Published in final edited form as:

Pharmacotherapy. 2014 June ; 34(6): 545–554.

Influence of Regular Physical Activity on Warfarin Dose and Risk of Hemorrhagic Complications:

Physical Activity and Warfarin Response

Aditi Shendre¹, T. Mark Beasley², Todd M. Brown³, Charles E. Hill⁴, Donna K. Arnett¹, and Nita A. Limdi^{1,5,*}

¹Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama

²Department of Biostatistics, Section on Statistical Genetics, University of Alabama at Birmingham, Birmingham, Alabama

³Division of Cardiovascular Diseases, University of Alabama at Birmingham, Birmingham, Alabama

⁴Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia

⁵Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama

Summary

Objective—To determine the influence of regular physical activity on stable warfarin dose and risk of major hemorrhage in patients on chronic anticoagulation therapy.

Design, setting and participants—Regular physical activity (maintained over >80% of visits) was ascertained by self-report at initiation of warfarin therapy (target INR = 2–3) in 1272 patients, with changes documented at monthly anticoagulation clinic visits in a population-based prospective cohort. Multi-variable linear regression and survival analysis, respectively, were used to assess influence on warfarin and risk of hemorrhage.

Outcomes—Warfarin dose (mg/day) and major hemorrhage.

Results—There were 683 (53.7%) patients who were regularly physically active (≥ 30 minutes 3 times/week). Physically active patients required warfarin doses that were 6.9% higher (p=0.006) than in physically inactive patients after controlling for sociodemographic factors, vitamin K intake, clinical factors, and genetic variations.

The overall incidence of major hemorrhagic events was 7.6/100 person-years (p-yrs) (95% CI: 6.4–8.9) in our population. The incidence was lower for physically active patients (5.6/100p-yrs; 95% CI: 4.2–7.2) than in inactive patients (10.3/100 p-yrs; 95% CI: 8.2–12.9; p=0.0004). Active

*Corresponding Author: Nita A. Limdi, Department of Neurology, University of Alabama at Birmingham, 1235 Jefferson Tower, 625 19th Street South, Birmingham AL 35294-0021, nlimdi@uab.edu Phone: (205) 934-4385 Fax: (205) 996-9912.

Financial Disclosures: None reported.

Conflict of Interest: None reported.

patients had a 38% lower risk of hemorrhage (HR: 0.62; 95% CI: 0.42–0.98; $p=0.03$) compared to inactive patients.

Conclusions—Regular physical activity is associated with higher warfarin dose requirements and lower risk of hemorrhage. The influence of physical activity on drug response needs to be further explored, and the mechanisms through which it exerts these effects need to be elucidated.

Keywords

Physical activity; warfarin; dose; bleeding risk; major hemorrhage

Introduction

Physical inactivity shortens life expectancy and increases the risk of hypertension, coronary heart disease, stroke, diabetes mellitus, depression, and breast and colon cancers.^{1–3} Despite recognition of the substantial health benefits of physical activity and recommendations from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA),⁴ sedentary behaviors are common in the US and globally.^{5, 6} Physical inactivity is estimated to account for 6–10% of the burden of major non-communicable diseases worldwide (6–12% in the United States). A study determined the effects of physical inactivity on burden of disease and life expectancy, by country, and reported that increasing physical activity could prevent 5.3 million deaths annually and extend life expectancy by an average of 0.68 years.⁶ The impact of physical inactivity on public health is substantial and far reaching.⁷

Beyond the beneficial effects of physical activity on health, there is increasing recognition of its effects on disease states and drug response. Physical activity is associated with a significant inverse relation to salt sensitivity in patients with hypertension⁸ and has a significant and independent effect on reducing mortality in patients with dyslipidemia treated with statins.⁹ These data suggest an additive benefit of physical activity in attenuating cardiovascular risk and mortality for patients receiving drug therapy for chronic conditions.^{8–11} Although another study reported that increased physical activity (rehabilitation therapy) in four warfarin-treated patients resulted in sub-therapeutic International Normalized Ratio (INR) levels,¹² the influence of physical activity on warfarin dose requirements and bleeding risk is largely unknown. Herein we report the influence of regular physical activity on warfarin dose and risk of major hemorrhage in 1272 patients from a prospective inception cohort of warfarin users.

Methods

Data were derived from two on-going prospective inception warfarin pharmacogenetics cohort studies. The objectives of the Pharmacogenetic Optimization of Anticoagulation Therapy (POAT) and the Genetic and Environmental Determinants of Warfarin (GEDWR) studies are to determine the effects of disease state and comorbidities, genetics, and lifestyle on warfarin response. Patients older than 20 years of age were eligible if warfarin therapy was prescribed with a target INR range of 2–3 for a duration of >6 months and was managed at the anticoagulation clinic. The study was approved by the Institutional Review Boards of

the University of Alabama at Birmingham, Emory University, and Jefferson County Health System.

Patients were enrolled and followed from initiation of warfarin therapy. A detailed history documented information about self-reported race, demographics, education, income, medical insurance, height and weight, blood urea nitrogen, serum creatinine, hemoglobin and hematocrit, indication for therapy, co-morbid conditions, medications, smoking status, dietary vitamin K (number of servings of foods rich in vitamin K consumed per week)¹³ alcohol intake (number of alcoholic drinks per week) as detailed in recent publications.^{14–17} Patients were followed monthly for up to 2 years. The INR and factors influencing warfarin response were recorded at each visit, including warfarin dose, concurrent medications, level of physical activity, dietary vitamin K intake,¹³ alcohol intake, and adherence. Changes in concomitant medications that influence warfarin pharmacodynamics (e.g. antiplatelet agents) or pharmacokinetics (e.g. cytochrome p450 2C9 [*CYP2C9*] inhibitors [e.g. amiodarone] and *CYP2C9* inducers [e.g. rifampin])^{18, 19} were documented at each visit and verified through medical record review and pharmacy refill records.

Patient self-reported physical activity was defined as regular exercise (>80% of the visits) for 30 minutes at least three times a week. Activities considered to be moderate to vigorous exercise as defined by the ACSM and AHA guidelines^{4, 20} included brisk walking, swimming, jogging/running, heavy gardening, lawn mowing, basketball, and tennis.

Pharmacogenetic studies have identified several genes that influence warfarin response.^{21–29} The bulk of evidence supports the influence of polymorphisms in two genes, *CYP2C9* (the principal enzyme that metabolizes warfarin) and vitamin K epoxide reductase complex 1 (*VKORC1*, the target protein inhibited by warfarin).^{15, 16, 30–37} For this study *CYP2C9*, *CYP4F2*, and *VKORC1* genotypes were assessed using DNA extracted from whole blood as detailed in recent publications.^{16, 17} Genotypes were categorized as variant (one or both variant alleles) or homozygous wild-type.

The warfarin dose in mg/day, log-transformed to attain normality of residuals, was calculated as the average dose required to maintain therapeutic anticoagulation. The proportion of time spent in target range (PTTR) was estimated using the Rosendaal linear interpolation method.³⁸ The time in target range was defined as the percentage of interpolated INR values within the target range of 2.0–3.0 after attainment of first INR in target range (INR of 2.0–3.0).

Hemorrhagic events were classified as reported by Fihn and colleagues.³⁹ Major hemorrhages included serious, life threatening, and fatal bleeding episodes. At the time of the major hemorrhagic event, the complication site (e.g. gastrointestinal endoscopy), severity of the event (e.g. requiring transfusion, surgical intervention), and laboratory findings (INR, hemoglobin/hematocrit) were documented. Isolated sub-therapeutic or supra-therapeutic INRs in the absence of evidence of bleeding were not classified as major bleeding events.

During follow-up, all major hemorrhagic events were captured and verified through review of admission and emergency department records, and minor hemorrhages were documented

by patient self-report. Only medically documented events were included in the analyses. On-study deaths were verified by the Alabama Centre for Health Statistics to ensure inclusion of deaths due to major hemorrhagic events. All complications were documented by the study nurse, confirmed by the principal investigator, and reviewed independently by the Medical Director of the Anticoagulation Clinic.

Statistical Methods: Analysis of variance was used to assess group differences for continuous variables and χ^2 test of independence for categorical variables. The association between level of physical activity and warfarin dose and risk of major hemorrhage was evaluated using bivariate and multivariable regression analyses.

Multivariable linear regression analysis evaluated the influence of physical activity on warfarin dose after accounting for demographic (age, race, gender, body mass index [BMI]), lifestyle (vitamin K and alcohol intake), clinical factors (comorbid conditions including congestive heart failure [left ventricular ejection fraction <55%]) kidney impairment, based on the National Kidney Foundation staging using the Modification of Diet in Renal Disease Study equation and categorized on estimated glomerular filtration rate (eGFR) >60, 30–59, <30mL/min/1.73 m²,⁴⁰ concurrent amiodarone therapy, and genetic (CYP2C9, CYP4F2 and VKORC1) factors.

Incidence rates of hemorrhage and confidence intervals were calculated using OpenEpi version 2.3.1.⁴¹ Cox proportional hazards (PH) regression with the counting process format to account for individuals with more than one event was used to assess the influence of physical activity on risk of major hemorrhagic events.^{42, 43} Robust variance estimation corrected for the dependence among multiple events per individual and provided 95% confidence intervals (CIs) for the hazard ratios (HRs) of interest. Departures from the PH assumption were assessed by evaluating interactions between predictors and survival time.

To understand the influence of physical activity on risk of major hemorrhage, bleeding risk was assessed with the HAS-BLED score.⁴⁴ The HAS-BLED score assigns 1 point each to hypertension, abnormal renal (GFR<30ml/min) and/or liver function, stroke, bleeding history or predisposition, labile INR (PTTR <60%), old age (>65 years), and drug (antiplatelet agent) or alcohol use. The HAS-BLED scores were grouped as <3 (reference group) or ≥3, based on the incidence of hemorrhage in patients with varying HAS-BLED scores in our cohort (eTable 1), which was concordant with prior literature.⁴⁵ The unadjusted model was then further adjusted for the HAS-BLED score and sequentially adjusted for demographic, clinical factors, genetic factors and INR at the time of the event. Model 1 included physical activity and HAS-BLED score. Model 2 included model 1 factors and gender, race (black vs. others), number of risk factors/comorbid conditions; chronic kidney disease, and concurrent amiodarone use. Model 3 also included genetic variants for CYP2C9, VKORC1 and CYP4F2, and finally model 4 also adjusted for over-anticoagulation categorized as INR ≤4 (reference group) and INR >4 at the time of the event.

The risk-adjusted association of physical activity with hemorrhage was evaluated with the Outpatient Bleeding Risk Index (OBRI).⁴⁶ Based on the incidence of major hemorrhage by OBRI score (eTable 2), the association of physical activity with major hemorrhage using

OBRI score ≥ 3 (high risk) versus <3 (reference) was also evaluated. Potential risk factors not included in the OBRI score, such as race, gender, BMI, moderate chronic kidney disease (CKD; GFR 30–45), concurrent antiplatelet therapy, and genetic variations, were also included in the model. Factors known to influence or alter physical activity levels (e.g. age, BMI, race, education, and level of comorbidity) were evaluated to determine if the risk of hemorrhage was modified by interaction effects of these factors with physical activity. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) at a non-directional α (significance level) of 0.05.

Results

A total of 1276 patients were enrolled, and four were excluded because their level of physical activity was not documented. Of the 1272 patients, 683 (53.7%) exercised regularly for ≥ 30 min ≥ 3 times per week and were considered physically active. The remaining 589 (46.3%) patients were considered inactive. Physically active patients were younger, had lower BMI, accrued a longer follow-up, were more likely to be male and European American with health insurance and higher levels of education and income compared with inactive patients (Table 1). Patients in the physically active group had fewer comorbidities, including chronic kidney disease, had a lower risk score for bleeding, and were more likely than inactive patients to be on concurrent statin therapy. Genotypic frequencies for the *CYP2C9* and *VKORC1* variants were similar in the two groups, whereas physically active patients were more likely to have the *CYP4F2* variant.

Compared with physically inactive patients, active patients required a 6.9% higher warfarin dose after adjusting for demographic, clinical, and genetic factors ($p=0.006$). Age, gender, BMI, left ventricular ejection fraction (LVEF) $<55\%$, poor kidney function, concurrent amiodarone use, and the *CYP2C9*, *VKORC1*, and *CYP4F2* variants were significantly associated with warfarin dose (Table 2). Neither primary indication for therapy ($p=0.15$) nor concomitant statin use ($p=0.56$) was significantly associated with dose; both were excluded from the final model. After accounting for demographic, clinical, and genetic factors, there was no difference in PTTR (50% vs. 48%; $p=0.13$) or the percent time below (34.3% vs. 35.5%; $p=0.49$) or above range (15.5 vs. 16.6%; $p=0.29$) for active versus inactive patients. However, physically active patients had fewer clinic visits than inactive patients (1.9 vs. 2.5 INR assessments/patient/ month, respectively; $p<0.0001$).

There were 137 major hemorrhagic events over 1801 person-years (p-yrs) of follow-up (incidence 7.6/100 p-yrs; 95% CI: 6.4 – 8.9 per 100 p-yrs). Gastrointestinal hemorrhage was most common ($n=84$), followed by hematoma ($n=26$), genitourinary hemorrhage ($n=12$), intracranial hemorrhage ($n=9$), and hemoptysis ($n=6$). Patients experiencing a major hemorrhage were more likely to be older, physically inactive, and have less than a high school education (Table 3). Approximately 30% of patients with a major hemorrhage had chronic kidney disease with an eGFR <45 ml/min/m² and were at a significantly higher risk of bleeding as assessed by the HAS-BLED and the OBRI scores. Patients with a major hemorrhage were more likely to be on antiplatelet therapy, have a longer duration of time above the target INR range (19% vs. 15%, $p=0.002$), and a marginally shorter time within target INR range (46% vs. 49%; $p=0.07$) compared to patients without a major hemorrhage.

Physically active patients experienced 58 major hemorrhagic events over 1037 p-yrs of follow-up (incidence 5.6/100 p-yrs; 95% CI: 4.2 – 7.2 per 100 p-yrs). In contrast, the physically inactive patients encountered 79 major hemorrhagic events over 764 p-yrs (incidence 10.3/100 p-yrs; 95% CI: 8.2 – 12.9 per 100 p-yrs). The incidence rate ratio for major hemorrhage was 1.8 fold higher among physically inactive patients (95% CI 1.3 – 2.6; $p=0.0004$).

After accounting for clinical features, genetic variants, and the HAS-BLED score and INR at the time of the event, physically active patients had a lower risk of major hemorrhage (HR: 0.62, 95% CI: 0.40 to 0.96 $p=0.03$, Table 4) than inactive patients. Results were similar when risk of hemorrhage was assessed with the OBRI instead of the HAS-BLED score (eTable 3).

The association between physical activity and hemorrhage was not influenced by age (<50, 50–65, >65 years, $p=0.51$), race (African Americans vs. European Americans, $p=0.54$), education (high school or less vs. any college, $p=0.58$), or BMI (< 20, 20–24.9, 25–29.9, 30–39.9, 40, $p=0.69$). Similarly, the association of physical activity and hemorrhage was not modified by the level of comorbidity (<3 vs. ≥ 3 comorbid conditions; $p=0.76$) or bleeding risk as measured by the HAS-BLED (≥ 3 vs. <3, $p=0.32$) or OBRI scores (≥ 3 vs. <3, $p=0.96$).

Discussion

There is emerging evidence that physical activity has a beneficial effect on drug response.^{8–11} For example, exercise has demonstrated significant inverse relation to salt sensitivity among patients with hypertension⁸ and has demonstrated a significant and independent effect on reducing mortality among patients with dyslipidemia treated with statins.⁴⁷ Moreover one report demonstrated the influence of exercise among four warfarin treated patients undergoing cardiopulmonary rehabilitation.¹² These support our hypothesis that physical activity modifies warfarin response.

We demonstrated in this prospective inception cohort of patients initiated on warfarin therapy that physically active patients require a 6.9% higher warfarin dose than inactive patients. There was no difference between groups in percent time spent in the target INR range. However, physically active patients required fewer clinic visits than inactive patients. More importantly, this study is to our knowledge the first to demonstrate that regular physical activity is associated with an independent and significant reduction in risk of hemorrhage in a largely older population (average age 61 ± 15.9 years) on chronic anticoagulation therapy. Physically active warfarin users were at a lower risk of major hemorrhagic complications (5.6 events/100 p-yrs) compared with the inactive group (10.3 events/ 100 p-yrs). Physical activity was associated with a 38% lower risk of major hemorrhage. The independent effect of physical activity remained significant even after controlling for known bleeding risk indices, such as the OBRI or HAS-BLED score and other clinical and genetic factors.

Our results shed light on the effect of physical activity on warfarin response, but not the potential mechanisms by which physical activity may exert these effects. Multiple complex biological aging processes are linked mechanistically to altered drug handling, altered physiological reserve, and variable pharmacodynamic responses.^{48, 49} Plausible explanation for increased warfarin dose could be mediated through increased hepatic perfusion or improved metabolism through increased physical activity. In a case series of 10 warfarin-treated patients, it was demonstrated that initiation of physical activity resulted in sub-therapeutic INRs. They postulated that increased binding of warfarin to albumin in physically active patients may be responsible for decreased plasma concentrations possibly resulting in the need for higher doses. The lower risk of hemorrhage in physically active patients may be mediated through improved endothelial function^{50–52} and effects on hemostasis and inflammation.⁵³ We also recognize that the risk of hemorrhage may be modified by frailty, which is not completely accounted for by age or comorbid conditions.⁵⁴

Our prospective inception cohort has several strengths. Specifically, we have successfully recruited >90% of patients approached at initiation of warfarin therapy. The cohort largely reflects patients served at UAB (94% of patients recruited reside in the 5-county Birmingham metropolitan area and 84% residing in Jefferson County) and represents the sociodemographic (42.3% African Americans, 48.2% female) characteristics of the Birmingham metropolitan population in 2010. Therefore our findings are applicable to African Americans and European Americans. Patients of Asian and Hispanic descent were underrepresented. Further research is needed to understand effects of physical activity in these populations. Moreover our analysis accounted for clinical and genetic factors, overall anticoagulation control, and anticoagulation intensity (INR) at the time of hemorrhage. We focused on major hemorrhage as these events are associated with morbidity, mortality, and increased health care costs.

We assessed physical activity by patient self-report defined as regular exercise for 30 or more minutes at least three times a week. This measure allows a quick and structured assessment of physical activity that is simple to reproduce in a clinical setting while incorporating elements of intensity, frequency, and duration of physical activity as recommended by AHA.⁵⁵

We recognize that physical activity assessment based on objective measures (e.g. energy expenditure, physiological changes) or assessed with motion-sensing devices provides a more accurate and well-defined assessment than patient self-report. However, these techniques are expensive and require technical expertise,⁵⁵ which is beyond the reach of our clinical setting. We also recognize that our physically inactive group is heterogeneous and includes patients who are sedentary as well as those who are only occasionally physically active. Although we controlled for environmental and genetic factors, residual confounding cannot be ruled out.

In summary, we found that regular physical activity is associated with higher warfarin dose requirements and lower risk of hemorrhage in a large cohort of patients on chronic anticoagulation therapy. The beneficial effects of physical activity on drug response need to be better understood and the mechanisms through which it exerts these effects need to be

elucidated. Whether and to what extent physical activity influences response to other medications, including novel anticoagulants needs to be ascertained. Although further research is needed, our results strongly suggest that physical activity may have broader benefits that previously recognized.⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by a grant from the National Heart Lung and Blood Institute (R01HL092173), National Institute of Neurological Disorders and Stroke (K23NS45598). This project is supported by grant number UL1 TR000165 and 5KL2RR025776 from the National Centre for Advancing Translational Sciences.

We are grateful to all the patients that participated in the study. We thank our research nurses for their untiring efforts with patient recruitment and the medical faculty and staff of the Anticoagulation Clinic at The Kirklin Clinic, Emory University and the Cooper Green Hospital and Jefferson Clinic P.C for their help with identification of potential patients. Thanks to the Office of Data Resources for their work with the study database and quality assurance.

This study has contributed samples to the NINDS Human Genetics Resource Centre DNA and Cell Line Repository (<http://ccr.coriell.org/ninds>), NINDS Repository sample numbers corresponding to the samples used are ND04466, ND04556, ND04604, ND04605, ND04626, ND04869, ND04907, ND04934, ND04951, ND05036, ND05108, ND05175, ND05176, ND05239, ND05605, ND05606, ND05701, ND05702, ND05735, ND06147, ND06207, ND06385, ND06424, ND06480, ND06706, ND06814, ND06871, ND06983, ND07057, ND07234, ND07304, ND07494, ND07602, ND07711, ND07712, ND08065, ND08596, ND08864, ND08932, ND09079, ND09172, ND09760, ND09761, ND09809.

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Table 1

Sociodemographic and clinical characteristics by level of physical activity

Characteristics	Physically active ^a n=683	Physically inactive n=589	P
	Mean (SD)	Mean (SD)	
Follow-up (years)	1.5 (0.9)	1.3 (0.9)	<0.001
Age (years)	58.9 (15.9)	63.4 (15.7)	<0.001
Hematocrit	37.8 (10.6)	35.4 (7.3)	<0.001
Blood urea nitrogen	17.6 (11.8)	19.9 (19.8)	0.07
BMI	29.2 (6.5)	31.1 (8.3)	<0.001
	N (%)	N (%)	
Female	281 (41.1)	334 (56.7)	<0.001
Race			
European Americans	434 (63.5)	281 (47.7)	<0.001
African Americans	246 (36.0)	303 (51.4)	
Other	3 (0.4)	5 (0.9)	
Education			
High school or less	274 (40.2)	321 (54.9)	<0.001
More than high school	407 (59.8)	236 (45.0)	
Medical insurance ^b	557 (52.5)	505 (47.6)	0.04
Current alcohol use	244 (36.0)	97 (16.8)	<0.001
Current smoker	77 (11.9)	74 (13.7)	0.37
Indication for warfarin therapy			
Venous thromboembolism	271 (39.7)	266 (45.2)	0.05
Stroke/TIA	31 (4.5)	45 (7.6)	0.02
Atrial fibrillation	311 (45.5)	230 (39.1)	0.02
Other	70 (10.3)	45 (7.6)	0.11
Number of comorbid conditions ^c			
Low (0 or 1)	204 (29.9)	123 (20.9)	<0.001
Medium (2 to 4)	227 (33.2)	187 (31.7)	
High (5)	252 (36.9)	279 (47.4)	
Chronic kidney disease			
eGFR 60ml/min/1.73m ²	453 (66.3)	336 (57.1)	0.002
eGFR 30 to 59ml/min/1.73m ²	179 (26.2)	190 (32.3)	
eGFR <30 ml/min/1.73m ²	51 (7.5)	63 (10.7)	
Ejection fraction			
Ejection fraction 0.55	523 (76.5)	436 (74.0)	0.57
Ejection fraction 0.35 to 0.54	84 (12.3)	81 (13.8)	
Ejection fraction < 0.35	76 (11.1)	72 (12.2)	
HAS-BLED score			
<3	319 (46.8)	209 (35.5)	<0.001

Characteristics	Physically active ^a n=683	Physically inactive n=589	P
3	363 (53.2)	380 (64.5)	
OBRI score			
<3	655 (95.9)	547 (92.9)	0.02
3	28 (4.1)	42 (7.1)	
Concurrent medications			
Statins	179 (26.3)	109 (18.6)	0.001
Anti-platelets ^d	386 (56.8)	332 (56.7)	0.99
Amiodarone	66 (9.7)	48 (8.2)	0.35
NSAIDs	128 (18.8)	106 (18.1)	0.75
Single nucleotide variants ^e			
<i>CYP2C9</i> variant	173 (27.2)	125 (23.1)	0.11
<i>VKORC1</i> variant	292 (44.0)	224 (39.7)	0.13
<i>CYP4F2</i> variant	240 (40.7)	166 (34.2)	0.03

SD: Standard deviation, BMI: Body Mass Index, TIA: Transient ischemic attack, HAS-BLED: (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly), OBRI: Outpatient Bleeding Risk Index, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

^aPhysical activity was defined as regular exercise for 30 minutes 3 times week.

^bHealth insurance consists of private coverage, such as Blue Cross Blue Shield, Aetna, Travelers, Viva, Medicare.

^cComorbidity was defined as concomitant diseases (e.g. hypertension, high cholesterol, diabetes, renal failure/insufficiency, myocardial infarction, coronary artery disease, cardiac interventions, atrial fibrillation, congestive heart failure, peripheral vascular disease, any cancer and history of prior hemorrhage). Low comorbidity refers to presence of 0 or 1 condition; moderate comorbidity denotes 2–3 conditions and severe comorbidity denotes four or more conditions.

^dConcurrent antiplatelet agents included aspirin, clopidogrel, and dipyridamole as mono or dual therapy. Statins included any of the HMG-CoA reductase inhibitors.

^eGenotype information was not available in 45 patients for *VKORC1*, 197 for *CYP4F2*, and 93 for *CYP2C9*. Percent genotype within each physical activity category was based on number of patients with available sample genotype information. *CYP2C9* variant genotype includes *2, *3 alleles among European Americans and *2, *3, *5, *6 and *11 alleles among African Americans. Variant *VKORC1* includes 'TT or CT' Variant *CYP4F2* includes 'AG or AA'.

Table 2

Influence of physical activity, demographic, clinical, and genetic factors on warfarin dose requirements

Variable	Effect on Warfarin Dose (95% CI)		
	Dose (mg/day)	% Dose Change	P
White male age <50 years ^a	7.93 (7.18 to 8.74)		
Regular physical activity	8.48 (7.32 to 9.81)	6.94 (1.94 to 12.19)	0.006
Age 50–65 years	7.26 (6.18 to 8.52)	−8.45 (−13.98 to −2.56)	0.006
Age >65 years	6.09 (5.19 to 7.14)	−23.21 (−27.79 to −18.33)	<0.001
African American	8.03 (6.87 to 9.39)	1.29 (−4.43 to 7.35)	0.67
Female	7.1 (6.14 to 8.22)	−10.37 (−14.59 to −5.95)	<0.001
BMI (per unit increase over 25 kg/m ²)	8 (7.23 to 8.85)	0.93 (0.61 to 1.25)	<0.001
Alcohol use	8.24 (7.07 to 9.59)	3.93 (−1.54 to 9.71)	0.16
Heart failure (LVEF <55%)	7.55 (6.61 to 8.62)	−4.78 (−7.99 to −1.47)	0.005
Chronic kidney disease (CKD)	7.26 (6.35 to 8.31)	−8.35 (−11.62 to −4.95)	<0.001
Vitamin K intake ^b	8 (7.16 to 8.94)	0.96 (−0.34 to 2.28)	0.15
Concurrent amiodarone use	6.45 (5.41 to 7.69)	−18.61 (−24.69 to −12.04)	<0.001
Single nucleotide variants			
CYP2C9 variant	6.22 (5.35 to 7.24)	−21.48 (−25.55 to −17.18)	<0.001
VKORC1 variant	5.54 (4.78 to 6.42)	−30.09 (−33.44 to −26.56)	<0.001
CYP4F2 variant	8.4 (7.25 to 9.74)	6.01 (0.89 to 11.4)	0.02

CI: confidence intervals, BMI: body mass index, LVEF: left ventricular ejection fraction.

^aThe referent is a physically inactive <50 year old white male with a BMI of 25 kg/m², an average of 2 servings of vitamin K rich foods/week, wild-type for *VKORC1*, *CYP2C9* and *CYP4F2* variants and no alcohol use, heart failure (LVEF <55%), CKD, or concurrent amiodarone therapy.

^bVitamin K rich foods (per unit increase in servings over 2).

Table 3

Sociodemographic and clinical characteristics by major hemorrhage

Characteristics	Major Hemorrhage ^a n=119	No Hemorrhage n=1156	P
Age (years)	65.8 (14.4)	60.5 (16.0)	<0.001
Years of follow-up accrued	49.7	1755.8	
BMI	30.6 (7.8)	30.1 (7.4)	0.49
Hematocrit	34.9 (6.9)	36.9 (9.5)	0.02
Blood urea nitrogen	22.6 (16.3)	18.3 (15.9)	0.005
Percent total time in target INR	46.0 (17.0)	49 (22.0)	0.07
Regular physical activity	51 (42.9)	632 (54.9)	0.01
Age >65 years	67 (56.3)	507 (43.7)	0.009
Female	62 (52.1)	554 (47.9)	0.39
African American	59 (49.6)	493 (42.7)	0.15
Education			
High school or less	67 (56.8)	529 (46.0)	<0.001
More than high school	51 (43.2)	621 (54.0)	
Medical insurance	104 (90.0)	960 (87.5)	0.16
Alcohol > 8 drinks/day	10 (8.5)	75 (6.6)	0.43
Current smoker	14 (12.4)	136 (12.6)	0.94
Indication for warfarin therapy			
Venous thromboembolism	37 (31.1)	503 (43.5)	0.009
Stroke /TIA	4 (3.4)	71 (6.1)	0.22
Atrial fibrillation	63 (52.9)	479 (41.4)	0.02
Myocardial infarction	4 (3.4)	19 (1.6)	0.18
Peripheral arterial disease	3 (2.5)	8 (0.7)	0.04
Other	8 (6.7)	73 (6.3)	0.86
Number of comorbidities			
Low (0 or 1)	11 (9.2)	313 (27.1)	<0.001
Medium (2 to 4)	24 (20.2)	391 (33.8)	
High (5)	84 (70.6)	452 (39.1)	
Chronic Kidney disease			
eGFR 60ml/min/1.73m ²	60 (50.4)	730 (63.2)	0.001
eGFR 45 to 59ml/min/1.73m ²	22 (18.5)	234 (20.2)	
eGFR 30 to 45ml/min/1.73m ²	17 (14.3)	96 (8.3)	
eGFR <30 ml/min/1.73m ²	20 (16.8)	96 (8.3)	
Ejection fraction			
Ejection fraction 0.55	83 (69.8)	878 (75.9)	0.31
Ejection fraction 0.35 to 54	18 (15.1)	147 (12.7)	
Ejection fraction < 0.35	18 (15.1)	131 (11.3)	
HAS-BLED score			
<3	21 (17.6)	507 (43.9)	<0.001
3	98 (82.4)	649 (56.1)	

Characteristics	Major Hemorrhage ^a n=119	No Hemorrhage n=1156	P
OBRI score			
<3	103 (86.6)	1102 (95.3)	<0.001
3	16 (13.5)	54 (4.7)	
Concurrent medications			
Statins	32 (26.9)	258 (22.4)	0.27
Anti-platelets	82 (68.9)	638 (55.5)	0.005
Amiodarone	9 (7.6)	56 (4.8)	0.19
NSAIDs	23 (19.3)	215 (18.7)	0.87
Single nucleotide variants			
<i>CYP2C9</i> variant	31 (29.5)	266 (24.7)	0.29
<i>VKORC1</i> variant	46 (41.1)	471 (42.1)	0.83
<i>CYP4F2</i> variant	37 (40.7)	370 (37.5)	0.57

SD: standard deviation, BMI: body mass index, TIA: transient ischemic attack, HAS-BLED: (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly), OBRI: Outpatient Bleeding Risk Index, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

^aMajor hemorrhage includes serious, life threatening and fatal bleeding episodes as described by Fihn et al ³⁹.

Table 4

Absolute incidence (per 100 person-years) and relative risk (hazard ratio and 95% CI) of major hemorrhage by physical activity

	N	Events	FU years	Incidence	P
Physically active	683	58	1036.5	5.60 (4.25 – 7.23)	<0.001
Physically inactive	589	79	764.1	10.34 (8.19 – 12.89)	

Unadjusted		Adjusted HR (95% CI)		
HR (95% CI)	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
Physically active	0.56 (0.39 – 0.81)	0.62 (0.43 – 0.89)	0.68 (0.47 – 0.99)	0.64 (0.41 – 0.99)
p-value	0.002	0.009	0.05	0.03

CI: confidence intervals, FU years: follow-up years, HR: hazards ratio.

^aModel 1: Physical activity and HAS-BLED score (<3 and 3) (score assigns 1 point each to hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile INR (defined as PTTR <60%), old age (>65 years) and drug or alcohol use).

^bModel 2: Model 1 factors and gender, race (black vs. others), number of risk factors/comorbid conditions; chronic kidney disease eGFR 60 (no CKD or mild CKD stage 1 and 2), eGFR=30–59 (moderate CKD; stage 3) and eGFR<30 (severe CKD; stage 4 and 5), and concurrent amiodarone use.

^cModel 3: Model 2 factors and genetic variants for CYP2C9, VKORC1 and CYP4F2.

^dModel 4: Model 3 and adjustment for over-anticoagulation (INR > 4, reference group being INR 4) at the time of the event.