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Effect of Left Ventricular Systolic Dysfunction on Response to Warfarin

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Abstract

Candidates for chronic warfarin therapy often have co-morbid conditions, such as heart failure, with reduced left ventricular ejection fraction. Previous reports have demonstrated an increased risk of over-anticoagulation due to reduced warfarin dose requirement in patients with decompensated heart failure. However, the influence of left ventricular systolic dysfunction (LVSD), defined as left ventricular ejection fraction <40%, on warfarin response has not been evaluated. Here, we assess the influence of LVSD on warfarin dose, anticoagulation control (percent time in target range), and risk of over-anticoagulation (international normalized ratio >4) and major hemorrhage. Of the 1,354 patients included in this prospective cohort study, 214 patients (16%) had LVSD. Patients with LVSD required 11% lower warfarin dose compared with those without LVSD ($p < 0.001$) using multivariate linear regression analyses. Using multivariate Cox proportional hazards model, patients with LVSD experienced similar levels of anticoagulation control (percent time in target range: 51% vs 53% $p = 0.15$), risk of over-anticoagulation (international normalized ratio >4; hazard ratio 1.01, 95% confidence interval 0.82 to 1.25; $p = 0.91$), and risk of major hemorrhage (hazard ratio 1.11; 95% confidence interval 0.70 to 1.74; $p = 0.66$). Addition of LVSD variable in the model increased the variability explained from 35% to 36% for warfarin dose prediction. In conclusion, our results demonstrate that patients with LVSD require lower doses of warfarin. Whether warfarin dosing algorithms incorporating LVSD in determining initial doses improves outcomes needs to be evaluated.

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Disclosures

The authors have no conflicts of interest to disclose.

Warfarin has been the mainstay of oral anticoagulant therapy since the 1950s.¹ Despite extensive experience with its use, patients remain in the therapeutic range only half of the time.² Whereas subtherapeutic anticoagulation leads to inadequate protection, supratherapeutic anticoagulation can lead to life-threatening bleeding. This significant variability in dose requirements suggests an unmet need for identifying the clinical and genetic predictors of warfarin dose-response in individual patients.^{3–5} Previous studies have identified gender, age, smoking, co-morbid conditions (e.g., chronic kidney disease [CKD]) and the use of concomitant drugs (e.g., amiodarone) as influential clinical predictors, and variation in cytochrome P4502C9 (*CYP2C9*; the principal metabolic pathway for warfarin) and vitamin K epoxide reductase complex 1 (*VKORC1*; the target protein inhibited by warfarin) as important genetic predictors.^{3,4} Although, these efforts have improved the prediction of warfarin dose requirements, a significant proportion (40% to 60%) of dose variation remains unexplained.⁵ Previous studies have suggested that patients with decompensated heart failure (HF)⁶ require lower dose of warfarin. However, the influence of left ventricular systolic dysfunction (LVSD) on warfarin dose requirement, anticoagulation control, and over-anticoagulation and bleeding risk have not been systematically evaluated. Here, we assess the influence of LVSD on warfarin dose, anticoagulation control as measured by percent time in target range (PTTR), risk of excessive anticoagulation, and risk of major hemorrhage while accounting for the known clinical and genetic predictors of warfarin response.

Methods

The prospective Warfarin Pharmacogenetics Cohort recruited patients 20 years initiating warfarin therapy with a target international normalized ratio (INR) of 2 to 3 and managed at an anticoagulation clinic under the approval of the Institutional Review Board at the University of Alabama at Birmingham and at Emory University.

Participants were enrolled at the initiation of warfarin therapy and followed up for up to 2 years or for the duration of therapy if <2 years (e.g., for venous thromboembolism). At enrollment, a detailed history was obtained including self-reported race, education, income, medical insurance, height and weight, blood urea nitrogen, serum creatinine, hemoglobin and hematocrit, indication for warfarin therapy, co-morbid conditions, medications, smoking status, alcohol use, and vitamin K intake (number of servings of foods rich in vitamin K consumed per week) as detailed in previous publications.^{7–10}

In addition to *VKORC1* (rs9923231), and *CYP2C9* (*2 [rs1799853], *3 [rs1057910], *5 [rs28371686], *6 [rs9332131], and *11 [rs28371685]), we also assessed *CYP4F2* (rs2108622), and the *CYP2C* single-nucleotide polymorphism rs12777823 as reported.^{9,11}

LVSD was defined as left ventricular ejection fraction (LVEF <40%) by echocardiography.¹² LVEF was missing in 9.6% of the patients (143 of 1,497), and therefore, these patients were not included in the analysis. Kidney function was assessed using the estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease Study equation. Patients were categorized into 3 groups: (1) reference group (normal, stage 1 CKD, or stage 2 CKD), (2) stage 3 CKD, and (3) stage 4 or 5 CKD.

Warfarin dose (mg/day; log transformed to attain normality of residuals) was calculated as the average dose required for maintenance of therapeutic anticoagulation. Proportion of PTTR was estimated for each patient using the Rosendaal linear interpolation method.¹³ This method assumes that a linear relation exists between 2 consecutively measured INR values and allows one to allocate a specific INR value to each day for each patient. Time in target range for each patient was assessed by the percentage of interpolated INR values within the target range of 2.0 to 3.0 after attainment of first INR in target range. Over-anticoagulation was defined as INR >4.

Hemorrhagic complications were classified as reported by Schulman et al.¹⁴ Major hemorrhage events included serious, life-threatening, and fatal bleeding episodes. During the follow-up, all major hemorrhagic complications were captured and verified through review of admissions and emergency department visits. The Alabama Center for Health Statistics was queried to verify cause of death for all deceased to ensure inclusion of deaths due to hemorrhagic complications. All complications were adjudicated independently by the Medical Director of the Anticoagulation Clinic. Only adjudicated events were included in the analyses.

ANOVA was used to assess group differences for continuous variables and the chi-square test of independence for categorical variables. The Hardy-Weinberg equilibrium assumption was tested using the chi-square test. Multivariable linear regression analysis was performed to evaluate the association between the LVSD on warfarin dose after accounting for sociodemographic (age, race, body mass index), lifestyle (vitamin K and alcohol intake), clinical factors (co-morbid conditions, e.g., atrial fibrillation and diabetes mellitus), concurrent medications (e.g., amiodarone, statins), and genetic factors (*CYP2C9*, and *VKORC1*, *CYP4F2*, and rs12777823).

To assess the relation between LVSD with over-anticoagulation (INR >4) and risk of major hemorrhagic events, we used the Cox proportional hazards (PH) model with the counting process format. Robust variance estimation was used to correct for the dependence among multiple events per subject and provide 95% confidence intervals (CIs) for the hazard ratios (HRs) of interest.¹⁵ There were no departures from the PH assumption as assessed by evaluating interactions of the predictors and a function of survival time.

We also assessed the influence of LVSD on risk of hemorrhage after adjustment for bleeding risk as assessed by the HAS-BLED score.¹⁶ The score assigns 1 point each to hypertension, abnormal renal (defined as GFR <30 ml/min) and/or liver function, stroke, bleeding history or predisposition, labile INR (defined as PTTR <60%), old age (>65 years), and drug (antiplatelet agent) or alcohol use. Both the cumulative score and the individual component risk factors were evaluated.

All analyses were performed using backward stepwise regression with the full model with exclusion set at $p = 0.2$. All analyses were performed using SAS, version 9.3, at a non-directional alpha level of 0.05.

Results

The study population included 1,354 patients who received warfarin for therapeutic anticoagulation and were followed for 1.4 ± 0.9 years (Table 1). Among the study population, 16% of the patients had LVSD, defined as LVEF $<40\%$. Indications for anticoagulant therapy in patients with LVSD more commonly included atrial fibrillation, myocardial infarction, or other cardiac-related outcomes/procedures. Patients with LVSD were more likely to be men, and African-American, with higher prevalence of hyperlipidemia, coronary artery disease, chronic kidney disease, and use of statin, antiplatelet, or amiodarone therapy. Possession of variants known to influence warfarin response did not differ by LVEF categories, and their distribution was observed to be in Hardy-Weinberg equilibrium (all p values >0.15).

Patients with LVSD had a lower warfarin dose requirements compared with those without LVSD (4.9 and 5.7 mg/day, respectively, $p < 0.001$). Using backward stepwise linear regression, the variables that were retained in the final model are listed in Table 2. On multivariate adjustment for the earlier mentioned variables, LVSD was independently and significantly associated with lower warfarin dose requirements. LVSD was associated with 11% lower warfarin dose, compared with those without LVSD (Table 2, Figure 1). Addition of LVSD variable in the model increased the variability explained from 35% to 36% for warfarin dose prediction.

LVSD did not significantly influence anticoagulation control. PTTR was similar in patients with and without LVSD (51% vs 53%; Figure 2). This finding remained unchanged after accounting for clinical and genetic factors known to influence anticoagulation control. After accounting for known predictors of anticoagulation control, age ($p < 0.001$), race ($p = 0.03$), current smoking ($p = 0.002$), atrial fibrillation ($p = 0.001$), chronic kidney disease ($p < 0.001$), concurrent statin use ($p = 0.02$), and antiplatelet therapy ($p = 0.05$) were significantly associated with anticoagulation control and body mass index ($p = 0.09$) and diabetes mellitus ($p = 0.08$) were marginally significantly associated with anticoagulation control.

Similarly, patients with LVSD were not at an increased risk for over-anticoagulation (INR >4 ; HR 0.98, 95% CI 0.81 to 1.18; $p = 0.82$). This association remained unchanged even after accounting for clinical, demographic, and genetic factors (HR 1.01, 95% CI 0.82 to 1.25; $p = 0.91$). After accounting for known predictors of over-anticoagulation, race ($p = 0.004$), chronic kidney disease ($p < 0.001$), antiplatelet therapy ($p < 0.001$), and *CYP2C9* variant status ($p = 0.02$) were associated with higher risk of over-anticoagulation, whereas atrial fibrillation ($p = 0.02$) was significantly associated with lower risk of over-anticoagulation. Gender ($p = 0.08$) and *VKORC1* variant status ($p = 0.06$) were marginally significantly associated with higher risk of over-anticoagulation.

A total of 162 major hemorrhagic events were encountered over 1,889 person-years (p-yrs.) of follow-up (incidence 8.6/100 p-yrs.; 95% CI 7.3 to 9.9/100 p-yrs.). The incidence of hemorrhage was similar among patients with LVSD compared with those without (9.3/100 p-yrs. vs 8.4/100 p-yrs.; incidence rate ratio = 1.10; 95% CI 0.72 to 1.64; $p = 0.63$).

After accounting for clinical and genetic factors, compared with those without LVSD, patients with LVSD were not at an increased risk for major hemorrhage (HR 1.11; 95% CI 0.70 to 1.74; $p = 0.66$).

We accounted for factors known to be associated with risk of hemorrhage. As both anticoagulation control (PTTR) and over-anticoagulation (INR >4) are associated with increased risk, we categorized anticoagulation control ($<60\%$ vs 60%) for the analysis. History of hemorrhage ($p < 0.001$), poor anticoagulation control (PTTR $<60\%$; $p = 0.007$), and INR >4 at the time of the event ($p < 0.001$) were associated with an increased risk of hemorrhage. Hypertension ($p = 0.08$) and concurrent antiplatelet use ($p = 0.07$) were marginally significantly associated with higher risk of hemorrhage.

Discussion

Our study demonstrates that patients with LVSD have reduced warfarin dose requirements. There are a few small studies that have assessed the association of HF on warfarin dose, but most of them have not adjusted for genetic markers or used LVEF to define systolic dysfunction.^{6,17} Lee et al¹⁷ showed that in 63 Chinese patients, presence of HF was associated with lower warfarin dose requirement ($p = 0.02$). In our study, we have shown that presence of LVSD, as opposed to a history of HF, is associated with an 11% lower warfarin dose requirement after accounting for genetic variants known to influence warfarin dose. Future studies are required to assess the association of different stages of HF with warfarin dose as advanced HF may have more robust effects on warfarin dose.

In a related retrospective study of predictors of warfarin dose, Oates et al¹⁸ found that presence of right-sided HF predicted lower warfarin dose. Although the investigators did not study left-sided HF, the most common cause of right-sided HF is left-sided HF. Thus, the findings of Oates et al are also consistent with our findings of an association between lower dose requirements of warfarin and LVSD. Unfortunately, there are no studies till date that have evaluated the effect of RV systolic dysfunction on warfarin dose, independent of LVSD.

Several mechanisms can explain the reduced warfarin dose in patients with HF. Previous studies have shown that reduced vitamin K intake leads to an exaggerated response to warfarin.¹⁹ This finding was confirmed in our study where we found that reduced vitamin K intake had an independent association with warfarin dose. Patients with LVSD have poor oral intake, and congestion of GI tract may lead to reduced absorption of drugs and nutrients.²⁰ In our study, we found no difference in vitamin K intake between patients with and without LVSD. However, we cannot exclude the possibility of unreported differences in vitamin K intake between the 2 populations.

Another possible mechanism is the presence of ischemic liver and/or congestive hepatopathy. As liver is the site of synthesis of clotting factors and INR is elevated in chronic liver disease, it is plausible that reduced warfarin dose requirement in patients with HF could be because of chronic liver disease.⁶ Hylek et al²¹ studied predictors of INR >4 2 days after stopping warfarin in patients who were over-anticoagulated (INR >6). The authors

found that patients who had decompensated HF had a higher propensity of having INR >4 even after holding 2 doses of warfarin.²¹ This suggests that decompensated HF lowers the clearance of warfarin resulting in lower warfarin dose requirement and for an equivalent dose, over-anticoagulation. Unfortunately, we did not have information on the hepatic panel of the study patients to identify whether the hepatic component of the cardio-hepatic syndrome was an independent predictor of warfarin dose.

Among the models that incorporate clinical and genetic factors to predict warfarin doses, the algorithm proposed by Gage et al⁵ is widely used. However, this model explained only 30% of the variance in our cohort of patients (data not shown). Our study has identified many nongenetic variables, including LVSD, that were not used to build previous predictive models. We suggest that using multiple variables, including LVSD, in prediction modeling can increase generalizability, as it will be applicable to a larger variety of patient populations. Our findings are supported by the recent report from the Clarification of Anticoagulation through Genetics trial where dosing was determined using the algorithm proposed by Gage et al. Patients with HF were more 2 times more ($p < 0.01$) likely to require doses that were significantly different than that predicted by the algorithm.²²

To our knowledge, this is the first report to assess the influence of LVSD on PTTR, risk of over-anticoagulation, and risk of hemorrhage. There are limited studies that have evaluated the association of LVSD with anticoagulation control and hemorrhage. In a study of 172 hospitalized patients, Doecke et al⁶ compared empirical titration of warfarin dose with a protocol-driven titration of dose, for a period of 4 weeks. They reported that patients who were elderly or had any of the complicating factors, for example interfering drugs, stable or unstable HF, or history of chronic alcohol abuse, had an increased risk of over-anticoagulation.⁶ In a small retrospective review of over-anticoagulated patients, defined as INR ≥ 6 , Brigden et al²³ found that 28% of the 65 patients with high INR had HF. PTTR is a strong inverse predictor of hemorrhage, with studies consistently showing that higher PTTR ($\geq 60\%$) is associated with lower risk of hemorrhage.¹⁶ Because PTTR is a summary measure of anticoagulation intensity over time, it does not capture the short-term risks associated with over-anticoagulation (INR >4). Therefore, in assessing the risk of hemorrhage, we accounted for both PTTR to capture anticoagulation control and INR at the time of the event to capture the heightened risk associated with over-anticoagulation. After accounting for PTTR, INR at the time of the event, and clinical and genetic factors that have been associated with increased risk of hemorrhage, the risk of hemorrhage was similar in patients with LVSD and those without.

We considered all the important variables that have been previously shown to influence warfarin dose and performed comprehensive statistical analyses to evaluate all the important clinical and genetic predictors of warfarin response. However, we recognize that there may be unmeasured variables (e.g., hepatic function) that influence the results. Moreover, although we show an association between the presence of LVSD and reduced warfarin dose, we cannot elucidate the mechanistic pathways that underpin this finding.

Our results demonstrate that patients with LVSD require lower doses of warfarin. Whether warfarin dosing algorithms incorporating LVSD in determining initial doses improves

outcomes needs to be evaluated. We show that the risk of over-anticoagulation was not different in patients with LVSD, and those with LVSD are not at an increased risk of major hemorrhage. Provision of monitoring through anticoagulation management services may explain these findings.

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Figure 1.
Forest plot of significant predictors of warfarin dose.

Figure 2.

Bar diagram comparing the percentage time patients were (A) subtherapeutic, (B) therapeutic, and (C) supratherapeutic, in subgroups of patients with and without LVSD.

Table 1

Baseline characteristics in patients with and without left ventricular systolic dysfunction (LVSD)

Variables	LVSD		<i>P value</i>
	Absent (n = 1140)	Present (n = 214)	
	Mean $\pm$ SD	Mean $\pm$ SD	
Follow-up (years)	1.4 $\pm$ 0.9	1.4 $\pm$ 0.9	0.85
Visits/person/month	2.2 $\pm$ 1.6	2.3 $\pm$ 2.0	0.49
Age (years)	61 $\pm$ 16	61 $\pm$ 16	0.79
Hematocrit (%)	37 $\pm$ 6.8	39 $\pm$ 6.4	<0.001
Body mass index (kg/m ²)	31 $\pm$ 7.9	29 $\pm$ 6.2	0.001
Average vitamin K intake	2.1 $\pm$ 1.8	1.8 $\pm$ 1.3	0.08
	N (%)	N (%)	
Female	595 (52%)	58 (27%)	<0.001
Race			
European American	655 (58%)	106 (50%)	0.03
African American	485 (43%)	108 (51%)	
Current alcohol use	326 (28%)	67 (31%)	0.42
Current smoker	134 (12%)	31 (15%)	0.26
Indication for warfarin therapy			
Venous thromboembolism	521 (46%)	30 (14%)	<0.001
Stroke / Transient Ischemic Attack	57 (5.0%)	16 (7.5%)	0.14
Atrial Fibrillation	483 (42%)	109 (51%)	0.02
Myocardial infarction	12 (1.1%)	10 (4.7%)	<0.001
Peripheral arterial disease	15 (1.3%)	1 (0.5%)	0.29
Other	51 (4.5%)	48 (22%)	<0.001
Hypertension	777 (69%)	149 (70%)	0.78
Hyperlipidemia	551 (49%)	121 (57%)	0.03
Diabetes mellitus	362 (32%)	75 (35%)	0.38
Coronary artery disease	328 (29%)	108 (51%)	<0.001
Chronic Kidney disease			
Stage 2	719 (63%)	110 (52%)	0.005
Stage 3	308 (27%)	79 (37%)	
Stage 4	108 (10%)	24 (11%)	
Concurrent medications			
Statins*	617 (54%)	150 (70%)	<0.001
Anti-platelets [†]	689 (61%)	161 (76%)	<0.001
Amiodarone	109 (10%)	41 (19%)	<0.001
Percent patients possessing > 1 minor allele ^{‡,§}			

<i>CYP2C9</i> variant [¶]	238 (25%)	40 (21%)	0.37
<i>VKORC1</i> variant ^{//}	425 (43%)	77 (41%)	0.64
<i>CYP4F2</i> variant [#]	356 (38%)	63 (35%)	0.45
<i>rs12777823</i> ^{**}	336 (36%)	67 (37%)	0.69

Vitamin K intake presented as the average number of servings of foods rich in vitamin K consumed per week.

* Statins included any of the HMG-CoA reductase inhibitors.

[†] Antiplatelet agents included aspirin, clopidogrel, and dipyridamole as mono or dual therapy.

[‡] *CYP2C9*, and *VKORC1*, *CYP4F2*, and *rs12777823* were categorized as 0 if no variants and 1 if heterozygous or homozygous for the variant allele. *CYP2C9* *2, *3, *5, *6, and *11 were combined together to create a single *CYP2C9* variable.

[§] Genotyping not completed at the time of analysis and therefore genotype information is not available in 194 patients for

[¶] *CYP2C9*, 167 patients for

^{//} *VKORC1* (*rs9923231* “T” allele); 225 patients for

[#] *CYP4F2* (*rs2108622*; “A” allele) and 226 patients for

^{**} *rs12777823* (“A” allele).

Table 2

Significant predictors of warfarin dose based on linear regression

Variable	Effect on Warfarin Dose (95% CI)		
	Beta coefficient	% Dose Change	p value
Reference *	2.24		
Left Ventricular Systolic Dysfunction	-0.165	-15 (-21 to -9)	<0.001
Female	-0.136	-13 (-17 to -8)	<0.001
Alcohol use	0.066	7 (1 to 13)	0.02
Diabetes mellitus	0.059	6 (1 to 12)	0.03
Chronic Kidney Disease	-0.069	-7 (-10 to -3)	<0.001
Statin use	-0.051	-5 (-10 to 0.1)	0.05
Amiodarone use	-0.208	-19 (-25 to -12)	<0.001
<i>CYP2C9</i> variant	-0.275	-24 (-28 to -20)	<0.001
<i>VKORC1</i> variant	-0.311	-27 (-30 to -23)	<0.001
rs12777823 variant	-0.075	-7 (-12 to -3)	0.003
Age (per 10 years)	-0.067	-6 (-8 to -5)	<0.001
Body Mass Index (every 5 units)	0.056	6 (4 to 8)	<0.001

* The reference is a male without left ventricular systolic dysfunction, not consuming alcohol, without chronic kidney disease or diabetes mellitus, not using statins or amiodarone and having wild-type genotype for *CYP2C9*, *VKORC1*, and *rs12777823*.