Published in final edited form as:

Am Heart J. 2017 February ; 184: 150–155. doi:10.1016/j.ahj.2016.08.017.

Incidence of severe renal dysfunction among individuals taking warfarin and implications for non–vitamin K oral anticoagulants

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Abstract

Background—The purpose of this study is to assess incidence and risk factors for severe renal dysfunction in patients requiring oral anticoagulation to help guide initial drug choice and provide a rational basis for interval monitoring of renal function for patients prescribed non–vitamin K oral anticoagulants.

Methods—Patients on warfarin for atrial fibrillation or venous thromboembolism were consecutively enrolled from January 2007 to December 2010. Baseline kidney function was assessed, and patients were followed to their first decline of kidney function to creatinine clearance <30 mL/min. Multivariate regression assessed independent risk factors for the primary outcome. Severe renal impairment based on baseline kidney function was assessed by Kaplan-Meier analyses.

Results—Of 787 patients identified, 34 were excluded for baseline CrCl <30 mL/min. The mean age was 71 years, and 74% and 31% had hypertension and diabetes mellitus, respectively. At baseline, 23% (n = 174) had moderate chronic kidney disease (CKD) (CrCl 30–59 mL/min), whereas 31% had mild CKD (CrCl 60–89 mL/min). Severe renal impairment occurred in 92 patients (12%), 25% of which was seen within 5.3 months. Of those with baseline stage 3 CKD, 37% developed severe renal impairment. Stage 3 CKD conferred a 14-fold increased risk in the development of severe renal dysfunction (odds ratio 14.5, 95% CI 6.7–31.3, $P < .001$). Coronary artery disease was also associated with severe renal impairment (odds ratio 2.2, 95% CI 1.3–3.8, $P = .004$).

Conclusions—Acute and chronic renal dysfunction is common among individuals requiring long-term anticoagulant therapy. Patients with moderate chronic kidney disease and coronary

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Disclosures

Drs Fanola, Cowan, Ko, and Mooney have no conflicts of interest to disclose. Dr Hylek has served as an advisor to Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Medtronic, Pfizer, and Portola.

artery disease are at the highest short-term risk of developing severe renal impairment. More frequent monitoring of these patients is warranted.

Background

Vitamin K antagonists (VKAs) have been the standard of care for stroke prevention in atrial fibrillation (AF) and treatment of venous thromboembolism (VTE). Because of its variable dose response and narrow therapeutic window, one of the major limiting factors in the use of warfarin anticoagulation among adults is hemorrhage,^{1–4} and thus, frequent monitoring of its anticoagulant effect is mandated.⁵ The randomized trials of dabigatran, rivaroxaban, edoxaban, and apixaban for stroke prevention among individuals with atrial fibrillation have all demonstrated a reduction in fatal bleeding and intracranial hemorrhage compared with warfarin.^{6–9}

Translation of these trial results to patients in clinical practice assumes similarity of baseline risk. Importantly, unlike warfarin, all of the non-vitamin K oral anticoagulants (NOACs) are eliminated to some degree via renal mechanisms. In addition, each drug has a different threshold of renal function that mandates a reduction in dose, and none were studied in individuals with severe renal impairment in the randomized trials. Current guidelines suggest that NOACs at reduced dosing may be considered for subjects with moderate to severe chronic kidney disease (CKD); however, safety and efficacy have not been established because these patients were purposefully excluded from the trials.^{10,11} Renal-specific dosing introduces an additional challenge in clinical practice, as renal function fluctuates and this variability is not easily predictable. Changes in renal function, depending on the degree and duration, could result in higher concentrations of these drugs, thereby exposing patients to potential bleeding risk during periods of renal compromise. To date, there is limited information on the stability of renal function and therefore stability of anticoagulant dose over time among patients on long-term anticoagulant therapy in clinical practice. Current guidelines recommend a baseline assessment of renal function prior to drug initiation and at least annually thereafter.¹¹

Aims

The goals of our study were (1) to define baseline renal function in a cohort of patients prescribed long-term warfarin therapy for either AF or VTE, (2) to determine the incidence of *severe renal impairment* defined by a creatinine clearance (CrCl) <30 mL/min during the follow-up period, and (3) to identify the highest-risk patient subgroups that may warrant more frequent monitoring of renal function.

Methods

Study population

Eligible patients that met inclusion and exclusion criteria for the cohort study were identified and consecutively enrolled from a university hospital-based anticoagulation clinic from January 1, 2007, to December 31, 2010, and followed through December 2011. To ensure a broad representation of age, we included individuals whose primary indication for long-term

warfarin therapy was either AF or VTE. The primary indication for warfarin therapy was verified at the time of referral to the anticoagulation clinic and validated by study investigators through rigorous medical record review. Individuals were eligible if they had a baseline CrCl close to enrollment and 2 outpatient creatinine measurements during the warfarin exposure period. Individuals with a mechanical heart valve, baseline CrCl <30 mL/min, or expected short duration of warfarin therapy (<3 months) were excluded. The study was approved by the local institutional review board.

Data collection

Study subjects' baseline clinical and demographic factors were extracted from the medical record through rigorous clinician medical record review. Data collection was performed with a standardized case report form. Data collected included indication for anticoagulant therapy, age, sex, race, history of hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), congestive heart failure (CHF), and stroke. The variables ascertained through medical record review had the additional following criteria: *HTN* was defined by the presence of 2 or more blood pressure readings >140/90 mm Hg plus the presence of 1 or more antihypertensive medications. *CHF* was diagnosed by the presence of left ventricular dysfunction (ejection fraction <40%) by echocardiography or *CHF* with New York Heart Association Class II or higher symptoms. *DM* was defined by the presence of insulin or oral diabetic medication, or documented hemoglobin A1C level >7.0% if not on medications. The diagnosis of stroke was confirmed by computed tomography or magnetic resonance imaging, and CAD was determined by myocardial infarction history, stress testing, and/or coronary angiography.

Renal function

We assigned the closest outpatient creatinine value within 6 months of the anticoagulant clinic enrollment date as the baseline creatinine; however, nearly all values were available within weeks of warfarin therapy initiation. All creatinine measurements were determined by a single laboratory, and those that occurred within the initial setting of an emergency department visit or hospital admission were included. Values greater than 24 hours into a hospitalization were excluded to avoid iatrogenic acute kidney decline. Renal function based on these values was estimated using the Cockcroft-Gault calculation¹² consistent with recent trials.^{6–9} The stage of baseline renal function was approximated using CrCl, and according to the National Kidney Foundation, we defined the following: stage 1: >90 mL/min, stage 2: 60–89 mL/min, stage 3: 30–59 mL/min, stage 4: 15–29 mL/min, and stage 5: <15 mL/min.¹³ We defined *mild*, *moderate*, and *severe renal impairment* as CKD stage 2, stage 3, and stage 4–5, respectively.

Statistical analyses

Baseline creatinine and CrCl measurements were presented as the median and interquartile range. The follow-up interval was determined for each patient and the median number of days, and interquartile ranges were calculated. Wilcoxon rank-sum testing was performed to assess differences in the distribution of the continuous variables, and Kruskal-Wallis testing assessed differences in baseline kidney function by clinical subgroups. Patients with a decline in CrCl to less than 30 mL/min during the follow-up period were compared with

those patients who did not experience this degree of decline. Categorical variables were analyzed using χ^2 analysis. Logistic regression was performed to assess the independent effects of candidate variables with $P < .10$ in the univariate analysis. A subsequent sensitivity analysis was performed which excluded those patients whose decline in renal function occurred as part of a hospitalization. Lastly, Kaplan-Meier survival analyses assessed the development of severe renal dysfunction according to baseline kidney function during the follow up period. Patients were censored at the time of first occurrence of CrCl <30 mL/min or upon termination of warfarin therapy.

Results

Baseline characteristics

We identified 787 individuals with 2 or more eligible creatinine measurements during the warfarin exposure period. Of these, 34 individuals had stage 4 or stage 5 CKD at baseline and were excluded. The mean age of the study population was 71 years; 45% were female, and 45% were black (Table I). The baseline prevalence of other comorbid illnesses was 74% HTN, 34% CHF, 31% DM, 24% CAD, and 9% prior stroke. At baseline, 23% (n = 174) had moderate renal impairment, CrCl 30–59 mL/min, and 31% had mild, CrCl 60–89 mL/min.

Longitudinal assessment of renal function

The median observation time was 28.5 months, and the median number of CrCl measurements was 10. The median interval between creatinine measurements was 68 days. There was no difference in monitoring frequency across baseline kidney function: median intervals were 62, 67, and 70 days, respectively, for moderate impairment, mild impairment, and normal renal function ($P = .23$). In our cohort of 753 individuals on long-term warfarin therapy, 12% (n = 92) developed severe renal impairment, and 25% of these patients experienced this decline within 5.3 months. Nineteen events occurred in the context of a hospitalization.

Of the 92 patients who developed severe renal impairment, 70% had a baseline CrCl 30–59 mL/min (Table I). Four percent of those with normal kidney function at baseline and 6% of those with mild renal impairment experienced a decline in CrCl to less than 30 mL/min. Overall, the magnitude of change in CrCl from baseline was 50% or greater for approximately one-half of those who developed severe renal impairment, and there was a 25% or greater decline for 91% (n = 84). Of those individuals with moderate renal impairment at baseline, CrCl 30–59 mL/min (n = 174), 37% (n = 64) experienced a decline in renal function to less than 30 mL/min. This represented a 25% or greater decline from baseline renal function for 88% of these patients. Only 3 individuals declined to <15 mL/min.

In univariate analysis, individuals with moderate renal impairment at baseline were more likely to develop severe renal impairment during follow-up as were patients with HTN, CHF, prior stroke, or CAD and those aged 75 years and older (Table I). Among those 75 years of age or older, 1 in 4 developed CrCl less than 30 mL/min compared with less than 1 in 10 for those younger than 75 years. Independent risk factors associated with the development of

CrCl less than 30 mL/min were moderate renal impairment at baseline, CrCl 30–59 mL/min, and CAD (Table II). After adjusting for age, CrCl of 30–59 mL/min at baseline was associated with greater than a 14-fold increased risk of developing severe renal impairment during the follow-up period (odds ratio [OR] 14.4, 95% CI 6.7–31.3, $P < .001$). Presence of CAD conferred a 2-fold increased risk (OR 2.2, 95% CI 1.3–3.8, $P = .004$). Age, HTN, CHF, and prior stroke were not independently associated with severe renal impairment after adjusting for baseline CrCl and CAD. A subsequent logistic regression sensitivity analysis, excluding the 19 events that occurred in the context of hospitalization, yielded similar results.

Age and renal function

An age-stratified logistic regression analysis was performed to better elucidate the relationship between age and renal impairment because these variables were highly correlated. Among individuals age 65 years or greater, 39% had moderate renal impairment at baseline compared with 7% of those less than 65 years of age, and in those older than 75 years, 60% had baseline moderate impairment. *Normal renal function*, defined as CrCl 90 mL/min or greater, characterized 3% of patients 75 years of age and older compared with 72% of those less than 65 years of age. When stratified by dichotomized age group category, there was no increased risk of developing severe renal dysfunction among individuals with normal function or mild impairment at baseline (Table III).

Survival analysis

Patients with moderate renal impairment at baseline, CrCl 30–59 mL/min, were compared with those with baseline CrCl ≥ 60 mL/min (Figure). A Kaplan-Meier analysis demonstrated that moderate renal impairment at baseline was significantly associated with the development of severe renal impairment (log-rank $P < .0001$).

Discussion

Among individuals on long-term warfarin therapy, renal impairment is common and increases with age.¹⁴ Thirty-one percent of our cohort had mild CKD at baseline, and 23% had moderate CKD. The baseline distribution of kidney function is similar to that reported from a large population of individuals with AF from Northern California in which nearly one-third had stage 3 or 4 CKD.¹⁵ Renal impairment is an independent risk factor for bleeding and, in some studies, has been shown to also increase the risk of ischemic stroke.^{16–19} Although warfarin has proven efficacy in patients with moderate renal impairment (CrCl 30–59 mL/min), the time in therapeutic range decreases and risk of bleeding increases in severe renal impairment (CrCl < 30 mL/min).²⁰ Because dabigatran and the factor Xa inhibitors were not studied in patients with severe renal dysfunction, warfarin remains the anticoagulant of choice for severe and end-stage CKD.^{11,21} During follow-up in our study, 4% of individuals with normal renal function, 6% of those with mild CKD, and 37% of those with moderate CKD at baseline experienced a decline in renal function to less than 30 mL/min. For 88% of patients with moderate impairment, the magnitude of decline was 25% or greater and therefore was not due to minimal random variation around the 30-mL/min threshold. Only 3 patients experienced a decline to less than 15 mL/min. Importantly,

regarding age, we found no increased risk among individuals aged 75 years or greater if renal function was normal or only mildly impaired at baseline.

Unlike warfarin, all of the NOACs undergo renal metabolism of varying degrees, which has raised concern for their use among patients with moderate CKD. A meta-analysis of 10 clinical trials with mean age of 55 to 73 years found NOACs to have similar safety and efficacy compared with control among patients with CrCl 30–49 mL/min; however, fewer than 20% of patients in the AF trials and less than 8% in the EINSTEIN-PE trial had moderate renal impairment at baseline.²² In addition, trial protocols mandated discontinuation of study drug for those who were found to have a decline in CrCl <30 mL/min during the follow-up period. The long-term stability of renal function on NOAC therapy over time is largely unknown, but it likely differs among patients in clinical practice because of variation in monitoring and greater fluctuations in health status.^{6–9,23}

For those on NOACs, the current recommendations for drug use include at least annual monitoring of kidney function with increased frequency in elderly patients and those with comorbidities who may be at higher risk for acute deterioration in function.^{24–27} As we expect our results in warfarin patients to be similar as those on NOACs, our results suggest that patients with moderate CKD and those with CAD may be at highest risk and require more frequent monitoring. Among individuals with normal renal function or mild impairment at baseline, there was no increased risk of developing severe renal impairment based on age alone. Having moderate renal impairment conferred a greater than 14-fold increased risk of developing severe renal impairment. Deterioration of CrCl to less than 30 mL/min marks a period of potential hazard given that the elimination half-lives and plasma drug concentrations of all of the NOACs would increase significantly with decrements in renal function to this level.²⁸ For example, dabigatran concentrations increased by 1.8-fold for subjects with a CrCl of 30 mL/min and by 1.2-fold for 50 mL/min when compared with the trial population median of 69 mL/min.²⁹ In those with moderate kidney impairment, maximal serum concentrations of rivaroxaban can be up to 50% higher, requiring at least a 25% dose reduction,^{25,30} and for edoxaban, concentrations up to 35% higher requiring a 50% dose reduction.^{27,31,32} Elevated dabigatran plasma concentrations were found to be an independent risk factor for major hemorrhage in the RE-LY trial.²⁹ Given the variability in renal function, especially among individuals with moderate renal impairment, our results lend support to recent recommendations to exhibit caution with use of dabigatran 150 mg in this subgroup.³³ The efficacy and safety of NOACs among dialysis patients are currently under study.

In our cohort, about one-quarter of patients who experienced deterioration to severe renal failure did so within 5.3 months. Because patients with moderate renal impairment at baseline were at the highest risk, this finding lends support to the 2015 European Heart Rhythm Association recommendation to base frequency of renal function measurement on baseline CrCl for patients prescribed NOACs.²¹ Dividing the baseline CrCl by 10 would provide an approximation for the interval frequency of creatinine measurement in months.

Coronary artery disease was associated with a 2-fold increase in risk of developing severe renal impairment and remained an independent risk factor after the exclusion of patients

whose decline in kidney function occurred in the context of a hospitalization or inpatient procedure. Possible connections between CKD and CAD could be explained via pathways of inflammation and oxidative stress. The immune-inflammation renal injury atherosclerosis paradigm suggests a bidirectional association between kidney disease and CAD by which an activated renal and systemic immune system associated with acute kidney injury could lead to accelerated atherogenesis.^{34–36}

Limitations

This study was performed at a single center. However, the baseline prevalence of renal dysfunction in our population is similar to previous reports. Our study by design longitudinally followed patients on warfarin therapy. Continuous warfarin exposure (adherence) was verified at clinic pharmacist visits. Warfarin, itself, may be associated with renal dysfunction either via its blockade of the vitamin K cycle and consequent acceleration of vascular calcification or via renal tubule obstruction by red blood cell casts in the setting of excessive anticoagulation.^{37,38} Thus, our estimates of renal function decline may overestimate the decrement in renal function for patients on NOAC therapy. However, recent data from the RE-LY and ARISTOTLE trials demonstrated a similar decline in renal function in both treatment arms.^{39,40} The degree of renal impairment and rate of decline in our study are more consistent with an acute kidney injury potentially secondary to changes in volume status, health status, or exposure to nephrotoxic drugs. Given the size of our study, we were limited in our ability to rigorously investigate all potential risk factors associated with this decline.

Conclusions

Patients on warfarin for stroke prevention in AF or treatment of VTE who have moderate renal impairment or stage 3 CKD and CAD are at a significantly increased risk for developing severe renal impairment. The findings of this study have implications on the prescribing and monitoring practices for NOACs and reinforce the importance of understanding the fluctuation of renal function common in patients requiring long-term anticoagulation. Further studies evaluating the safety and efficacy of NOACs in patients with impaired renal function and vascular disease are needed.

Acknowledgments

Funding sources: This work was supported by the National Institutes of Health–sponsored Boston University Medical Center Leadership Program in Vascular Medicine grant K12 HL083781, support for Drs Fanola and Hylek. Dr Hylek also receives funding from the National Institutes of Health: grant 1RO1NS070307.

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Figure.

Kaplan-Meier survival curve of patients who developed severe renal impairment (CrCl <30 mL/min) according to baseline renal function.

Table I

Baseline characteristics and univariate analysis in subjects who developed severe renal impairment

Characteristic	n (%)	Subjects with CrCl <30 mL/min	Subjects without CrCl <30 mL/min	P value
Baseline CrCl				
Total	753	92	661	
30–59 mL/min	174 (23.1)	64 (69.6)	110 (16.6)	<.0001
60–89 mL/min	237 (31.4)	14 (15.2)	223 (33.7)	
90 mL/min	342 (45.4)	14 (15.2)	328 (49.6)	
Race				.13
White	305 (40.5)	33 (35.9)	272 (41.2)	
Black	336 (44.6)	45 (48.9)	291 (44.0)	
Hispanic	76 (10.1)	13 (14.1)	63 (9.5)	
Other	36 (4.8)	1 (1.1)	35 (5.3)	
Sex				.42
Female	339 (45.0)	45 (48.9)	294 (44.5)	
Male	414 (55.0)	47 (51.1)	367 (55.5)	
Age (y)				<.0001
<65	372 (49.4)	28 (30.4)	344 (52.0)	
65–74	197 (26.2)	18 (19.6)	179 (27.1)	
75	184 (24.4)	46 (50.0)	138 (20.9)	
Hypertension	558 (74.1)	77 (83.7)	481 (72.8)	.025
CAD	182 (24.2)	40 (43.5)	142 (21.5)	<.0001
DM	231 (30.7)	30 (32.6)	201 (30.4)	.67
CHF	252 (33.5)	43 (46.7)	209 (31.6)	.004
Prior stroke	67 (8.9)	15 (16.3)	52 (7.9)	.008
Prior VTE	109 (14.5)	9 (9.8)	100 (15.1)	.17

Table II

Multivariate analysis of risk factors associated with the development of severe renal impairment

Characteristic	OR	95% CI	P value
Baseline CrCl (mL/min)			<.0001
30–59 (vs 90)	14.5	6.7–31.3	
60–89 (vs 90)	1.6	0.7–3.5	
Age category (y)			.2
<65 (vs 75)	1.4	0.7–2.7	
65–74 (vs 75)	0.7	0.3–1.3	
Hypertension	1.2	0.6–2.3	.6
CHF	1.3	0.8–2.1	.4
CAD	2.2	1.3–3.8	.004
Prior stroke	1.2	0.6–2.6	.6

Statistical significance at $P < .05$.

Table III

Risk for development of severe renal impairment stratified by age

Age	65	n (%)	OR	95% CI	P value
Baseline CrCl (mL/min)		381	–	–	<.0001
30–59 (vs 90)		148 (38.8)	19.7	4.6–84.0	
60–89 (vs 90)		158 (41.4)	2.0	0.4–9.6	
Baseline CrCl (mL/min)		372	–	–	<.0001
30–59 (vs 90)		26 (7.0)	17.0	6.0–48.7	
60–89 (vs 90)		79 (21.2)	1.9	0.7–5.3	