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Short Communication

A Race-Specific Interaction between Vitamin K Status and Statin Use

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Abstract

The oral anticoagulant warfarin is a vitamin K antagonist. Phylloquinone, the primary circulating form of vitamin K, is transported by triglyceride-rich lipoproteins and shares a metabolic pathway with cholesterol. Thus, there is biological plausibility for an interaction between serum phylloquinone and lipid-lowering medications (statins) in warfarin therapy. The objective of this study was to examine if serum phylloquinone and statin treatment interact during the initiation period of anticoagulation treatment in African Americans and Caucasians participating in the 2009-2013 International Normalized Ratio Adherence and Genetics II cohort. In a race-specific, cross-sectional analysis, the primary exposures were serum phylloquinone and statin use. Outcomes included days to maintenance and percent time in the therapeutic range (PTTR). A significant interaction between serum phylloquinone quartile and statin use with respect to days to maintenance was detected in Caucasians only (p=0.02). In Caucasians taking statins, those in the second and third serum phylloquinone quartiles reached maintenance 91% (HR=0.09, 95%CI 0.03-0.35) and 83% (HR=0.17, 95%CI 0.05-0.54) slower, respectively, compared to those in the lowest quartile. Days to maintenance did not differ between any quartiles among Caucasians not taking statins. In African Americans, serum phylloquinone was not associated with days to maintenance regardless of statin use. Serum phylloquinone and statin use were not associated significantly with PTTR in either race. In conclusion, race may be an important consideration in this diet-drug-drug interaction. Future studies are warranted to validate these findings and clarify the clinical relevance.

ABBREVIATIONS

INR: International Normalized Ratio; IN-RANGE: International Normalized Ratio Genetics and Adherence Study; PTTR: Percent Time in Therapeutic Range; OR: Odds Ratio; CI: Confidence Interval

INTRODUCTION

Vitamin K regulates coagulation by modulating the post-translational modification of various clotting factors [1]. The vitamin K antagonist, warfarin, is prescribed for the prevention and treatment of thromboembolism [2]. Warfarin is highly efficacious, but has a very narrow therapeutic range [3]. A multitude of factors have been shown to influence warfarin therapy, including vitamin K [4], race [5], and drug-drug interactions [2,6,7]. According to case-reports and small clinical trials, co-administration of statins and warfarin results in reduced warfarin dose requirements, increased international normalized ratio (INR), and/or bleeding [8-13]. The magnitude of these effects vary by and within statin type [6]. Owing to the number of factors that influence warfarin treatment, dosing for stable anticoagulation therapy is highly variable [14]. The dose-titration period, which is particularly vulnerable to bleeding and thromboembolic complications, can range from weeks to months [15,16]. Due to the lipophilic properties of vitamin K, and the lipid-lowering effect of statins, we hypothesized that vitamin K and statins would interact during the titration period of warfarin therapy initiation. Vitamin K status has been associated with percent time in the therapeutic range (PTTR), a measure of anticoagulant stability [4]. The objective of this study was to examine the inter-relationship of circulating vitamin K and statins in warfarin therapy initiation in a large cohort of Caucasians and African Americans.

MATERIALS AND METHODS

Data were obtained from the INR Adherence and Genetics (IN-RANGE) II study, a U.S. prospective cohort study designed to examine the associations between clinical and genetic factors in warfarin adherence and maintenance dose [14,17]. The 687 patients in this cohort were initiating warfarin treatment. Subjects were recruited between 2009 and 2013 from three outpatient anticoagulation clinics (Hospital of the University of Pennsylvania, the Corporal Michael J. Crescenz Veterans Affairs Medical Center, and Johns Hopkins Medical Center) [14]. African Americans and Caucasians were specifically recruited to investigate whether racial differences in warfarin dosing could be attributed to genetic background [18] so all of our analyses

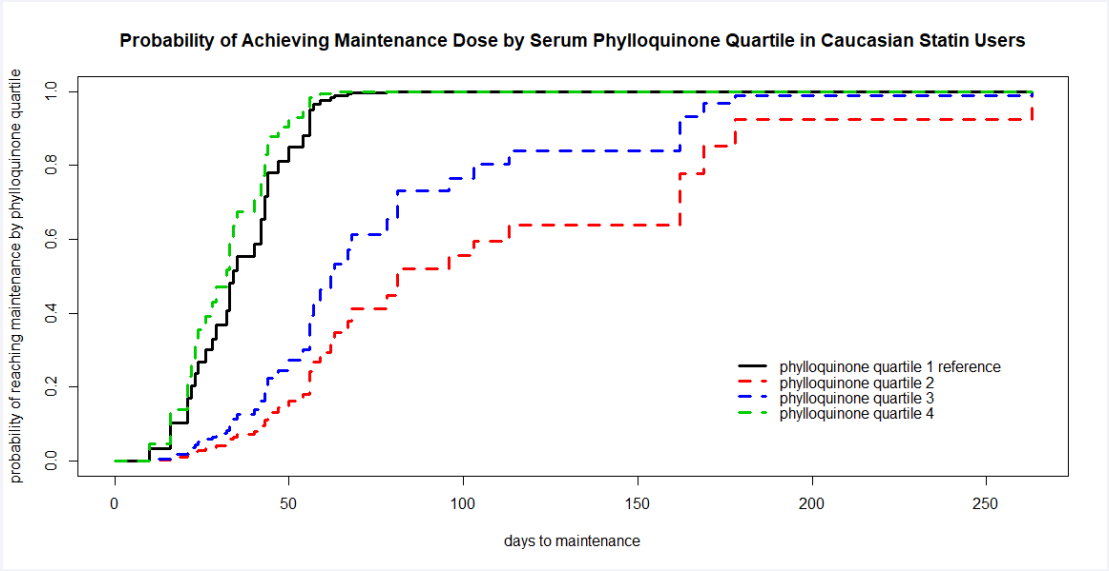

Figure 1 Probability of achieving maintenance dose by serum phylloquinone quartile in Caucasian statin users of the 2009-2013 IN-RANGE II cohort.

were race-specific. Clinic visits were done as per routine clinical care. INR and weekly warfarin dose were recorded. Maintenance dose was ascertained by two consecutive INRs in the therapeutic range, at least a week apart, without a dose change [14].

Of the 687 participants, 471 had data for all primary exposures, outcomes, and covariates, and were included in these analyses. Of these 471, 110 Caucasians and 240 African Americans reached maintenance dose before study completion. Phylloquinone is the primary form of vitamin K in circulation and is used to rank individuals' vitamin K status [19]. Baseline serum phylloquinone was measured using reversed-phase high performance liquid chromatography with post-column, solid phase chemical reduction of phylloquinone to hydroquinone, and fluorometric detection [20]. Serum phylloquinone did not normalize with logarithmic transformation so for statistical analyses, serum phylloquinone was categorized into evenly distributed quartiles (1: phylloquinone< 0.6, 2: 0.6 ≤ phylloquinone ≤ 1.0, 3: 1.0< phylloquinone ≤ 1.7, 4: phylloquinone> 1.7nmol/L). Participants reported statin use at baseline. Multinomial logistic regressions were used to determine if statin use influenced serum phylloquinone. Outcome measures of anticoagulation therapy control, days to maintenance, and PTTR [21], were modeled with Cox proportional hazard and linear regression models, respectively. Primary exposures included serum phylloquinone and statin use. In survival analyses, subjects who did not reach maintenance therapy were censored at their last INR visit. Reasons for censoring include stopping warfarin, loss to follow-up, and maintenance dose not reached before study completion. Covariates in all analyses included age, sex, smoking status (current or non-smoker), body mass index (kg/m^2), study site, and Triglycerides (mmol/L). Triglycerides were log transformed as needed to satisfy assumptions of linearity. Additional adjustments for genotype [CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910), and VKORC1 (rs72547529)] did not substantially alter the results (data not shown). Statistical analyses were performed using R Version 3.2.2. Significance was determined at $p < 0.05$.

RESULTS

The proportion of Caucasians and African Americans in the 471 subjects included in this analysis was similar to that of the entire cohort (p=0.7). All results are reported by race.

Statin use was similar between races (Table 1). Serum phylloquinone (included fasting and non-fasting) ranged from non-detectable to 10.6 nmol/L in Caucasians and non-detectable to 16.7 nmol/L in African Americans. The normal range for fasting serum phylloquinone using this assay is 0.29 – 2.64 nmol/L [22]. The distribution of subjects across serum phylloquinone quartiles is shown in Table 2. In African Americans, statin users were more likely to have high phylloquinone than low phylloquinone (odds ratio (OR) of the highest quartile of serum phylloquinone relative to the lowest quartile: 2.59, 95% confidence interval (CI): 1.16-5.70) (Table 3). In Caucasians, the odds of having a serum phylloquinone in a given quartile did not differ by statin use.

An interaction between serum phylloquinone and statin use was identified in Caucasians (P = 0.02). As reported in Table 4 and depicted in Figure 1, Caucasian statin users with moderate serum phylloquinone took longer to reach maintenance dose. Specifically, those with serum phylloquinone in the second and third quartiles were slower [HR=0.09, (95% CI 0.03-0.35) and HR=0.17 (95% CI 0.05-0.54), respectively] to reach maintenance dose compared to those with serum phylloquinone in the lowest quartile. Days to maintenance did not differ between Caucasian statin users with very low and very high serum phylloquinone and there was no effect of serum phylloquinone on days to maintenance among those not taking statins. In African Americans, serum phylloquinone was not associated with days to maintenance regardless of statin use (P for interaction = 0.91). There was also no influence of serum phylloquinone and statin use for the outcome of PTTR in either race.

Table 1: Demographics of the 2009-2013 IN-RANGE II sample examined for associations of statin use with plasma phylloquinone and anticoagulation.

	Caucasian		p-value[a]	African American		p-value[a]
	Statin Use			Statin Use		
	Yes	No		Yes	No	
	N=60	N=80		N=140	N=191	
	%			%		
Serum Phylloquinone, nmol/L[b]	1.05 (1.10)	1.20 (1.13)	0.12	1.15 (1.33)	1.00 (1.15)	0.01
Age, years			<0.001			<0.001
< 45	3	30		8	35	
45 – 54	10	21		23	19	
55 – 64	38	26		39	30	
65 – 74	25	11		21	10	
≥ 75	23	11		9	6	
Sex, % female	18	50	<0.001	34	45	0.08
Current smoker	13	11	0.91	26	21	0.30
Triglycerides, mmol/L[c]	1.92 (1.12)	1.97 (1.3)	0.58	1.60 (0.96)	1.49 (1.1)	0.32
Body Mass Index, kg/m^2			0.01			0.01
< 25	18	36		19	33	
25 - <30	30	35		30	25	
≥ 30	52	29		51	42	
Statin use, % taking statins	43			42		0.99
Statin Type[d]						0.36
Atorvastatin Calcium	22			15		
Rosuvastatin Calcium	17			12		
Simvastatin	43			56		
Other	18			16		
Study Site			<0.001			<0.001
Hospital of the University of Pennsylvania	15	34		17	28	
Corporal Michael J. Crescenz Veterans Affairs Medical Center	38	51		41	49	
Johns Hopkins Medical Center	47	15		42	23	

[a]Based on independent t-test for continuous outcomes or Chi-square test for categorical outcomes
[b]Comparison was based on Wilcoxon's rank-sum test because the measure did not achieve a normal distribution after in transformation; median and IQR shown in original scale
[c]Mean (standard deviation)
[d]Other includes: Atorvastatin/Amlodopine, Ezetimibe/Simvastatin, Fluvastatin, Lovastatin, Pravastatin, and undefined.

DISCUSSION

Prior to the IN-RANGE study, most investigations of the interaction of phylloquinone and warfarin in large cohorts focused on long-term oral anticoagulant stability and were limited to dietary phylloquinone as a marker of vitamin K status [23,24]. This study offered a unique opportunity to investigate the potential interaction between serum phylloquinone and statin use during the initiation phase, when we predicted an interaction would be observed.

We predicted that those with serum phylloquinone at the highest and lowest quartiles would take longer to achieve maintenance dose because moderate dietary vitamin K has been previously associated with better anticoagulation control [4]. Due to the lipid-lower effect of statins, we presumed that statin use would reduce intra-individual variability in serum phylloquinone and blunt the effect of serum phylloquinone on anticoagulation instability. Our results are not consistent with these hypotheses.

Plasma phylloquinone concentrations reflect the level of

Table 2: Outcome measures of the 2009-2013 IN-RANGE II sample examined for associations of statin use with plasma phylloquinone and anticoagulation.

	Caucasian		p-value[a]	African American		p-value[a]
	Statin Use			Statin Use		
	Yes	No		Yes	No	
	N=60	N=80		N=140	N=191	
	Mean (SD)[b]			Mean (SD)[b]		
Serum Phylloquinone Quartile, nmol/L[c]			0.42			0.06
Phylloquinone < 0.6	0.22 (0.17) 22%	0.24 (0.16) 14%		0.22 (0.17) 21%	0.20 (0.15) 29%	
0.6 ≤ Phylloquinone ≤1	0.78 (0.14) 28%	0.79 (0.13) 23%		0.85 (0.13) 24%	0.80 (0.13) 26%	
1< Phylloquinone ≤1.7	1.4 (0.19) 27%	1.35 (0.23) 34%		1.32 (0.20) 21%	1.35 (0.20) 24%	
Phylloquinone > 1.7	2.63 (0.67) 23%	3.35 (2.02) 30%		3.15 (2.10) 34%	3.70 (3.41) 21%	
Days to Maintenance, days[d]	N=46 63 (51)	N=64 64 (45)	0.91	N=111 80 (80)	N=129 76 (85)	0.68
Percent time in the therapeutic range	40.0 (20.5)	34.7 (17.7)	0.11	39.6 (17.7)	34.4 (19.8)	0.01

[a] Based on independent t-test for continuous outcomes or Chi-square test for categorical outcomes
[b] SD=standard deviation
[c] Mean (SD) followed by percent of subjects per phylloquinone quartile
[d] Includes only those that reached maintenance phase

Table 3: Log odds of serum phylloquinone quartile for the 2009-2013 IN-RANGE II sample examined for associations of statin use with plasma phylloquinone and anticoagulation.

	Caucasians			African Americans		
	0.6≤ Phylloquinone ≤1[a]	1 <Phylloquinone≤ 1.7[a]	1.7 <Phylloquinone[a]	0.6≤ Phylloquinone≤ 1[a]	1 <Phylloquinone≤ 1.7[a]	1.7 <Phylloquinone[a]
	N=35	N=43	N=38	N=82	N=76	N=89
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR(95% CI)	OR (95% CI)
Statin Use	0.61 (0.17, 2.27)	0.60 (6.69, 2.39)	0.66 (0.15, 3.06)	1.49 (0.74, 2.97)	1.19 (0.61, 2.48)	2.59 (1.16, 5.70)
Triglycerides (mmol/L)	1.00 (1.00, 1.01)	1.82 (1.00, 1.03)	1.03 (1.01, 1.04)	1.01 (1.00, 1.01)	1.02 (1.01, 1.02)	1.03 (1.01, 1.03)
Body Mass Index, kg/m^2						
< 25 (reference)	-	-	-	-	-	-
25 - <30	0.95 (0.20, 4.90)	0.55 (0.11, 2.97)	0.45 (0.07, 2.75)	1.35 (0.61, 3.03)	3.25 (1.23, 8.41)	3.82 (1.31, 11.13)
≥ 30	3.10 (0.55, 18.92)	3.06 (0.55, 18.17)	1.68 (0.25, 11.94)	0.89 (0.45, 1.88)	2.64 (1.08, 6.30)	3.60 (1.35, 9.49)
Study Site[c]						
Johns Hopkins Medical Center(reference)	-	-	-	-	-	-
Corporal Michael J. Crescenz Veterans Affairs Medical Center	5.75 (0.17, 5.47)	0.68 (0.06, 1.40)	0.66 (0.10, 3.39)	0.76 (0.37, 1.90)	0.57 (0.37, 2.08)	0.13 (0.14, 0.90)
Hospital of the University of Pennsylvania	0.94 (0.67, 51.94)	0.27 (0.08, 6.11)	0.57 (0.06, 7.85)	0.82 (0.30, 1.95)	0.84 (0.20, 1.67)	0.33 (0.04, 0.45)
Female	1.63 (0.30, 9.03)	5.21 (1.00, 27.94)	5.64 (1.00, 33.45)	1.13 (0.55, 2.44)	1.62 (0.74, 3.63)	0.99 (0.45, 2.36)
Smoking	0.03 (0.00, 0.27)	0.05 (0.01, 0.45)	0.00 (0.00, 0.10)	0.90 (0.45, 1.90)	0.80 (0.37, 1.82)	0.90 (0.37, 2.20)

Age, years						
< 45 (reference)	-	-	-	-	-	-
45 – 54	0.14 (0.01, 1.86)	0.06 (0.00, 0.82)	00.09 (0.01, 1.6)	0.66 (0.25, 1.80)	1.16 (0.41, 3.32)	0.75 (0.25, 2.46)
55 – 64	0.16 (0.01, 1.93)	0.19 (0.02, 2.34)	0.19 (0.01, 2.86)	0.70 (0.30, 1.72)	0.89 (0.33, 2.39)	0.51 (0.18, 1.51)
65 – 74	0.11 (0.01, 1.88)	0.06 (0.00, 1.17)	0.21 (0.01, 4.31)	0.39 (0.12, 1.34)	0.92 (0.27, 3.13)	1.38 (0.41, 4.76)
≥ 75	0.06 (0.00, 1.11)	0.06 (0.00, 1.03)	0.04 (0.00, 0.90)	1.48 (0.41, 5.87)	0.74 (0.14, 4.10)	2.48 (0.55, 11.36)

[a] Quartile reference group: Phylloquinone<0.6nmol/L, (Caucasian N=24, African American N=84

Table 4: Cox proportional hazards associations of plasma phylloquinone with days to maintenance in Caucasians and African Americans in the 2009-2013 IN-RANGE II cohort reported by statin use.

	Caucasians		**African Americans**	
	Statin Use		**Statin Use**	
	Yes	**No**	**Yes**	**No**
	N=60	**N=80**	**N=140**	**N=191**
	Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Serum Phylloquinone Quartile, nmol/L				
Phylloquinone < 0.6 (reference)	-	-	-	-
0.6 ≤ Phylloquinone ≤ 1	0.09 (0.03, 0.35)	1.05 (0.35, 3.17)	1.21 (0.65, 2.23)	1.58 (0.97, 2.57)
1 < Phylloquinone ≤ 1.7	0.17 (0.05, 0.54)	0.68 (0.21, 2.20)	1.07 (0.58, 1.98)	1.61 (0.93, 2.78)
Phylloquinone > 1.7	1.40 (0.41, 4.78)	0.51 (0.15, 1.69)	1.36 (0.72, 2.58)	1.67 (0.90, 3.12)
Triglycerides, mmol/L	0.45 (0.22, 0.91)	1.31 (0.99, 1.73)	1.03 (0.83, 1.26)	1.01 (0.83, 1.21)
Body Mass Index, kg/m				
< 25 (reference)	-	-	-	-
25-<30	4.03 (1.26, 12.85)	1.85 (0.87, 3.91)	1.05 (0.56, 1.97)	0.95 (0.57, 1.59)
≥ 30	1.76 (0.67, 4.59)	1.49 (0.66, 3.35)	1.37 (0.75, 2.48)	1.18 (0.75, 1.85)
Study Site				
Johns Hopkins Medical Center (reference)	-	-	-	-
Corporal Michael J. Crescenz Veterans Affairs Medical Center	2.23(0.73, 6.84)	0.62(0.20, 1.92)	1.26(0.63, 2.52)	1.79(1.01, 3.15)
Hospital of the University of Pennsylvania	1.56 (0.55, 4.46)	1.24 (0.61, 2.48)	3.49 (1.80, 6.77)	1.43 (0.88, 2.26)
Female (male reference)	0.80 (0.26, 2.47)	1.27 (0.65, 2.47)	0.59 (0.35, 1.00)	0.61 (0.39, 0.95)
Current smoker (non-smoker reference)	2.45 (0.57, 10.42)	1.06 (0.31, 3.64)	0.88 (0.55, 1.40)	0.88 (0.55, 1.42)
Age, years				
< 45 (reference)	-	-	-	-
45-54	1.60 (0.20, 12.82)	0.50 (0.21, 1.17)	3.68 (1.25, 10.82)	0.72 (0.41, 1.27)
55-64	0.55 (0.07, 4.09)	1.01 (0.42, 2.43)	4.10 (1.39, 12.08)	1.05 (0.61, 1.81)
65-74	1.27 (0.18, 8.92)	2.03 (0.74, 5.52)	3.27 (1.07, 9.98)	1.13 (0.63, 2.01)
≥ 75	1.77 (0.20, 15.86)	3.10 (1.18, 8.16)	3.90 (1.13, 13.41)	0.92 (0.39, 2.14)

dietary intake and rise and fall with short-term changes in intake [25,26]. Since green vegetables are a major source of dietary phylloquinone [27], we posit that serum phylloquinone fluctuates with vegetable intake. It is plausible that those with consistent high vegetable intake and those who completely avoid vegetables, would have stable serum phylloquinone, at high and low concentrations, respectively. In contrast, those with more sporadic vegetable intake would have moderate, but fluctuating serum phylloquinone. These patients would have more difficulty determining a warfarin dose that consistently results in proper anticoagulation. The reason for these findings in statin users only is not clear.

Since serum phylloquinone was measured at baseline and all subjects were new warfarin patients, INR at time of serum phylloquinone measurement would not yet reflect the effects

of warfarin. In contrast, PTTR represents the percentage of INR measurements within the therapeutic range over the observation period. However, PTTR does not describe how far out of range each measurement was [28]. Therefore, it is possible that the number of days to achieve maintenance dose better captures the degree of variability imparted by statin use and serum phylloquinone during the initiation period. The low PTTRs observed in this cohort are consistent with those seen in new warfarin patients [29].

The study was limited in sample size. Additionally, some blood samples were non-fasting, and diet assessments were not collected for most subjects. Thus, we were unable to determine the influence of the time of previous meal or regular phylloquinone intake. We did, however, adjust for triglyceride levels as this has been shown to correct for the influence of a recent meal on serum phylloquinone [19]. Due to the single measure of vitamin K in this study, it is possible that capturing changes in vitamin K over time could reveal different results. Secondary analyses by statin type were conducted in statin users, but interpretations were limited by sample size.

CONCLUSIONS

Overall, we found that the influence of vitamin K status and statin use on initiation of anticoagulation therapy varies by race. In African Americans, statin use appears to influence serum phylloquinone, but neither statin use nor serum phylloquinone are associated with outcome measures of anticoagulation treatment. In Caucasians, statin use did not influence serum phylloquinone, but the association between serum phylloquinone and days to maintenance differed by statin use. The time to reach maintenance may be prolonged by moderate serum phylloquinone in Caucasian statin users, relative to statin users with low serum phylloquinone. Further examination of statin use in conjunction with dietary and fasted serum phylloquinone during anticoagulation therapy initiation, in larger, multi-racial cohorts are warranted to validate these findings and clarify the clinical relevance.

CONFLICT OF INTEREST

Dr. Kimmel has received research funding from, and served as a consultant to, several pharmaceutical companies, all unrelated to warfarin or vitamin K. All other authors have no conflicts of interest to disclose.

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