IQR) in days from the initiation of warfarin to the first change experienced by an individual for the given variable.

[e] Hazard ratios are based on the mean estimate from 1,000 bootstrap replications. Hazard ratios can be interpreted as the effect of having one additional change in the given factor on TTM. Hazard ratios less than 1 indicate longer time to maintenance dose; hazard ratios greater than 1 indicate shorter time to maintenance dose.

[f] All P-values are based on the Wald test using the mean and variance of estimates from 1,000 bootstrap replications. Categorical variables were tested jointly.

[g] Adjusted for all baseline factors shown in Table 2, plus visit number to prevent visit frequency from confounding the time-varying covariates.

* $P < 0.05$

Table 5

Unadjusted and adjusted hazard ratios for time to maintenance dose in subcohort with adherence data.

Factor[a] (N = 143)[b]	N (%)	N (%) Reaching Maintenance Dose[c]	Unadjusted[d]		Adjusted (− Adherence)[d]		Adjusted (+ Adherence)[d,g]	
			Hazard Ratio[e]	P-value[f]	Hazard Ratio[e]	P-value[f]	Hazard Ratio[e]	P-value[f]
≥ 80% adherence[h]	—	—	1.95 (1.06, 3.59)	0.032*	—	—	1.70 (0.88, 3.27)	0.11
Race								
African American	60 (42)	39 (65)	0.88 (0.54, 1.43)	0.60	0.84 (0.44, 1.61)	0.61	0.90 (0.46, 1.76)	0.77
Caucasian or other	83 (58)	57 (69)	—		—		—	
Previous use of warfarin								
Yes	38 (27)	26 (68)	0.67 (0.41, 1.11)	0.12	0.58 (0.32, 1.03)	0.063	0.59 (0.32, 1.07)	0.084
No	105 (73)	70 (67)	—		—		—	
Current smoking status								
Yes	26 (18)	13 (50)	0.75 (0.39, 1.44)	0.39	0.68 (0.31, 1.47)	0.32	0.70 (0.33, 1.52)	0.37
No	117 (82)	83 (71)	—		—		—	
No. doctor's visits in previous year:								
< 4	48 (34)	27 (56)	0.52 (0.32, 0.85)	0.026*	0.47 (0.27, 0.82)	0.026*	0.51 (0.28, 0.91)	0.053
4 – 12	70 (49)	55 (79)	—		—		—	
> 12	25 (17)	14 (56)	0.67 (0.35, 1.29)		0.68 (0.29, 1.57)		0.61 (0.27, 1.41)	
General health status								
Fair/poor	50 (35)	31 (62)	0.64 (0.40, 1.01)	0.055	0.63 (0.36, 1.10)	0.10	0.69 (0.39, 1.22)	0.20
Excellent/very good/good	93 (65)	65 (70)	—		—		—	
History of arrhythmia								
Yes	77 (54)	53 (69)	1.14 (0.74, 1.78)	0.55	1.01 (0.57, 1.79)	0.97	1.00 (0.57, 1.76)	>0.99
No	66 (46)	43 (65)	—		—		—	
No. variants in *VKORC1*								
≥1	59 (41)	38 (64)	0.96 (0.62, 1.47)	0.84	1.06 (0.57, 1.98)	0.85	1.01 (0.54, 1.88)	0.97
0	84 (59)	58 (69)	—		—		—	

[a] All non-genetic factors, excluding adherence, are based on self-report. Age was excluded from this analysis to prevent over-adjustment, because it is a known strong predictor of warfarin adherence while being very weakly associated with TTM. Illegal injectable drug use was excluded because there were too few self-reported users in the subcohort to produce stable estimates.

[b] Both unadjusted and adjusted results are from the same complete-case dataset to improve comparability; only individuals with adherence data were included in this analysis.

[c] Individuals who failed to reach maintenance dose by the end of the study were considered censored.

[d] All models are stratified by anticoagulation clinic site.

[e] Hazard ratios and confidence intervals are based on the mean and variance from 1,000 bootstrap replications. Hazard ratios less than 1 indicate longer time to maintenance dose; hazard ratios greater than 1 indicate shorter time to maintenance dose.

[f] All P-values are based on the Wald test using the mean and variance of estimates from 1,000 bootstrap replications. Categorical variables were tested jointly.

[g] The adjusted model also included visit number to ensure that visit frequency was not confounding the time-varying covariate.

[h] Adherence was specified in a time-varying fashion, indicating whether the participant had correct adherence on ≥ 80% of the days over the last 3 visits, using medication event monitoring system (MEMS) data.

[*] $P < 0.05$