Published in final edited form as:
Am J Kidney Dis. 2010 November ; 56(5): 823–831. doi:10.1053/j.ajkd.2010.05.023.

Warfarin Dosing in Patients With Impaired Kidney Function

Nita A Limdi, PharmD, PhD, MSPH[1,2], **Mohit A Limdi**[1], **Larisa Cavallari, PharmD**[3], **Aaron M Anderson, M.D**[1], **Michael R Crowley, PhD**[4], **Melissa F Baird, MD**[5], **Michael Allon, MD**[8], and **T.Mark Beasley, PhD**[7]

[1] Departments of Neurology, University of Alabama at Birmingham, AL

[2] Departments of Epidemiology, University of Alabama at Birmingham, AL

[3] Department of Pharmacy Practice, University of Alabama at Birmingham, AL

[4] Department of Genetics, University of Alabama at Birmingham, AL

[5] Division of Hematology and Oncology, University of Alabama at Birmingham, AL

[6] Division of Nephrology, University of Alabama at Birmingham, AL

[7] Department of Biostatistics, Section on Statistical Genetics, University of Alabama at Birmingham, AL

[8] University of Illinois at Chicago

Abstract

Background—Warfarin, a drug primarily metabolized by the cytochrome P450 system, is initiated at similar doses and managed similarly in patients with kidney impairment as in the general medical population. Unfortunately, few data exist to guide dose adjustment in patients with reduced kidney function. Herein we determine the degree of warfarin dose reduction associated with kidney impairment and make recommendations for warfarin dosing.

Study Design—Cross-sectional analysis.

Setting & Participants—Chronic warfarin users followed at anticoagulation clinics (n=980); 708 participants from the University of Alabama (UAB) and 272 participants from the University of Chicago (UIC).

Predictor—No/mild (eGFR≥60ml/min/1.73 m^2), moderate (eGFR=30–59ml/min/1.73 m^2) and severe (eGFR<30ml/min/1.73 m^2) kidney impairment, *CYP2C9* and *VKORC1* genotype, age, race, gender, body mass, socio-demographic factors, smoking status, alcohol, vitamin K intake, comorbid conditions (e.g. CHF, etc.) and drug interactions (e.g. amiodarone, statins, etc.).

Outcome & Measurement—Warfarin dose (mg/day) was evaluated using linear regression after adjustment for clinical demographic and genetic factors.

Results—The prevalence of moderate kidney impairment (31.8% and 27.6%) and severe kidney impairment (8.9% and 6.6%) was similar in the UAB and UIC cohorts. Warfarin dose requirements were significantly lower in patients with moderate and severe kidney impairment compared to those with none/mild kidney impairment in the UAB (p<0.001) and UIC (p<0.001) cohorts. Compared to

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.

patients with no/mild kidney impairment, patients with moderate kidney impairment required 9.5% lower doses ($p<0.001$) and patients with severe kidney impairment required 19% lower doses ($p<0.001$).

Limitations—No measurement of warfarin, serum albumin, vitamin K and clotting factor levels, no evaluation of other markers (e.g. cystatin).

Conclusion—Moderate and severe kidney impairment were associated with a reduction in warfarin dose requirements.

Keywords

Warfarin; Dose adjustment; Pharmacogenetics; CYP2C9; VKORC1; Kidney impairment

Chronic kidney disease (CKD) has emerged as a major public health concern, with about 26 million adults affected in the US.[1, 2] These patients are at a substantially increased risk of cardiovascular disease, anemia, and bone disease, and require multiple drugs to treat these complications.[3–7] Not surprisingly, drugs with primarily renal excretion require substantial dose reductions in patients with kidney impairment. However, even among drugs eliminated primarily by metabolism or non-renal transport, 25% have a ~two-fold increase in area-under-the-curve in patients with severe kidney impairment, requiring significant dose reductions.[8] Although the mechanisms of altered pharmacokinetics in kidney impairment are not well understood, animal studies suggest down-regulation of various cytochrome (CYP) enzymes and transporters, thereby influencing the response to drugs with primarily non-renal clearance.[9–11]

Warfarin, the most commonly prescribed oral-anticoagulant, exhibits large inter-patient variability in dose requirements.[12, 13] Initiation and maintenance of therapy is challenging due to the multitude of factors (diet, medications, genetics, etc.) that influence warfarin pharmacokinetics and pharmacodynamics.[12] Although clinicians recognize that anticoagulation management is even more challenging among patients with kidney impairment, warfarin therapy is initiated at similar doses and managed similarly in patients with kidney impairment as in the general medical population.[14–16] Unfortunately, few published data exist to guide dose adjustments in patients with reduced kidney function. We recently reported that patients with reduced kidney function require lower warfarin doses, even after adjustment for clinical and genetic factors known to affect warfarin metabolism. These observations suggest that warfarin may need to be instituted at a lower dose in patients with moderate or severe kidney impairment, as compared to those with mild/no kidney impairment.[17]

This secondary cross-sectional analysis assesses the degree of warfarin dose reduction associated with moderate or severe kidney impairment in two independent cohorts and derives recommendations for warfarin dosing in patients with kidney impairment.

Methods

Cohorts

University of Alabama at Birmingham (UAB) cohort—The Pharmacogenetic Optimization of Anticoagulation Therapy (POAT) and the Genetic and Environmental Determinants of Warfarin (GEDWR) are ongoing prospective cohort studies aimed at defining the influence of polymorphisms in *CYP2C9* and other genes on warfarin response. Patients ≥20 years of age were considered eligible if the intended duration of anticoagulation therapy was ≥ 2 years, therapy was managed at the anticoagulation clinic and the INR was 2–3. The

study was conducted under the approval of the Institutional Review Boards of the University of Alabama at Birmingham and Jefferson County Health System.

University of Illinois in Chicago (UIC) cohort—The UIC cohort comprised of participants ≥18 years of age who achieved stable warfarin dosing, defined as the dose that produced stable anticoagulation (INR within 0.2 units of the therapeutic range) for at least 3 consecutive clinic visits. The patients were recruited at the University of Illinois at Chicago (UIC) under the approval of the Institutional Review Board. Patients with a documented history of liver dysfunction or amiotransferase levels at least twice the upper limit of normal were excluded.

Data Collection

A detailed history documented clinical information including self-reported race, age, height and weight, serum urea nitrogen (SUN), serum creatinine (SCr), warfarin dose, INR, indication for therapy, co-morbid conditions, medications, smoking, alcohol use as detailed in recent publications.[18, 19] Concurrent therapy with medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or antiplatelet agents or drugs that alter warfarin pharmacokinetics including *CYP2C9* inhibitors (e.g. amiodarone), *CYP2C9* inducers (e.g. rifampin), or *CYP2C9* substrates (e.g. losartan) [20, 21] were documented. Both cohorts documented information on clinical, demographic and genetic factors in a similar fashion.

Kidney function

The glomerular filtration rate (eGFR) was estimated by using the 4-variable MDRD Study equation.[22] Patients were categorized into 3 groups based on eGFR as recommended by the National Kidney Foundation. Patients with eGFR ≥60 ml/min/1.73 m^2 were categorized as having no/mild kidney impairment, those with eGFR =30–59 ml/min/1.73 m^2 were categorized as having moderate kidney impairment and those with eGFR <30 ml/min/1.73 m^2 were categorized as having severe kidney impairment. Patients receiving maintenance dialysis were categorized as having severe kidney impairment.[23, 24]

CYP2C9 and *VKORC1* Genotypes

Genotypes were determined using PCR-RFLP (polymerase chain reaction– restriction fragment length polymorphism) analysis, pyrosequencing, and iPLEX technology (a single-base extension multiplex PCR assay with mass spectrometric readout from Sequenom Inc [www.sequenom.com], and performed at the Broad Institute [Cambridge, MA]) from DNA extracted from whole blood or buccal cells as detailed in recent manuscripts.[19, 25, 26] Specifically, in the *CYP2CP* gene, we assessed the single-nucleotide polymorphisms (SNPs) with reference SNP (rs) identification numbers rs1799853, rs1057910, rs28371686, rs9332131, and rs28371685. These correspond to *CYP2C9* alleles *2, *3, *5, *6, and *11, respectively, which are polymorphisms 430C/T, 1075A/C, 1080C/G, 818delA, and 1003C/T in the CYP2C9 cDNA. In the *VKORC1* gene (which encodes vitamin K epoxide reductase complex, subunit 1), we assessed SNPs −1639G>A (rs9923231) and 1173C/T(rs9934438).

Outcome Definitions and Statistical Methods

Analysis of variance was used to assess group differences for continuous variables and χ^2 test of independence for categorical variables. The assumption of Hardy-Weinberg equilibrium was tested using the χ^2 test of independence.

Warfarin dosewas defined as the average mainte nance dose required to maintain therapeutic anticoagulation for the duration of therapy (UAB cohort) or the dose that produced stable anticoagulation for at least 3 consecutive clinic visits (UIC cohort). To improve model fit and

limit heteroscedascity, we used a logarithmic transformation of warfarin dose. Evaluation of the effects of individual predictor variables on warfarin dose employed both univariate and multivariable linear regression.

Linear-regression analysis was conducted to assess the influence of CKD, *CYP2C9* and *VKORC1* genotype, age, race, gender, body mass, socio-demographic factors, smoking status, alcohol, vitamin K intake, comorbid conditions (e.g. CHF, etc.) and drug interactions (amiodarone and statins). Backward elimination technique was used to select influential predictors ($p<0.2$). *CYP2C9* and *VKORC1* genotypes were assessed in both additive and dominant models. To assess model fit, we examined residuals, and median prediction error (mg/day). The influence of predictor variables was determined in the UAB cohort and UIC cohorts separately and then combined the two data sets to perform analysis (as described above) to provide robust estimates of the influence of genetic and clinical predictors. All analyses were performed using SAS version 9.1 (SAS Institute, www.sas.com) at a non-directional alpha level of 0.05.

Results

Of the 797 eligible participants at the University of Alabama at Birmingham (UAB cohort), 76 participants (9.5%) declined participation in the study, and thirteen were excluded due to missing serum creatinine values. The remaining 708 participants (mean age 61±15 years, 50.0% men) comprised the UAB cohort (327 African Americans, 377 European Americans, 3 Hispanic and 1 Asian). Of the 303 eligible participants at UIC, 31 (10.2%) declined participation. The UIC cohort (n=272) was comprised of 207 African Americans, 23 European Americans, 42 Hispanic participants (mean age 56±16 years, 25.7% men).

Clinical, demographic and genetic characteristics for participants are presented in Table 1. Genotype distributions for *CYP2C9* and *VKORC1* were in within each race group (all p-values >0.2). As reported previously, European Americans had a higher frequency of variant *CYP2C9* (35.4%) and *VKORC1 1173* (59.7%)genotypes as compared to African Americans (11.2% and 18.4%, respectively <0.001). Genotype frequencies did not differ across GFR categories (Table 1).

Estimation of kidney function based on eGFR categorized the majority of UAB and UIC participants (59.3% and 65.8%) as no/mild kidney impairment, 31.8% and 27.6% as moderate kidney impairment, and 8.9% and 6.6% as severe kidney impairment, respectively. The distribution of kidney impairment categories did not differ across the UAB and UIC cohorts (Table 1, p=0.2). Decreased kidney function was associated with lower dose requirements among participants of the UAB and UIC cohorts (Figure 1). Warfarin dose requirements were significantly lower in patients with moderate ($p<0.001$) and severe ($p<0.001$) kidney impairment compared to those with none/mild kidney impairment.

This association remained significant after adjustment for clinical and genetic factors. Among participants of the UAB cohort, moderate kidney impairment was associated with a 10.9% (95% CI: 4.2%–17.1%) and severe kidney impairment was associated with a 21.3% (95% CI, 11.9%–29.6%) decrease in warfarin dose requirements. This kidney impairment-warfarin dose association was consistent in the UIC cohort. Among participants of the UIC cohort, moderate kidney impairment was associated with a 7.2% (95% CI, 2.6%–13.7%) and severe kidney impairment was associated with a 13.9% (95% CI, 5.1%–25.5%) decrease in warfarin dose requirements (p=0.04).

In the combined UAB-UIC cohort, alcohol (p=0.1), concomitant use of statins (p=0.9), current smoking (p=0.6), gender (p=0.4), race (p=0.2) and site (UAB vs. UIC, p=0.5) did not have a significant influence on warfarin dose. Table 2 displays dose requirements and percent dose-

changes accounted for by significant clinical and genetic predictors. As compared to patients with no/mild kidney impairment, patients with moderate kidney impairment required 9.5% lower doses ($p<0.001$) and patients with severe kidney impairment required 19.1% lower doses ($p<0.001$). Reduced kidney function, was associated with lower warfarin dose requirements independently of *CYP2C9* and *VKORC1* genotype and clinical factors. In the combined cohort (Table 3), incorporation of kidney function improved prediction of the variance in warfarin dose requirements ($F_{2,966}=16.7$; $p<0.001$) over that explained by other clinical variables only. Consistent with previous reports, incorporation of *CYP2C9* and *VKORC1* genotypes significantly improved prediction and decreased mean prediction error ($F_{2,834}=83.3$; $p<0.001$).

Discussion

The influence of kidney function on disposition of drugs excreted by the kidney is widely recognized, and used to derive dosing reductions in patients with kidney impairment. However, there is now an increasing appreciation that kidney impairment can also reduce non-renal clearance and alter the bioavailability of and response to drugs predominantly metabolized by the liver.[8, 24] The current study demonstrates that dose requirement for warfarin, a drug primarily metabolized by the hepatic cytochrome P450 system, is influenced by kidney function. Patients with moderate and severe kidney impairment require lower (~10% and 20%, respectively) warfarin doses compared to those with none/mild kidney impairment. To our knowledge, this is the first report that provides guidance on warfarin dose adjustments in patients with impaired kidney function.

Animal studies in end-stage-renal-disease (ESRD) have shown a significant down-regulation (40–85%) of hepatic cytochrome P450 metabolism.[27, 28] Invitro-invivo correlations in human subjects have also demonstrated a substantial decrease in non-renal clearance and increase in the area under the curve [8, 29, 30] of hepatically cleared drugs. These findings are corroborated by clinical data demonstrating significantly higher systemic exposure of hepatically cleared drugs at equivalent doses among patients with kidney impairment and may at least partially account for the high rates of drug toxicity in this population.[8, 30] Experience with rosuvastatin and telithromycin highlight that dosing adjustments are warranted in spite of a drug's non-renal route of elimination.[24] Most of these data are derived from observational studies and post-marketing analysis as patients with severe kidney impairment are routinely excluded from (or underrepresented in) randomized clinical trials.[31–34] Thus, observational studies are valuable in optimizing drug therapy management in the patients with kidney impairment.

In plasma, the ratio of the warfarin enantiomers (*S*)-warfarin and (*R*)-warfarin (ie, the warfarin *S/R* ratio) offers a convenient in vivo probe for monitoring relative changes in *CYP2C9* activity, because (*S*)-warfarin is metabolized almost exclusively by *CYP2C9* whereas (*R*)-warfarin is metabolized by multiple CYP and non-CYP pathways.[35, 36] Utilizing this approach, Dreisbach et al[14] demonstrated a 50% increase in the plasma warfarin *S/R* ratio among ESRD patients compared to those without ESRD after accounting for *CYP2C9* genotype, providing supportive evidence of decrease in hepatic *CYP2C9* activity in kidney failure. This may explain why patients with reduced kidney function require lower warfarin doses. We previously showed the 2.5-fold higher risk of hemorrhage among warfarin users with severe kidney impairment after accounting for genetic and clinical factors.[17] The current study demonstrates that both moderate and severe kidney impairment is associated with significantly lower warfarin dose requirements in order to maintain therapeutic anticoagulation.

The current FDA recommendations suggest kidney function staging can be based on eGFR[22] or CCr,[37] but, ideally, adjustments should be provided for both methods of staging.[24] Historically creatinine clearance (CCr) estimated by using the Cockcroft–Gault equation was widely used as a measurement of kidney function to provide guidance on dosing in patients

with impaired renal function.[37] However, in the past few years the estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease Study (MDRD) equation [22] has supplanted the CCr as the best overall measure of kidney function [38, 39] Therefore we provide warfarin dose adjustments staging kidney function based on eGFR. The high prevalence of kidney impairment (34%–40%) in our cohorts of chronic warfarin users highlights the size of the population that stands to benefit from incorporating kidney function in dosing decisions. The value of eGFR is further enhanced as it can be easily calculated using the standardized serum creatinine reported as part of the fluid balance profile which is available in most patients. Moreover as eGFR reporting is a key component of a public-health strategy for CKD,[40–42] more than 75% of laboratories now reporting eGFR (along with SCr) in the US. [43] This enhances the ease of application of the eGFR in clinical practice, patient care, and public health.

This study has limitations worth noting. First, the UAB and UIC cohorts did not routinely collect blood samples for warfarin (enantiomers and metabolites) or albumin concentration determinations. Thus we could not conduct analysis to understand alterations in albumin binding and resultant changes in warfarin pharmacokinetics.[44] Second, as vitamin K levels or levels of coagulation factors were not measured we could not evaluate their contribution on differences in warfarin dosing noted herein. Third, we did not assess other biomarkers, such as cystatin level[45–49] or eGFR calculated using the CKD Epidemiology Collaboration (CKD-Epi) equation,[50] which have demonstrated more accurate prediction of kidney function. However, the disparity between temporal trends when kidney function is assessed with different measurements suggests that estimating trends in disease burden remains an open question.[47] Moreover, eGFR is a clinically feasible method of estimating kidney function, and thus, our data are readily applicable to warfarin dosing decisions.

The significance of these findings is underscored by the increasing (10 to 13% from 1988 to 2004) prevalence of reduced kidney fucntion.[1] The prevalence of CKD in persons aged 64 years or older varies from 23.4% to 35.8%.[51] The higher kidney impairment prevalence in our cohort is perhaps explained by the higher cardiovascular comorbidity associated with warfarin candidacy.[4, 5, 52–56] Our racially diverse cohort is representative of the aging population of warfarin users. Moderate and severe kidney impairment were associated with a reduction in warfarin dose requirements. The high prevalence of kidney impairment in our cohort highlights that diminished kidney function may have implications for a larger proportion of warfarin users than previously estimated. Moreover, as the prevalence of disease (e.g. atrial fibrillation) and risk factors (e.g. obesity, diabetes) associated with thrombosis increases,[57] the use of warfarin in individuals with reduced kidney function will likely increase as well.

In conclusion, moderate and severe kidney impairment was associated with a reduction in warfarin dose required to maintain target international normalized ratio (INR). The increasing prevalence of CKD in the general population and the high prevalence in patients with cardiovascular morbidity suggests that diminished kidney function may have implications for a larger proportion of warfarin users than previously estimated.

Acknowledgments

The authors thank Dr. Joyce Goldstein and Joyce Blaisdell for their work with *CYP2C9* genotyping. We are grateful to all the patients that participated in the study. We thank Janice Ware, Joseph Huffstutler, Roberta Hill and Alison Del Carmen, Edith Nutescu, and Nancy Shapiro for their untiring efforts with patient recruitment and the staff of the Anticoagulation Clinic at The Kirklin Clinic, the Cooper Green Hospital and Jefferson Clinic P.C for their help with identification of potential participants. We also thank the physicians, especially Drs. Mark Wilson, and Melissa Baird; at the University of Alabama at Birmingham and the Health Service Foundation for their support of this research. We appreciate the work of Steve Duncan and Darlene Green and the Office of Data Resources related to the database and quality assurance.

This study has contributed samples to the National Institute of Neurological Disorders and Stroke (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.

Support: This work was supported in part by grants from the National Heart Lung and Blood Institute (R01 HL092173), NINDS (K23NS45598), and the NIH National Center for Research Resources (5UL1RR025777-02). Additional support was provided by the University of Illinois, Chicago; American Association of Colleges of Pharmacy New Investigator Award; and a University of Illinois at Chicago Hans Vahlteich Research Award. Work performed at the Broad Institute Center for Genotyping and Analysis is supported by grant U54 RR020278-01 from the National Center for Research Resources.

References

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. Jama Nov 7;2007 298(17):2038–2047. [PubMed: 17986697]
2. Bash LD, Coresh J, Kottgen A, et al. Defining incident chronic kidney disease in the research setting: The ARIC Study. American Journal of Epidemiology Aug 15;2009 170(4):414–424. [PubMed: 19535543]
3. Weiner DE. Public health consequences of chronic kidney disease. Clinical Pharmacology & Therapeutics Nov;2009 86(5):566–569. [PubMed: 19641489]
4. Weiner DE, Rifkin DE. Kidney function and the risk of cardiovascular disease. BMJ 2009;338:b1307. [PubMed: 19564177]
5. Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol Apr;2009 20(4):705–711. [PubMed: 19092127]
6. Knauf F, Aronson PS. ESRD as a window into America's cost crisis in health care. J Am Soc Nephrol Oct;2009 20(10):2093–2097. [PubMed: 19729435]
7. Anderson S, Halter JB, Hazzard WR, et al. Prediction, progression, and outcomes of chronic kidney disease in older adults. J Am Soc Nephrol Jun;2009 20(6):1199–1209. [PubMed: 19470680]
8. Zhang Y, Zhang L, Abraham S, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. Clinical Pharmacology & Therapeutics Mar;2009 85(3):305–311. [PubMed: 19020495]
9. Nolin TD. Altered nonrenal drug clearance in ESRD. Curr Opin Nephrol Hypertens Nov;2008 17(6): 555–559. [PubMed: 18941346]
10. Michaud J, Naud J, Chouinard J, et al. Role of parathyroid hormone in the downregulation of liver cytochrome P450 in chronic renal failure. J Am Soc Nephrol Nov;2006 17(11):3041–3048. [PubMed: 17021269]
11. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. Expert Opin Drug Metab Toxicol Aug;2008 4(8):1065–1074. [PubMed: 18680441]
12. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest Jun;2008 133(6 Suppl):160S–198S. [PubMed: 18574265]
13. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med Dec 4;2007 147(11):755–765. [PubMed: 18056659]
14. Dreisbach AW, Japa S, Gebrekal AB, et al. Cytochrome P4502C9 activity in end-stage renal disease. Clinical Pharmacology & Therapeutics May;2003 73(5):475–477. [PubMed: 12732848]
15. Elliott MJ, Zimmerman D, Holden RM. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. Am J Kidney Dis Sep;2007 50(3):433–440. [PubMed: 17720522]
16. Genovesi S, Vincenti A, Rossi E, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. Am J Kidney Dis Feb;2008 51(2):255–262. [PubMed: 18215703]

17. Limdi NA, Beasley TM, Baird MF, et al. Kidney Function Influences Warfarin Responsiveness and Hemorrhagic Complications. J Am Soc Nephrol Feb 18;2009 20:912–921. [PubMed: 19225037]
18. Limdi NA, Beasley TM, Crowley MR, et al. VKORC1 polymorphisms, haplotypes and haplotype groups on warfarin dose among African-Americans and European-Americans. Pharmacogenomics Oct;2008 9(10):1445–1458. [PubMed: 18855533]
19. Momary KM, Shapiro NL, Viana MA, Nutescu EA, Helgason CM, Cavallari LH. Factors influencing warfarin dose requirements in African-Americans. Pharmacogenomics Nov;2007 8(11):1535–1544. [PubMed: 18034618]
20. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol 1998;45(6):525–538. [PubMed: 9663807]
21. Rettie AE, Jones JP. Clinical and toxicological relevance of CYP2C9: drug-drug interactions and pharmacogenetics. Annual Review of Pharmacology & Toxicology 2005;45:477–494.
22. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med Aug 15;2006 145(4):247–254. [PubMed: 16908915]
23. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med Jul 15;2003 139(2):137–147. [PubMed: 12859163]
24. Huang SM, Temple R, Xiao S, Zhang L, Lesko LJ. When to conduct a renal impairment study during drug development: US Food and Drug Administration perspective. Clinical Pharmacology & Therapeutics Nov;2009 86(5):475–479. [PubMed: 19844224]
25. Limdi N, Goldstein J, Blaisdell J, Beasley T, Rivers C, Acton R. Influence of CYP2C9 Genotype on warfarin dose among African American and European Americans. Per Med May 1;2007 4(2):157–169. [PubMed: 19802360]
26. Limdi NA, McGwin G, Goldstein JA, 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. Clinical Pharmacology & Therapeutics Feb;2008 83(2):312–321. [PubMed: 17653141]
27. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on hepatic drug metabolism and drug disposition. Semin Dial Jan-Feb;2003 16(1):45–50. [PubMed: 12535300]
28. Leblond F, Guevin C, Demers C, Pellerin I, Gascon-Barre M, Pichette V. Downregulation of hepatic cytochrome P450 in chronic renal failure. J Am Soc Nephrol Feb;2001 12(2):326–332. [PubMed: 11158222]
29. Elston AC, Bayliss MK, Park GR. Effect of renal failure on drug metabolism by the liver. British Journal of Anaesthesia Aug;1993 71(2):282–290. [PubMed: 8123408]
30. Nolin TD, Frye RF, Le P, et al. ESRD impairs nonrenal clearance of fexofenadine but not midazolam. J Am Soc Nephrol Oct;2009 20(10):2269–2276. [PubMed: 19696225]
31. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J May;2009 157 (5):805–810. e801–802. [PubMed: 19376304]
32. Young AM, Billingham LJ, Begum G, et al. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. Lancet Feb 14;2009 373(9663): 567–574. [PubMed: 19217991]
33. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. New England Journal of Medicine Jul 21;2005 353(3):238–248. [PubMed: 16034009]
34. Strippoli GF, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ Mar 22;2008 336 (7645):645–651. [PubMed: 18299289]
35. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. Pharmacology & Therapeutics 1997;73(1):67–74. [PubMed: 9014207]
36. Rettie AE, Korzekwa KR, Kunze KL, et al. Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-4502C9 in the etiology of (S)-warfarin-drug interactions. Chemical Research in Toxicology Jan-Feb;1992 5(1):54–59. [PubMed: 1581537]

37. Spruill WJ, Wade WE, Cobb HH 3rd. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. Clinical Pharmacology & Therapeutics Nov;2009 86(5):468–470. [PubMed: 19844221]
38. Stevens LA, Levey AS. Use of the MDRD study equation to estimate kidney function for drug dosing. Clinical Pharmacology & Therapeutics Nov;2009 86(5):465–467. [PubMed: 19844220]
39. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol Nov;2009 20(11):2305–2313. [PubMed: 19833901]
40. Jain AK, McLeod I, Huo C, et al. When laboratories report estimated glomerular filtration rates in addition to serum creatinines, nephrology consults increase. Kidney International Aug;2009 76(3): 318–323. [PubMed: 19436331]
41. Levey AS, Schoolwerth AC, Burrows NR, Williams DE, Stith KR, McClellan W. Comprehensive public health strategies for preventing the development, progression, and complications of CKD: report of an expert panel convened by the Centers for Disease Control and Prevention. American Journal of Kidney Diseases Mar;2009 53(3):522–535. [PubMed: 19231739]
42. Stevens LA, Levey AS. Impact of reporting estimated glomerular filtration rate: it's not just about us. Kidney International Aug;2009 76(3):245–247. [PubMed: 19904255]
43. Miller WG. Reporting estimated GFR: a laboratory perspective. American Journal of Kidney Diseases Oct;2008 52(4):645–648. [PubMed: 18805345]
44. Meijers BK, Bammens B, Verbeke K, Evenepoel P. A review of albumin binding in CKD. American Journal of Kidney Diseases May;2008 51(5):839–850. [PubMed: 18436096]
45. Selvin E, Kottgen A, Coresh J. Kidney function estimated from serum creatinine and cystatin C and peripheral arterial disease in NHANES 1999–2002. European Heart Journal Aug;2009 30(15):1918–1925. [PubMed: 19487236]
46. Taglieri N, Koenig W, Kaski JC. Cystatin C and cardiovascular risk. Clinical Chemistry Nov;2009 55(11):1932–1943. [PubMed: 19713275]
47. Foley RN, Wang C, Snyder JJ, Collins AJ. Cystatin C levels in U.S. adults, 1988–1994 versus 1999–2002: NHANES. Clin J Am Soc Nephrol May;2009 4(5):965–972. [PubMed: 19339409]
48. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. American Journal of Kidney Diseases Mar;2008 51(3):395–406. [PubMed: 18295055]
49. Tidman M, Sjostrom P, Jones I. A Comparison of GFR estimating formulae based upon s-cystatin C and s-creatinine and a combination of the two. Nephrol Dial Transplant Jan;2008 23(1):154–160. [PubMed: 17911090]
50. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med May 5;2009 150(9):604–612. [PubMed: 19414839]
51. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. BMC Public Health 2008;8:117. [PubMed: 18405348]
52. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol Jan;2008 19(1):135–140. [PubMed: 18032796]
53. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol Feb;2007 18(2):629–636. [PubMed: 17215445]
54. Weiner DE, Tighiouart H, Amin MG, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol May;2004 15(5):1307–1315. [PubMed: 15100371]
55. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J Oct;2009 158(4):629–636. [PubMed: 19781424]
56. Mahajan A, Qiu J, Stark PC, et al. Prevalence of ICD-9-CM codes for chronic kidney disease in individuals with cardiovascular disease risk factors. J Nephrol Jul-Aug;2009 22(4):523–533. [PubMed: 19662609]

57. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation Jan 27;2009 119(3):480–486. [PubMed: 19171871]

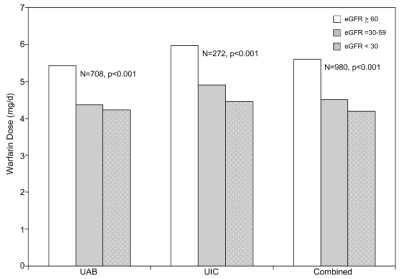

Figure 1. Influence of kidney function on warfarin dose requirements

Average warfarin dose by stratified by cohort. UAB denotes cohort of participants from the University of Alabama at Birmingham. UIC denotes participants from the University of Illinois in Chicago. The combined cohort includes participants from UAB and UIC. Patients eGFR ≥60 were categorized as having no/mild kidney impairment, those with eGFR =30–59 were categorized as having moderate kidney impairment and those with eGFR <30 ml/min/1.73 m^2 were categorized as having severe kidney impairment. Patients receiving maintenance dialysis were categorized as having severe kidney impairment.

Table 1

Baseline cohort characteristics by level of kidney function

	eGFR ≥ 60 (n=599)	eGFR 30–≤59 (n=300)	eGFR <30 (n=81)	*P*
Age (years)	56.8 ±15.7	66.3 ± 13.4	56.9 ± 15.3	<0.001
BMI (kg/m^2)	31.2 ± 8.5	30.1 ± 7.7	30.2 ± 6.3	0.3
Height (in inches)	67.2 ± 4.1	66.2 ± 4.1	66.9 ± 3.9	0.07
Weight (in lbs)	199.9 ± 55.1	190 ± 80.9	193.1 ± 47.1	0.1
Ideal Body Weight (kg)	61.2 ± 11.3	62.5 ± 11.0	63.3 ± 10.4	0.09
Warfarin dose (mg/day)	6.1 ± 2.6	5.0 ± 2.2	4.6 ± 1.9	<0.001
Serum urea nitrogen (mg/dl)	13.2 ± 5.0	21.9 ± 11.8	38.2 ± 18.4	<0.001
Serum creatinine (mg/dl)	0.93 ± 0.2	1.37 ± 0.3	5.9 ± 4.1	<0.001
Race				<0.001
European American	219 (36.6%)	156 (52.0%)	22 (27.1%)	
African American	353 (58.9%)	126 (42.0%)	55 (67.9%)	
Hispanic or Asian	27 (4.5%)	18 (6.0%)	4 (0.05%)	
Gender				0.4
Male	269 (44.9%)	120 (40.0%)	35 (43.2%)	
Female	330 (55.1%)	180 (60.0%)	46 (56.8%)	
Indication/comorbidities				
Venous thromboembolism	283 (47.1%)	102 (34.0%)	38 (46.9%)	<0.001
Stroke/TIA	108 (18.0%)	51 (16.9%)	7 (8.7%)	0.1
Atrial Fibrillation	185 (30.8%)	147 (46.7%)	32 (40.0%)	<0.001
Congestive heart failure	88 (14.7%)	78 (26.0%)	20 (24.7%)	<0.001
Coronary artery disease	141 (23.5%)	112 (37.3%)	29 (35.8%)	<0.001
Diabetes mellitus	162 (27.0%)	112 (37.3%)	36 (44.4%)	<0.001
Hypertension	329 (54.9%)	202 (67.3%)	76 (93.8%)	<0.001
Cancer	71 (11.8%)	41 (13.7%)	10 (12.3%)	0.7
Current smokers	84 (14.0%)	30 (10.0%)	15 (18.5%)	0.08
Current alcohol use	175 (29.3%)	70 (23.3%)	10 (12.3%)	0.002
Concurrent amiodarone	33 (5.6%)	33 (11.0%)	8 (9.9%)	0.01
Concurrent statin	241 (40.5%)	135 (45.0%)	40 (49.4%)	0.2
VKORC1 variant[a]	170 (32.4%)	101 (39.8%)	26 (37.1%)	0.1
CYP2C9 variant[b]	108 (20.1%)	57 (22.1%)	16 (21.9%)	0.8
Site				0.1
UAB	420 (70.1%)	225 (75.0%)	63 (77.8%)	
UIC	179 (29.9%)	75 (25.0%)	18 (22.2%)	

Note: Values shown are mean ± standard deviation or number (percentage). P-values for continuous variables are based on t-test/Kruskal-Wallis test; P values for categorical variables based on chi-square test. eGFR (estimated glomerular filtration rate) is based on National Kidney Foundation staging using the Modification of Diet in Renal Disease Study equation, and is reported in mL/min/1.73 m2 (factor for conversin to mL/s/1.73 m2, ×0.01667). Patients eGFR ≥60 were categorized as having no/mild kidney impairment, those with eGFR =30–59 as having moderate kidney impairment and those with eGFR <30 as having severe kidney impairment. Patients receiving maintenance dialysis were categorized as having severe kidney

impairment. For UAB participants, information missing for SUN (n=3), statin (n=3), amiodarone (n=3), alcohol (n=2). For UIC participants, information missing for SUN (n=13), statin (n=1), amiodarone (n=1).For UAB participants *VKORC1* (n=131) *CYP2C9* (n=113) remain to be determined.

[a] *VKORC1* variant refers to −1173C>T allele, and includes genotypes TT or CT.

[b] *CYP2C9* variant genotype includes *2, *3 alleles among European Americans and *2, *3, *5, *6 and *11 alleles among African Americans.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; UAB, University of Alabama at Birmingham; UIC, University of Illinois at Chicago; TIA, transient ischemic attack.

Table 2

Influence of kidney function, clinical factors, and*VKORC1* and *CYP2C9* genotype on warfarin dose requirements in the combined cohort

	Warfarin Dose[d] (mg/d)	% Dose Change	*p* value
Referent patient[a]	7.0 (6.5–7.7)		
Variable			
Age (per decade increase over 40)	6.5 (6.0–6.9)	−7.2 (−5.6 to −8.7)	<0.001
Weight (per 10 lb increase over 180)	7.0 (6.5–7.7)	1.7 (1.5 to 2.3)	<0.001
Height (per inch increase over 68 inches)	7.0 (6.5–7.7)	1.4 (0.7 to 2.0)	<0.001
Concurrent amiodarone	5.8 (5.0–6.6)	−17.2 (−9.1 to −24.5)	<0.001
VKORC1 variant[b]	5.2 (4.7–5.7)	−25.6 (−21.6 to −29.3)	<0.001
CYP2C9 variant[c]	5.5 (4.7–6.4)	−19.9 (−15.0 to −24.6)	<0.001
Moderate kidney impairment (eGFR 30–59)	6.4 (5.5–7.3)	−9.5 (−4.4 to −13.6)	<0.001
Severe kidney impairment (eGFR<30)	5.7 (4.8–6.8)	−19.1 (−11.4 to −26.1)	<0.001

Note: Combined cohort includes University of Alabama at Birmingham and University of Illinois at Chicago participants. Values in parentheses are 95% confidence intervals. eGFR (estimated glomerular filtration rate) is based on National Kidney Foundation staging using the Modification of Diet in Renal Disease Study equation, and is reported in mL/min/1.73 m2 (factor for conversin to mL/s/1.73 m2, ×0.01667). Patients eGFR >60 were categorized as having no/mild kidney impairment, those with eGFR =30–59 as having moderate kidney impairment and those with eGFR <30 as having severe kidney impairment. Patients receiving maintenance dialysis were categorized as having severe kidney impairment.

[a]The referent patient is a 40 year old man weighing 180 pounds, 68” tall, with wild-type *CYP2C9* and *VKORC1* genotype, GFR ≥60, not on current amiodarone therapy.

[b]*VKORC1* variant refers to −1173C>T allele, and includes genotypes TT or CT.

[c]*CYP2C9* variant genotype includes *2, *3 alleles among European Americans and *2, *3, *5, *6 and *11 alleles among African Americans.

Abbreviations: eGFR, estimated glomerular filtration rate.

[d]Dose is equal to the exponent of 1.94–0.074 (for each decade of age over 40) + 0.0174 (for each 10 pound increment over 180lbs) + 0.0137 (for each inch of height over 68”) – 0.188 (if concurrent amiodarone therapy) – 0.222 (if *CYP2C9* variant) – 0.295 (if *VKORC1* variant) – 0.094 (if eGFR=30–59) – 0.212 (if eGFR <30).

Table 3

Dosing accuracy in the combined cohort

	Clinical variables[1]	**Clinical + eGFR** [2]	**Clinical + eGFR + Genes**[3]
UAB cohort R^2	22.6%	25.2%	37.8%
UIC cohort R^2	28.0%	29.0%	42.6%
Combined cohort R^2	22.8%	25.3%	38.0%

Note: Combined cohort includes University of Alabama at Birmingham and University of Illinois at Chicago participants. eGFR (estimated glomerular filtration rate) is based on National Kidney Foundation staging using the Modification of Diet in Renal Disease Study equation. Patients eGFR >60 in mL/min/1.73 m2 were categorized as having no/mild kidney impairment, those with eGFR =30–59 in mL/min/1.73 m2 as having moderate kidney impairment and those with eGFR <30 in mL/min/1.73 m2 ml/min/1.73 m2 as having severe kidney impairment. Patients receiving maintenance dialysis were categorized as having severe kidney impairment.

[1] Clinical variables include age, gender, race, weight and concurrent amiodarone use

[2] Clinical + eGFR includes clinical variables and eGFR category.

[3] Clinical + eGFR + genes includes clinical variables, eGFR category and *CYP2C9* and *VKORC1* genotype (*CYP2C9* variant genotype includes *2, *3 alleles among European Americans and *2, *3, *5, *6 and *11 alleles among African Americans; *VKORC1* variant refers to −1173C>T allele, and includes genotypes TT or CT).