Published in final edited form as:

Pharmacogenet Genomics. 2017 October ; 27(10): 347–355. doi:10.1097/FPC.0000000000000298.

Quality of anticoagulation control and hemorrhage risk among African American and European American warfarin users

Nita A. Limdi, PhD^a, Todd M. Brown, MD^b, Aditi Shendre, MPH^c, Nianjun Liu, PhD^d, Charles E. Hill, MD^e, and T. Mark Beasley, PhD^d

^aDepartment of Neurology, University of Alabama at Birmingham, AL, USA

^bDivision of Cardiovascular Diseases, Department of Medicine, University of Alabama at Birmingham, AL, USA

^cDepartment of Epidemiology, University of Alabama at Birmingham, AL, USA

^dDepartment of Biostatistics, University of Alabama at Birmingham, AL, USA

^eDepartment of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA

Abstract

Objective—We evaluated whether PTTR, risk of over-anticoagulation (INR>4) and risk of hemorrhage differs by race. As PTTR is a strong predictor of hemorrhage risk, we also determined the influence of PTTR on risk of hemorrhage by race.

Methods—Among 1326 warfarin users, PTTR was calculated as the percentage of interpolated INR values within the target range of 2.0–3.0. PTTR was also categorized as poor (PTTR <60%), good (PTTR 60–70%), or excellent (PTTR ≥70%) anticoagulation control. Over-anticoagulation was defined as INR>4 and major hemorrhages included serious, life threatening and fatal bleeding episodes. Logistic regression and survival analyses were performed to evaluate association of race with PTTR (<60 vs. ≥60) and major hemorrhages, respectively.

Results—Compared to African Americans, European Americans had higher PTTR (57.6% vs. 49.1%; $p<0.0001$) and were more likely to attain PTTR 60–70% (22.9% vs. 13.1%; $p<0.001$) or PTTR ≥70% (26.9% vs. 18.2%; $p=0.001$). Older (>65yrs) patients without venous thromboembolism indication and chronic kidney disease were more likely to attain PTTR ≥60%. After accounting for clinical and genetic factors, and PTTR, African Americans had a higher risk of hemorrhage (HR: 1.58; 95% CI 1.04–2.41; $p=0.034$). Patients with PTTR 60–70% (HR 0.62; 0.38–1.02; $p=0.058$) and PTTR ≥70% (HR 0.27; 0.15–0.49; $p<0.001$) had a lower risk of hemorrhage compared to those with PTTR<60%.

Conclusion—Despite provision of warfarin management through anticoagulation clinics, African Americans achieve a lower overall PTTR and have a significantly higher risk of

Corresponding Author: Nita A. Limdi, Pharm.D, PhD, MSPH, 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.
current: Richard M. Fairbanks School of Public Health, Indianapolis University Purdue University Indianapolis, IN, USA

Conflicts of Interest: The authors report no conflict of interest.

hemorrhage. Personalized medicine interventions tailored to the African American warfarin users need to be developed.

Keywords

Race; warfarin; percent time in target range; PTTR; anticoagulation control; hemorrhage

Introduction

Racial differences in outcomes related to cardiovascular disease, obesity, cancer, hypertension, asthma, and diabetes mellitus in minorities are well established. Although minorities shoulder a disproportionate burden of disease and are more likely to suffer poor outcomes, they remain under-represented in clinical trials [1, 2]. Under-representation is especially pronounced in cardiovascular trials. For example, African Americans comprise less than 2% of trial participants for the four non-vitamin K antagonist oral anticoagulants (NoAC; dabigatran, rivaroxaban, apixaban, and edoxaban) approved since 2010 [3–6]. Therefore racial differences in drug response, if one exists, cannot be assessed from trial data [7]. For warfarin, the most widely used oral anticoagulant; investigators have led the charge to ensure that the evidence base for treatment is based on broad racial representation. Observational studies and clinical trials provide a robust case-study for illustrating race-related differences in anticoagulation response and factors that underpin this variable response [8–13].

Evidence from large cohorts supports the significant influence of clinical (e.g. age, amiodarone) and genetic (*CYP2C9* and *VKORC1* variants) factors on warfarin dose among European Americans and African Americans [8–10, 12–17]. However, as we have recently shown [9], the impact, percent dose reduction associated with *VKORC1* variants differs by race; European Americans require a larger dose decrease compared to African Americans. Moreover, *CYP2C9**2 and *CYP4F2* influenced dose in European Americans while rs12777823 influenced dose in African Americans only [9]. The latter findings are supported by other reports [8, 10, 18]. This differential influence may explain why genotype-guided warfarin initiation predicted dose less accurately among African Americans compared to European Americans in the Clarification of Oral Anticoagulation through Genetics (COAG) trial and may explain divergent results wherein percent-time-in-target-range (PTTR) was increased by 3% among European Americans but decreased by 8% among African Americans receiving genotype-guided dosing [11].

Although racial differences in warfarin dose requirements and contributors of these differences have been evaluated, limited data exist on racial differences in PTTR, risk of over-anticoagulation, and major hemorrhage. Herein we evaluate whether PTTR, risk of over-anticoagulation (INR>4) and risk of hemorrhage differs by race and assess the influence of clinical and genetic factors on these outcomes. Moreover, as PTTR is a strong predictor of hemorrhage risk, and often used as a surrogate outcome measure, we determine the influence of PTTR on risk of hemorrhage by race.

Materials and methods

Participants >20 years of age initiating warfarin therapy were enrolled in an inception warfarin pharmacogenetics cohort study if the target international normalized ratio (INR) range was 2–3 and therapy was managed at the anticoagulation clinic. Patients did not receive genotype guided dosing. The study was conducted under the approval of the Institutional Review Boards of the University of Alabama at Birmingham and Emory University.

Patient demographics, indication for therapy, co-morbidity, laboratory measurements, medications, were documented as previously reported [8, 9, 17, 19–22]. During the monthly follow-up, dose, INR, and changes in concomitant medications that influence warfarin pharmacodynamics (antiplatelet agents) or pharmacokinetics (e.g. amiodarone) were documented. We assessed *CYP2C9* (*2 [rs1799853], *3 [rs1057910], *5 [rs28371686], *6 [rs9332131], and *11 [rs28371685]), *CYP24F2* (rs2108622), *CYP2C* SNP (rs12777823)[10] and *VKORC1* (rs9923231) as previously described [21, 22].

Outcomes Definitions

Proportion of time spent in target range (PTTR) and quality of anticoagulation control—Time (in days) to attain target INR and stable dose (defined as the average maintenance dose after the attainment of three consecutive INRs in target range measured at least 2 weeks apart) was assessed in each patient. For each patient, PTTR was calculated as the percentage of interpolated INR values within the target range of 2.0–3.0 after attainment of first INR in target range using the Rosendaal linear interpolation method [23]. We also present proportion of time spent below (PTBR) and above (PTAR) target range. As PTTR is a recognized risk factor of hemorrhage; we categorized patients' quality of anticoagulation control based on cumulative PTTR in two ways. First we considered PTTR $\geq 60\%$ (vs. $<60\%$) as this has been evaluated as a predictor for hemorrhage among warfarin users in recent clinical trials and included in the recently proposed Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile INR (defined as PTTR $<60\%$), Elderly, Drug consumption/alcohol abuse (HAS-BLED) score [24]. Second, as the effectiveness of warfarin compared to the newer oral anticoagulants is related to the level of PTTR achieved we also categorized PTTR as: poor anticoagulation control (PTTR $<60\%$), good control (PTTR $\geq 60\%$), and excellent control (PTTR $\geq 70\%$) [25–30].

Over-anticoagulation and Major Hemorrhage—Over-anticoagulation was defined as INR >4 . Major hemorrhages included serious, life threatening and fatal bleeding episodes [31]. As the focus of this manuscript was to evaluate the association of race on risk of major hemorrhages, minor hemorrhages (mild nosebleeds, microscopic hematuria, mild bruising, and mild hemorrhoidal bleeding) were excluded. During the 2-year follow-up, for all major hemorrhagic complications, the complication site (e.g. endoscopy of gastrointestinal tract), gravity of the event (e.g. requiring transfusion, surgical intervention, etc.), and laboratory findings (INR, hemoglobin/hematocrit, etc.) at the time of the event were objectively documented. Isolated sub-therapeutic or supra-therapeutic INRs in the absence of evidence of bleeding were not classified as events. The 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 reviewed independently by the Medical Director (TMB) of the Anticoagulation Clinic. Only medically documented, adjudicated events were included in the analyses.

Statistical Analysis

Analysis of variance was used to assess group differences for continuous variables and χ^2 test for categorical variables. The assumption of Hardy Weinberg Equilibrium (HWE) was tested using the χ^2 test and was satisfied for all SNPs ($p>0.20$). Multivariable logistic regression analysis was used to assess differences in PTTR (≥ 60 vs. <60) by race. The influence of race on the risk of over-anticoagulation ($\text{INR}>4$) and hemorrhage was assessed using the counting process format in the proportional hazard (PH) model. Additionally, the hemorrhage analysis accounted for PTTR categorized as: poor anticoagulation control ($\text{PTTR}<60\%$), good control ($\text{PTTR} \geq 60\%$), and excellent control ($\text{PTTR} \geq 70\%$). All analyses were performed using SAS version 9.3 at a non-directional alpha level of 0.05 accounting for demographic (e.g. age, race, gender, BSA), clinical (comorbid conditions including e.g. diabetes mellitus, chronic kidney disease [CKD; categorized on estimated glomerular filtration rate $\text{eGFR} \geq 60$, $30\text{--}59$, $<30\text{ml/min/1.73 m}^2$]), concurrent amiodarone use, and genetic (*CYP2C9*, *CYP4F2*, *VKORC1* and rs12777823) factors.

Results

Baseline characteristics of the 1326 participants (mean age 61.0 years; standard deviation (SD) ± 15.8) are presented in Table 1. African Americans comprised 43.6% of the cohort. Compared to European Americans, African Americans were younger, more likely to be female, be a current smoker, and more likely to have venous thromboembolism, while atrial fibrillation was more common among European Americans. Hypertension, diabetes and CKD were more prevalent among African Americans while hyperlipidemia was more prevalent among European Americans. The use of concurrent antiplatelet agents, statins, and amiodarone was more frequent among European Americans, as was the prevalence of variants in *CYP2C9* (*2, *3), *VKORC1* and *CYP4F2* whereas rs12777823 variants prevalence was higher among African Americans. *CYP2C9* (*5, *6, *11) were only encountered in African Americans.

Percent Time in Target Range (PTTR) and Quality of Anticoagulation Control

Compared to European Americans, time to attain therapeutic INR ($p=0.03$) and time to attain stable dose ($p<0.001$) was longer in African Americans (Table 2). Overall, patients spent 53.9% of time in target range, 28.6% time below range and 17.2% of time above range. European Americans spent 8.5% more time in target INR range compared to African Americans (PTTR 57.6% vs. 49.1%; $p<0.001$; Table 2) while African Americans spent more time below target INR range (PTBR; 32.9% vs. 25.2%; $p<0.001$). Moreover, PTTR was more variable among African Americans compared to European Americans (SD: 22.7% vs. 19.9%; $p=0.002$).

Overall, the quality of anticoagulation control was poor (PTTR <60%) in 58.3% of patients, good (PTTR 60–70%) in 18.6% of patients, and excellent (PTTR ≥70%) in 23.1% of patients. More African Americans (68.7%) achieved poor anticoagulation control compared to European Americans (50.3%; $p<0.001$), while more European Americans achieved good (22.9% vs. 13.1%; $p<0.001$) and excellent (26.9% vs. 18.2%; $p=0.001$, Table 2) anticoagulation control.

As PTTR ≥60% (vs. <60%) is considered the benchmark for good anticoagulation control among warfarin users, we evaluated which predictors were associated with attainment of good or excellent anticoagulation control in race-combined and race stratified analyses (Figure 1). In race-combined analyses European Americans, men, patients prescribed warfarin for non-venous thromboembolism and those older patients (age ≥65) and without chronic kidney disease were more likely to have of good or excellent anticoagulation control (PTTR ≥60%). Concomitant therapy with amiodarone, statins, and antiplatelet agents of possession of variants in genes known to influence warfarin response did not demonstrate significant influence. Among European Americans, older patients (age ≥65) without chronic kidney disease, with non-venous thromboembolism indication were more likely to have of good or excellent anticoagulation control. Possession of *VKORC1* variants was associated with a lower likelihood of good or excellent anticoagulation control. Among African American patients, men and non-venous thromboembolism indication, older patients (age ≥65) without chronic kidney disease were more likely to have of good or excellent anticoagulation control (PTTR ≥60%). Possession of *VKORC1* variants was associated with a higher likelihood of good or excellent anticoagulation control.

Over-anticoagulation (INR>4)

Compared to European Americans, African Americans were more likely to experience over-anticoagulation (HR 1.45; 95% CI: 1.2–1.74; $p<0.001$). Factors associated with increased risk of over-anticoagulation included CKD (HR 1.43; 95% CI: 1.3–1.6; $p<0.001$), possession of *CYP2C9**2 (HR 1.22; 95% CI: 1.03–1.44; $p=0.02$), *CYP2C9**3 (HR 1.26; 95% CI: 1.01–1.56; $p=0.04$), and *VKORC1* (HR 1.15; 95% CI: 1.03–1.28; $p=0.016$) variants. Age ($p=0.19$) and possession of *CYP4F2* ($p=0.48$) and rs12777823 ($p=0.34$) did not significantly influence risk of over-anticoagulation in the entire cohort. Although possession of rs12777823 did not influence risk of over-anticoagulation in the combined cohort or in European Americans ($p=0.07$), rs12777823 significantly influenced the risk of over-anticoagulation among African Americans ($p=0.007$).

Incidence (Absolute Risk) of Hemorrhagic Events

One-hundred and fifty-six hemorrhagic events occurred during 1912 person-years (p-yrs) of follow-up (incidence rate (IR) 8.1/100 p-yrs; 95% CI: 6.9–9.5). Hemorrhages included gastrointestinal (n=94), genitourinary (n=19), retroperitoneal (n=7), intracranial (n=13) bleeds, hemoptysis (n=5), and hematomas (n=18). Compared to European Americans (7.0 p-yrs; 95% CI: 5.6–8.8), African Americans (9.7/100 p-yrs; 95% CI: 7.7–12.1) had a higher incidence of hemorrhage (Incidence rate ratio: 1.38, 95% CI 1.01, 1.89, $p=0.045$). The incidence of hemorrhage was lower among patients attaining higher quality of anticoagulation control (Figure 2—**top panel**) in race-combined and race-stratified analysis.

The incidence of hemorrhage did not differ by race among patients with poor (PTTR <60%; $p=0.37$), good (PTTR 60<70%; $p=0.89$) and excellent (PTTR 70, $p=0.11$) anticoagulation control.

Relative Risk of Hemorrhagic Events

Compared to European Americans, African Americans had a higher relative risk of hemorrhage (HR= 1.47, 95% CI 1.08, 2.01, $p=0.016$). The risk of hemorrhage was lower among patients attaining higher quality of anticoagulation control (Figure 2–**bottom panel**). Compared to patients who achieved poor anticoagulation control (PTTR <60%) the risk of hemorrhage was 34% lower among those achieving good control (PTTR 60<70%; $p=0.08$), and 72% lower among those achieving excellent control (PTTR 70; $p<0.001$).

After accounting for clinical and genetic factors, African Americans were at a 58% higher risk of major hemorrhage (HR: 1.58; 95% CI 1.04–2.41; $p=0.03$; Figure 3) compared to European Americans. Female gender, BSA, diabetes, amiodarone, statin, possession of *VKORC1*, *CYP4F2* and rs12777823 did not influence (p -values >0.2) risk of hemorrhage. Older age ($p=0.03$), hypertension ($p=0.02$), CKD ($p=0.003$), and concurrent antiplatelet use ($p=0.004$) were associated with an increased risk of hemorrhage. Possession of *CYP2C9*3* (HR 1.85; 95% CI: 1.07–3.2; $p=0.03$) increased the risk of hemorrhage while that of *CYP2C9*2* (HR 1.2; 95% CI: 0.78–1.85; $p=0.42$) did not. The influence of *CYP2C9*3* ($p=0.21$) or *CYP2C9*2* ($p=0.32$) on hemorrhage risk did not differ by race. PTTR demonstrated significant association with major hemorrhage ($p<0.001$). Compared to PTTR <60%; those with PTTR 60<70% (HR 0.62; 0.38–1.02; $p=0.058$) and those with PTTR 70% (HR 0.27; 0.15–0.49; $p<0.001$) had a lower risk of hemorrhage.

Discussion

To our knowledge, this is the first study to report PTTR and risk of hemorrhage among African American and European American warfarin users managed through an anticoagulation service. We report two major findings. First, African Americans achieve a lower PTTR and are less likely to be classified as achieving good or excellent anticoagulation control (PTTR 60%) compared to European Americans. Second, African Americans have a higher risk of hemorrhage even after accounting for clinical and genetic risk factors and PTTR.

PTTR, an established measure of anticoagulation control, often serves as a surrogate for hemorrhage in studies assessing efficacy of warfarin. Although numerous reports demonstrate the strong protective influence of higher PTTR on hemorrhage risk, most of these data are derived from patients of European descent, with limited representation of African Americans. For example, among participants in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) cohort, 59% of the measured INR values were between 2.0 and 3.0, with an overall mean TTR of $65\% \pm 20\%$. European Americans comprised 90% of the cohort ($n=5000$) with African Americans comprising only 5% [32]. Larger efforts ($n=48,830$) have assessed differences in anticoagulation control by indication; atrial fibrillation versus venous thromboembolism. However, due to the limited representation (<1%) of patients of African descent [33], differences in anticoagulation

control by race were not assessed. Similarly, in recent clinical trials that have led to the approval of four NoACs, patients of African descent comprised <2.0% of all participants [3–6]. This is the first report assessing the *VKORC1*-PTTR association in African Americans. Prior studies reporting gene-anticoagulation association have evaluated the gene-INR>4 relationship early in warfarin therapy. Although it seems intuitive that variants that influence dose would have similar association (direction and effect) on PTTR, there are no studies demonstrating this. Moreover, it is likely that the impact of gene variants on warfarin response is dependent on time. Ferder et al. recently demonstrated that the magnitude of the dose predictive ability of *VKORC1* and *CYP2C9* diminished over time (43% at day 0, 12% at day 7, 4% at day 14, and 1% at day 21) [34]. This can be explained by the fact that dose changes over treatment time are not influenced by genotype alone but also the action (dose adjustments) guided by INR assessments. As opposed to the gene-INR relationship early in therapy, the gene-PTTR relationship captures response over follow-up time accrued and is likely influenced by many factors (genetic, clinical, environmental) and interactions between these. We present both; differences in PTTR by race and differences in PTTR categories by race; demonstrating that this difference after accounting for clinical and genetic factors. These findings are concordant with the recent report on warfarin patients treated at the Veterans Health Administration [35], demonstrating racial differences in anticoagulation control despite of management through an anticoagulation clinic.

African Americans have a higher risk of hemorrhage after accounting for clinical and genetic factors and PTTR. Concordant with previous reports older age, hypertension, concurrent antiplatelet use and possession of *CYP2C9**3 (but not *CYP2C9**2) variant was associated with increased risk of hemorrhage [36]. Improved anticoagulation control was associated with a significantly lower risk of hemorrhage [24, 25, 30, 37, 38]. Because higher PTTR is associated with lower hemorrhage risk, it is convenient, and may even seem intuitive, to use PTTR as a continuous variable in evaluating its influence on hemorrhage. However, this approach may not conducive to meaningful clinical interpretation. A significant body of evidence exists that supports that poor anticoagulation control (PTTR<60%) is a predictor for hemorrhage among warfarin users [38–41]. Moreover, this is widely recognized as the accepted quality metric for anticoagulation management services and is incorporated into risk prediction rules [24]. Improvement in PTTR, especially if the improvement results in a PTTR category may be more meaningful. The fidelity of using PTTR categories is demonstrated by recent analysis of NoAC clinical trial data [30, 37, 39]. Among RELY trial participants on warfarin, increase in PTTR was associated with a decrease in risk of hemorrhage. Moreover, compared to dabigatran (150 mg dose), the risk of hemorrhage was higher for warfarin users with PTTR <57%. Compared to dabigatran users, the risk of hemorrhage among warfarin users with PTTR 57–72% was similar and among those PTTR>72%, the risk of hemorrhage was lower [30]. Similarly, compared to apixaban, the risk of hemorrhage was higher for warfarin users with PTTR <66% [37].

Our results demonstrate the influence of anticoagulation control on hemorrhage by categorizing PTTR (poor: PTTR <60%; good: PTTR 60<70%; and excellent: PTTR 70) in both among both African Americans and European Americans. Interventions that improve PTTR can be expected to produce a significant and similar reduction in the absolute and relative risk of hemorrhage in both race groups. PTTR 70% was associated with the lowest

risk of hemorrhage. Among European Americans with PTTR 70% the rate of major hemorrhage as similar to that reported in a large ($n > 89,000$) cohort of warfarin users from Sweden [40]. Our results suggest that risk of hemorrhage can be further reduced by achieving excellent anticoagulation (PTTR 70%). However, even with a PTTR 70%, African Americans have a higher risk of hemorrhage compared to European Americans.

Two trials tested whether an intervention designed to improve dose prediction would result in higher PTTR demonstrated incongruent results [41, 42]. Evidence emerging after the trial initiation resulted in revision of the sample size estimates. The EUPACT trial estimated 400 patients would provide 80% power at alpha of 0.05 to detect a 7.0% difference in PTTR based on a standard deviation of 23%. The COAG trial estimated that 1022 patients would provide 80% power at alpha of 0.05 to detect a 5.5% difference in PTTR based on a standard deviation of 25%. These estimates were based on results from studies conducted in patients of mainly European descent [43–46]. Our results demonstrate that variability (standard deviation) around the mean PTTR is higher among African Americans. Therefore, interventions designed to improve PTTR should account for this variability.

The EU-PACT trial showed improved PTTR (54.6% vs. 45.7% at 4 weeks and 67.4% vs. 60.3% at 12 weeks; $p < 0.001$) among patients receiving personalized warfarin dosing (using clinical and genetic factors) *versus* standard dosing in 455 patients, of largely European (99%) ancestry [47]. The COAG trial showed no overall improvement in PTTR (45.4% vs. 45.2%, $p = 0.91$ at 4 weeks) among patients receiving personalized warfarin dosing using clinical and genetic factors vs. those receiving dosing based on clinical factors alone. However, race-stratified analysis showed improved PTTR among European (48.9% vs. 46.1%, $p = 0.15$) but lower PTTR in African (35.2% vs. 43.5%, $p = 0.01$) Americans [11]. There was a significant interaction between dosing strategy and race ($P = 0.003$) in COAG. This could explain the observed differences in PTTR by race.

The heterogeneity introduced by race may explain the divergent findings across race groups in COAG. We have previously reported that the influence of known genetic variants on warfarin dose differs by race and that race-stratified pharmacogenetic algorithm, rather than race-combined algorithms should be used to guide warfarin dosing. Herein we show that African Americans achieve lower PTTR and fewer African Americans attain PTTRs 60%. We also show that African Americans have a significantly higher risk of hemorrhage after accounting for PTTR. Most importantly our results suggest that studies testing interventions designed to improve outcomes should be powered to show an increase in the proportion of patients attaining good or excellent anticoagulation control (PTTR 60%) and not solely on detecting a 5% improvement in PTTR.

Building on our previous work on racial differences in impact of predictors on warfarin dose, we show that anticoagulation control and risk of hemorrhage, the most feared complication among warfarin users, differs by race. Despite introduction of NOACs, warfarin remains the widely used, especially in African Americans [48–51]. As warfarin remains widely used, and improvement in anticoagulation control can reduce the risk of hemorrhage, personalized medicine interventions tailored to the African American warfarin users need to be developed.

Acknowledgments

Sources of Funding: This work was supported in part by grants from the National Heart Lung and Blood Institute (R01HL092173; 1K24HL133373), National Institute of General Medical Sciences (R01GM081488) and the National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program (UL1TR000165).

This study has contributed samples to the NINDS Human Genetics Resource Center 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.

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 for their help with identification of potential participants.

References

- Berger JS, Melloni C, Wang TY, Dolor RJ, Frazier CG, Samad Z, et al. Reporting and representation of race/ethnicity in published randomized trials. *Am Heart J*. 2009; 158:742–7. [PubMed: 19853691]
- Galvao M. Underrepresentation of minorities in clinical trials: a current problem with escalating future implications. *Heart & lung : the journal of critical care*. 2011; 40:391–2. [PubMed: 21784528]
- Connolly S, Ezekowitz M, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009; 361:1139–51. [PubMed: 19717844]
- Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011; 364:806–17. [PubMed: 21309657]
- Patel M, Mahaffey K, Garg J, Pan G, Singer D, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365:883–91. [PubMed: 21830957]
- Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013; 369:2093–104. [PubMed: 24251359]
- Jackson LR 2nd, Peterson ED, Okeagu E, Thomas K. Review of race/ethnicity in non vitamin K antagonist oral anticoagulants clinical trials. *J Thromb Thrombolysis*. 2015; 39:222–7. [PubMed: 25362508]
- Shendre A, Brown TM, Liu N, Hill CE, Beasley TM, Nickerson DA, et al. Race-Specific Influence of CYP4F2 on Dose and Risk of Hemorrhage Among Warfarin Users. *Pharmacotherapy*. 2016; 36:263–72. [PubMed: 26877068]
- Limdi NA, Brown TM, Yan Q, Thigpen JL, Shendre A, Liu N, et al. Race influences warfarin dose changes associated with genetic factors. *Blood*. 2015; 126:539–45. [PubMed: 26024874]
- Perera MA, Cavallari LH, Limdi NA, Gamazon ER, Konkashbaev A, Daneshjou R, et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet*. 2013; 382:790–6. PMID:3759580. [PubMed: 23755828]
- Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013; 369:2283–93. [PubMed: 24251361]
- Limdi NA, Wadelius M, Cavallari L, Eriksson N, Crawford DC, Lee MT, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood*. 2010; 115:3827–34. [PubMed: 20203262]
- Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*. 2009; 360:753–64. PMID:2722908. [PubMed: 19228618]

14. Limdi NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, et al. Warfarin Dosing in Patients With Impaired Kidney Function. *Am J Kidney Dis.* 2010; 56:823–31. PMC2963672. [PubMed: 20709439]
15. Caldwell MD, Awad T, Johnson JA, Gage BF, Falkowski M, Gardina P, et al. CYP4F2 genetic variant alters required warfarin dose. *Blood.* 2008; 111:4106–12. [PubMed: 18250228]
16. Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther.* 2008; 84:326–31. [PubMed: 18305455]
17. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, et al. Kidney Function Influences Warfarin Responsiveness and Hemorrhagic Complications. *J Am Soc Nephrol.* 2009; 20:912–21. PMC2663833. [PubMed: 19225037]
18. Ramirez AH, Shi Y, Schildcrout JS, Delaney JT, Xu H, Oetjens MT, et al. Predicting warfarin dosage in European-Americans and African-Americans using DNA samples linked to an electronic health record. *Pharmacogenomics.* 2012; 13:407–18. [PubMed: 22329724]
19. Shendre A, Beasley TM, Brown TM, Hill CE, Arnett DK, Limdi NA. Influence of regular physical activity on warfarin dose and risk of hemorrhagic complications. *Pharmacotherapy.* 2014; 34:545–54. [PubMed: 25032265]
20. Limdi NA, McGwin G, Goldstein JA, Beasley TM, Arnett DK, Adler BK, et al. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. *Clin Pharmacol Ther.* 2008; 83:312–21. PMCID2683398. [PubMed: 17653141]
21. Limdi NA, Beasley TM, Crowley MR, Goldstein JA, Rieder MJ, Flockhart DA, et al. VKORC1 polymorphisms, haplotypes and haplotype groups on warfarin dose among African-Americans and European-Americans. *Pharmacogenomics.* 2008; 9:1445–58. [PubMed: 18855533]
22. Limdi NA, Arnett DK, Goldstein JA, Beasley TM, McGwin G, Adler BK, et al. Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics.* 2008; 9:511–26. [PubMed: 18466099]
23. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost.* 1993; 69:236–9. [PubMed: 8470047]
24. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010; 138:1093–100. [PubMed: 20299623]
25. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med.* 1998; 158:1641–7. [PubMed: 9701098]
26. Van Spall HG, Wallentin L, Yusuf S, Eikelboom JW, Nieuwlaat R, Yang S, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. *Circulation.* 2012; 126:2309–16. [PubMed: 23027801]
27. Gallego P, Vilchez JA, Lane DA. Apixaban compared with warfarin for stroke prevention in atrial fibrillation: implications of time in therapeutic range. *Circulation.* 2013; 127:2163–5. [PubMed: 23640972]
28. Gallego P, Roldan V, Marin F, Galvez J, Valdes M, Vicente V, et al. SAME-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. *Am J Med.* 2014; 127:1083–8. [PubMed: 24858062]
29. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation.* 2008; 118:2029–37. [PubMed: 18955670]
30. Wallentin L, Yusuf S, Ezekowitz M, Alings M, Flather M, Franzosi M, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for

stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010; 376:975–83. [PubMed: 20801496]

31. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005; 3:692–4. [PubMed: 15842354]
32. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. *Am Heart J*. 2015; 170:141–8. [PubMed: 26093875]
33. Macedo AF, Bell J, McCarron C, Conroy R, Richardson J, Scowcroft A, et al. Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink. *Thromb Res*. 2015; 136:250–60. [PubMed: 26073321]
34. Ferder NS, Eby CS, Deych E, Harris JK, Ridker PM, Milligan PE, et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. *J Thromb Haemost*. 2010; 8:95–100. [PubMed: 19874474]
35. Yong C, Azarbal F, Abnoui F, Heidenreich PA, Schmitt S, Fan J, et al. Racial Differences in Quality of Anticoagulation Therapy for Atrial Fibrillation (from the TREAT-AF Study). *Am J Cardiol*. 2016; 117:61–8. [PubMed: 26552504]
36. Kawai VK, Cunningham A, Vear SI, Van Driest SL, Oginni A, Xu H, et al. Genotype and risk of major bleeding during warfarin treatment. *Pharmacogenomics*. 2014; 15:1973–83. [PubMed: 25521356]
37. Wallentin L, Lopes RD, Hanna M, Thomas L, Hellkamp A, Nepal S, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation*. 2013; 127:2166–76. [PubMed: 23640971]
38. Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. *Chest*. 2013; 143:179–84. [PubMed: 22722228]
39. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. *J Am Heart Assoc*. 2013; 2:e000067. [PubMed: 23525418]
40. Sanden P, Renlund H, Svensson PJ, Sjalander A. Warfarin treatment complications do not correlate to cTTR when above 70. *Thromb Res*. 2015; 136:1185–9. [PubMed: 26508465]
41. French B, Joo J, Geller NL, Kimmel SE, Rosenberg Y, Anderson JL, et al. Statistical design of personalized medicine interventions: the Clarification of Optimal Anticoagulation through Genetics (COAG) trial. *Trials*. 2010; 11:108. [PubMed: 21083927]
42. van Schie RM, Wadelius MI, Kamali F, Daly AK, Manolopoulos VG, de Boer A, et al. Genotype-guided dosing of coumarin derivatives: the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial design. *Pharmacogenomics*. 2009; 10:1687–95. [PubMed: 19842940]
43. Burmester JK, Berg RL, Yale SH, Rottschert CM, Glurich IE, Schmelzer JR, et al. A randomized controlled trial of genotype-based Coumadin initiation. *Genet Med*. 2011; 13:509–18. [PubMed: 21423021]
44. Jonas DE, Evans JP, McLeod HL, Brode S, Lange LA, Young ML, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. *Pharmacogenomics*. 2013; 14:1593–603. [PubMed: 24088130]
45. Borgman MP, Pendleton RC, McMillin GA, Reynolds KK, Vazquez S, Freeman A, et al. Prospective pilot trial of PerMIT versus standard anticoagulation service management of patients initiating oral anticoagulation. *Thromb Haemost*. 2012; 108:561–9. [PubMed: 22836303]
46. Anderson JL, Horne BD, Stevens SM, Woller SC, Samuelson KM, Mansfield JW, et al. A Randomized and Clinical Effectiveness Trial Comparing Two Pharmacogenetic Algorithms and Standard Care for Individualizing Warfarin Dosing (CoumaGen-II). *Circulation*. 2012; 125:1997–2005. [PubMed: 22431865]

47. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013; 369:2294–303. [PubMed: 24251363]
48. Bhavé PD, Lu X, Girotra S, Kamel H, Vaughan Sarrazin MS. Race- and sex-related differences in care for patients newly diagnosed with atrial fibrillation. *Heart Rhythm*. 2015; 12:1406–12. [PubMed: 25814418]
49. Kilickiran Avci B, Vatan B, Tok OO, Aidarova T, Sahinkus S, Uygün T, et al. The Trends in Utilizing Nonvitamin K Antagonist Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation: A Real-Life Experience. *Clin Appl Thromb Hemost*. 2015
50. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. *Am J Cardiol*. 2015; 115:1095–101. [PubMed: 25724781]
51. Xu Y, Holbrook AM, Simpson CS, Dowlatshahi D, Johnson AP. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. *CMAJ open*. 2013; 1:E115–9.

Figure 1.
Predictors of attainment of good anticoagulation control (PTTR ≥ 60 vs. <60%) among European American (middle panel) and African American (right panel) patients on warfarin therapy

Figure 2.

Risk of hemorrhage stratified by quality of anticoagulation control assessed based on percent time in target range

Top: Absolute (incidence rate) stratified by quality of anticoagulation control: poor anticoagulation control (PTTR <60%), good control (PTTR ≥60<70%), and excellent control (PTTR ≥70%).

Bottom: Relative risk of hemorrhage stratified by quality of anticoagulation control assessed by percent time in target range: poor anticoagulation control (PTTR <60%), good control (PTTR ≥60<70%), and excellent control (PTTR ≥70%).

Figure 3.

Estimated survival curve for major hemorrhage

Estimated survival curves from final Cox PH model adjusted for age, race, hypertension, chronic kidney disease, concurrent antiplatelet use, *VKORC1*-1639 genotype, possession of *CYP2C9**2 and *CYP2C9**3 variants and anticoagulation control (poor: PTTR <60%; good: PTTR 60<70%; and excellent: PTTR 70%).

Left: African American (dotted line) and European American (solid line) warfarin users

Middle: By level of anticoagulation control: poor (PTTR <60%; red lines), good (PTTR 60<70%; blue lines), and excellent (PTTR 70%; black lines).

Right: African American (dotted line) and European American (solid line) warfarin users by level of anticoagulation control: poor (PTTR <60%; red lines), good (PTTR 60<70%; blue lines), and excellent (PTTR 70%; black lines).

Table 1

Clinical, genetic and socio-demographic characteristics of participants by race

Characteristics	European Americans ^a n=748	African Americans n=578	P Value
	Mean ± SD	Mean ± SD	
Age, years	64.2 ± 15.2	57.2 ± 15.6	< 0.001
Height, inches	67.9 ± 4.0	67.4 ± 6.6	0.10
Weight, pounds	192.8 ± 50.0	200.9 ± 50.7	0.002
BSA, m ²	2.0 ± 0.3	2.0 ± 0.3	0.10
	N (%)	N (%)	
Female	321 (42.9)	330 (57.1)	<0.001
Current smoker	69 (9.2)	95 (16.4)	<0.001
Indication for Warfarin therapy			
Venous thromboembolism	260 (34.8)	307 (53.1)	<0.001
Stroke / Transient Ischemic Attack	33 (4.4)	39 (6.8)	0.06
Atrial Fibrillation	394 (52.7)	166 (28.7)	<0.001
Myocardial infarction	12 (1.6)	9 (1.6)	0.95
Peripheral arterial disease	7 (0.9)	7 (1.2)	0.63
Other	42 (5.6)	49 (8.5)	0.04
Comorbid conditions			
Hypertension	456 (61.7)	416 (72.6)	<0.001
Hyperlipidemia	404 (54.7)	234 (40.8)	<0.001
Diabetes mellitus	199 (26.9)	222 (38.7)	<0.001
Chronic Kidney disease ^b			
eGFR ≥ 60 ml/min/1.73m ²	449 (60.1)	367 (63.6)	<0.001
eGFR 30–59 ml/min/1.73m ²	254 (34.0)	132 (22.9)	
eGFR < 30 ml/min/1.73m ²	44 (5.9)	78 (13.5)	
Concurrent medications			
Statins ^c	438 (58.7)	286 (49.9)	0.002
Antiplatelet ^d	462 (61.8)	313 (54.6)	0.009
Amiodarone	99 (13.2)	41 (7.2)	<0.001
Minor Allele frequency ^e			
CYP2C9*2	13.7%	2.4%	<0.001
CYP2C9*3	6.5%	1.2%	<0.001
CYP2C9 *5	0	0.5%	-
CYP2C9 *6	0	0.4%	-
CYP2C9 *11	0	1.0%	-
VKORC1	37.1%	9.8%	<0.001
CYP4F2	30.4%	8.4%	<0.001
rs12777823	16.9%	24.8%	<0.001

SD: Standard Deviation, BSA: Body Surface Area, eGFR: estimated Glomerular Filtration Rate.

^aAsians (n=4; 0.3% and Hispanics (n=5; 0.4%) were combined with the European Americans group

^bKidney function was categorized into 3 categories: eGFR at least 60 (no CKD or mild CKD stage 1 and 2), eGFR=30–59 (moderate CKD; stage 3) and eGFR less than 30 (severe CKD; stage 4 and 5).

^cStatins included any of the HMG-CoA reductase inhibitors

^dAntiplatelet agents included aspirin, clopidogrel, and dipyridamole as mono or dual therapy

^eGenotyping was not complete for some patients at the time of analysis and therefore genotype information is not available in 86 patients for *CYP2C9*; 57 patients for *VKORC1* (rs9923231 'T' allele); 117 patients for *CYP4F2* (rs2108622; 'A' allele) and 118 patients for rs12777823 ('A' allele).

Table 2

Measures of anticoagulation control among European American and African American patients on warfarin with a target INR of 2–3

Characteristics	European Americans n=748	African Americans n=578	<i>P</i> Value
	Mean ± SD	Mean ± SD	
Time (days) to target INR ^a	10.0 (5–24)	11.5 (5–27.0)	0.03
Time (days) to stable dose (days) ^a	51.0 (30.0–90.0)	69.0 (33.0–132.0)	<0.001
Follow-up months/patient	17.8 ± 10.3	16.6 ± 10.8	0.04
Visit/person/month	2.1 ± 1.4	2.2 ± 1.8	0.03
Percent time spent in and outside target INR range			
Percent time below range (PTBR)	25.2±21.1	32.9±30.2	<0.001
Percent time in range (PTTR)	57.6±19.9	49.1±22.7	<0.001
Percent time above range (PTAR)	17.2±14.9	17.9±22.4	0.39
Quality of anticoagulation control attained			
Poor (PTTR<60)	50.3%	68.7%	<0.001
Good (PTTR 60<70)	22.9%	13.1%	<0.001
Excellent (PTTR 70)	26.9%	18.2%	0.001

^aTime to target INR and time to stable dose is represented in median number of days and inter-quartile range