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INFLUENCE OF KIDNEY FUNCTION ON RISK OF HEMORRHAGE AMONG PATIENTS TAKING WARFARIN: A COHORT STUDY

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Chronic kidney disease (CKD) affects more than 26 million Americans, of which 15.5 million have Stage 3 CKD (eGFR 30 <60 ml/min/1.73 m²).¹ This broad categorization fails to recognize important differences between patients with Stage 3a (eGFR 45-59 ml/min/1.73m²) and 3b (eGFR 30-44 ml/min/1.73m²) CKD.^{2,3} Compared to warfarin users with eGFR ≥ 60 ml/min/1.73 m² those with Stage 3 CKD (eGFR 30-59 ml/min/1.73m²) had a similar risk of hemorrhage while those with Stage 4/5 CKD (eGFR <30 ml/min/1.73m²) had a higher risk.⁴ Herein we evaluate whether the risk of bleeding warfarin-related hemorrhage differs among patients with Stage 3a and 3b CKD.

The Pharmacogenetic Optimization of Anticoagulation Therapy and the Genetic and Environmental Determinants of Warfarin are ongoing prospective incident cohort studies enrolling participants (> 20 years; 43% Black) with a target INR of 2-3 under the approval of the IRB. Detailed medical and social history was obtained at baseline. At each monthly visit INR, warfarin dose, medication changes, including antiplatelet therapy were recorded (see supplemental material). The glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation⁵ at initiation of therapy.

Major hemorrhagic events were defined per Fihn et al.⁶ During a 2 year follow-up, all medically documented hemorrhages were adjudicated by an independent physician before analysis. Incidence rate of hemorrhage and confidence intervals were calculated using OpenEpi version 2.3.1 (<http://www.openepi.com/OE2.3/Menu/OpenEpiMenu.htm>). The influence of kidney function on risk of hemorrhage was tested without and with adjustment for age, race, gender, INR, treatment with amiodarone, antiplatelet drugs, statins, number of comorbid conditions, *VKORC1* and *CYP2C9* genotypes using Cox proportional hazards regression using the counting process format in SAS version 9.2 as previously reported.^{7,8} For all analysis a p-value of ≤ 0.05 was considered statistically significant.

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The authors report no conflict of interest.

We studied 1245 (3 were not included due to missing eGFR) patients followed in anticoagulation clinics (mean age 61 +16 years; 48.2% female; 43% black and 56.2% white). The distribution of patients by kidney function is shown in Table 1. Thirty-five percent of patients had impaired kidney function ($\text{eGFR} < 60 \text{ ml/min/1.73m}^2$).

There were 127 major hemorrhagic events observed during 1667 years of follow-up (incidence 7.6/100 patient-years; 95% CI: 6.4-9.0). As the eGFR decreased the incidence rate of hemorrhage increased. The incidence of hemorrhage was similar for eGFR categories 90, 75-89, 60-74 and 45-59 ml/min/1.73m^2 (p-values >0.3). The incidence of hemorrhage was significantly higher among patients with $\text{eGFR} < 30$ and 30-44 ml/min/1.73m^2 compared to the other eGFR categories (Table 2).

The hazard ratios for major hemorrhage for each eGFR group are presented in Table 2. Patients with $\text{eGFR} < 45 \text{ ml/min/1.73m}^2$ were at a higher risk of hemorrhage even after adjustment for age, race, gender, INR at the time of the event, CYP2C9 and VKORC1 genotypes and concurrent antiplatelet therapy. After adjustment of the other factors, patients with high INR, CYP2C9 variants, were taking antiplatelet agents and higher comorbidity also had an elevated risk ($p < 0.05$, data not shown).

This study shows that impaired kidney function increases the risk of hemorrhage in a racially diverse prospective cohort of incident warfarin users representative of the complex patients seen in clinical practice. Compared to patients with $\text{eGFR} \geq 60 \text{ ml/min/1.73m}^2$, those with $\text{eGFR} 30-44 \text{ ml/min/1.73 m}^2$ are at a 2-fold higher risk of hemorrhage and those with $\text{eGFR} < 30 \text{ ml/min}$ are at a 5.6-fold higher risk.

This study has several strengths including a large incident cohort, prospective data collection, and availability of clinical and genetic variables. However factors such as diet and other genes that may affect risk of hemorrhage were not accounted for. As urine albumin levels were not available categorization of kidney function based on eGFR and albuminuria was not possible. Although antiplatelet treatment was captured, drug names and dose(s) were not available. Therefore we could not account for antiplatelet dosage. Moreover the current analysis was not adequately powered to assess the antiplatelet-eGFR interaction.

As this study showed an increase risk of major hemorrhage with decreased kidney function, the net benefit of warfarin therapy may be lower in patients with a lower eGFR. Therefore, the tradeoff between benefit versus risk of treatment is likely to be different based of kidney function. However as this study did not ascertain thromboembolic events, we cannot provide guidance on the "Treat/ Do not treat" decision. To enable better clinical decisions, future studies that capture both thromboembolic and hemorrhagic events are needed to evaluate the risk-benefit of warfarin in patients with varying degrees of kidney impairment.

Thirty-five percent of participants had reduced renal function ($\text{eGFR} < 60 \text{ ml/min/1.73m}^2$) and 17.8% of patients were at a higher risk of hemorrhage. These findings highlight that impaired kidney function may have implications for a larger proportion of warfarin users than previously estimated. Moreover this calls attention several overarching issues: to the recognition of the influence of kidney function on response to medications, including those with predominantly non-renal clearance; to the representation of patients with impaired kidney function in clinical trials; to the assessment of risk-benefit of treatment in patients with varying degrees of kidney impairment and to and to development of treatment recommendations tailored to patients with CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical and Demographic characteristics of 1245 patients on chronic warfarin therapy by baseline kidney function *

Characteristics	Glomerular Filtration Rate (ml/min/1.73m ²)					
	90 (N=298)	75-89 (N=224)	60-74 (N=282)	45-59 (N=219)	30-44 (N=109)	<30 (N=113)
Age (years)	48.6 ±14.8	61.4 ±13.7	65.4 ± 13.2	68.5 ± 12.4	72.7 ± 12.9	57.8 ± 15.9
Follow-up (months)	13.7 ±10.5	17.4 ±12.0	17.6 ±11.2	16.9 ±11.6	16.6 ±10.5	13.3 ±10.1
BMI (kg/m ²)	30.8 ± 8.5	30.0 ±7.0	30.3 ±7.3	29.0 ±7.5	29.3 ±7.2	30.1 ±6.9
Race						
African American	166 (55.7%)	79 (35.3%)	110 (39.0%)	72 (32.9%)	35 (32.1)	75 (66.4%)
European American	126 (42.3%)	144 (64.3%)	172 (61.0%)	146 (66.7%)	74 (67.9%)	38 (33.6%)
Other	6 (2%)	1(0.33%)	0	1(0.46%)	0	0
Gender						
Female	148 (49.7%)	89 (29.8%)	134 (47.5%)	116 (53.0%)	56 (51.4%)	58 (51.3%)
Male	150 (50.3%)	135 (45.1%)	148 (52.5%)	103 (47.0%)	53 (48.6%)	55 (48.7%)
Indication for warfarin						
Atrial Fibrillation	69 (23.1%)	101 (45.1%)	137 (48.6%)	125 (57.1%)	61 (55.9%)	38 (33.6%)
Stroke	19 (6.4%)	15 (6.70%)	16 (5.7%)	16 (7.3%)	9 (8.26%)	2 (1.8%)
Venous Thromboembolism	178 (59.7%)	92 (41.1%)	102 (36.2%)	64 (15.5%)	30 (27.5%)	57 (50.4%)
Other	32 (10.7%)	16 (7.14%)	27 (9.57%)	14 (6.39%)	9 (8.26%)	16 (14.2%)
Number of Comorbid Conditions						
Low (0 or 1)	151 (50.7%)	70 (31.2%)	54 (19.1%)	38 (17.3%)	11 (12.8%)	0 (00.0%)
Medium (2 to 4)	115 (38.6%)	108 (48.2%)	156 (55.3%)	106 (48.4%)	54 (49.5%)	56 (49.6%)
High (5 or more)	32 (10.7%)	46 (20.5%)	72 (25.5%)	75 (34.2%)	44 (40.4%)	57 (50.4%)
Concurrent Medications						
Antiplatelet agents	122 (40.8%)	118 (52.7%)	167 (59.2%)	140 (63.9%)	72 (66.1%)	56 (49.6%)
Statins	42 (14.0%)	55 (24.6%)	79 (28.0%)	58 (26.5%)	27 (24.8%)	29 (25.7%)
Amiodarone	11 (3.7%)	22 (9.82%)	27 (9.57%)	28 (12.8%)	18 (16.5%)	11 (9.73%)
Genotype **						
CYP2C9 Variant	35 (20.5%)	24 (21.0%)	27 (18.4%)	35 (26.3%)	10 (18.5%)	15 (21.4%)
VKORC1 Variant	61 (35.7%)	44 (39.3%)	43 (30.3%)	50 (38.8%)	28 (52.8%)	19 (27.5%)

* All patients on warfarin therapy with target INR of 2-3. Serum Creatinine was determined by the Jaffe rate method standardized to IDMS. eGFRs were estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and presented as ml/min/1.73m². Information on serum creatinine and GFR was missing in 3 patients. Continuous variables are represented as Mean ± standard deviation; Categorical variables represented as number and (column percent) Other race includes 3 Asian and 5 Hispanic patients Other indications include cardiac thrombus, peripheral vascular disease, low ejection fraction, etc. Comorbidity was defined as concomitant diseases (e.g. hypertension, high cholesterol, diabetes, congestive heart failure etc.) Low comorbidity refers to presence of 0 or 1 condition; moderate comorbidity denotes 2-3 conditions and severe comorbidity denotes four or more conditions. Concurrent antiplatelet agents included aspirin, clopidogrel, and dipyridamole as mono or dual therapy.

** Genotype information was not available for 584 patients for VKORC1 and 571 for CYP2C9 as these samples had not been genotyped. Percent genotype within each eGFR 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 *VKORC1-1173C/T* (rs9934438) includes *TT* or *CT*

Table 2

Incidence (per 100 patient years) and Hazard ratio for Major hemorrhage by level of kidney function

Category (ml/min/1.73m ²)	N=1245	Events	Years	Incidence [95%CI]	P-value*
eGFR 90	298	20	340.9	5.9 [3.7,8.9]	Referent
eGFR 75-89	224	20	326.0	6.1 [3.9,9.3]	0.83
eGFR 60-74	282	22	415.0	5.3 [3.4,7.9]	0.74
eGFR 45-59	219	21	308.6	6.8 [4.3,10.2]	0.64
eGFR 30-44	109	17	151.0	11.3 [6.8,17.7]	0.053
eGFR <30	113	27	125.3	21.5 [14.5,30.9]	<0.0001

	Unadjusted HR [95% CI]	P Value	Adjusted HR [95% CI]	P-value
eGFR 90	Referent	-	Referent	-
eGFR 75-89	1.1 [0.51, 2.33]	0.82	1.14 [0.54, 2.41]	0.73
eGFR 60-74	0.93 [0.45, 1.92]	0.86	1.00 [0.49, 2.03]	0.99
eGFR 45-59	1.21 [0.59, 2.46]	0.60	1.27 [0.63, 2.57]	0.50
eGFR 30-44	1.98 [0.93, 4.23]	0.07	2.13 [1.01, 4.50]	0.048
eGFR <30	3.65 [1.83, 7.29]	0.0002	3.98 [2.0, 7.90]	<0.0001

eGFR 60	Referent	-	Referent	-
eGFR 45-59	1.21 [0.71,2.04]	0.49	1.11 [0.55,2.25]	0.78
eGFR 30-44	1.97 [1.10,3.55]	0.024	2.11 [1.01,4.41]	0.048
eGFR <30	3.64 [2.18,6.07]	<0.0001	5.65 [3.11,10.27]	<0.0001

All patients on warfarin therapy with target INR of 2-3. Serum Creatinine was determined by the Jaffe rate method standardized to IDMS. eGFRs are estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and presented as ml/min/1.73m². Information on serum creatinine and GFR was missing in 3 patients. Major Hemorrhagic complications include serious, life threatening and fatal bleeding episodes as defined by Fihn et al. All major hemorrhagic complications were adjudicated by the Director of the Anticoagulation Clinic blinded to genotype. Gastrointestinal hemorrhage was most common (n=74), followed by hematoma (n=27), Genitourinary (n=10), Intracranial hemorrhage (n=9), Hemoptysis (n=1); not recorded (n=6). Major hemorrhages occurred throughout followup; 26 in the first 3 months, 27 in 3-6 months and 74 after 6 months.

* P-values listed are based on comparison with the referent group

** Adjusted for race and INR at the time of the event for the analysis of hemorrhage risk across 6 categories and for gender, race, *CYP2C9* genotypes, and concurrent therapy with antiplatelet agents, and INR at the time of the event for analysis across 4 categories.