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Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin

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Abstract: The objective was to investigate the incidence of thromboembolic stroke in patients with chronic kidney disease (CKD) and atrial fibrillation (AF) treated with and without warfarin. We investigated the incidence of thromboembolic stroke and of major bleeding in 399 unselected patients with CKD and AF treated with warfarin to maintain an international normalized ratio (INR) between 2.0 and 3.0 (N = 232) and without warfarin (N = 167). Of the 399 patients, 93 (23%) were receiving hemodialysis, and 132 (33%) had an estimated glomerular filtration rate (GFR) of <15 mL/min/1.73 m^2 At the 31-month follow-up of patients treated with warfarin and 23-month follow-up of patients not treated with warfarin, thromboembolic stroke developed in 21 of 232 patients (9%) treated with warfarin and in 43 of 167 patients (26%) not treated with warfarin ($P < 0.001$). Major bleeding occurred in 32 of 232 patients (14%) treated with warfarin and in 15 of 167 patients (9%) not treated with warfarin (*P* not significant). Stepwise Cox regression analysis showed that significant independent predictors of thromboembolic stroke were use of warfarin (odds ratio, 0.28; $P < 0.0001$) and prior stroke or transient ischemic attack (odds ratio, 2.9; $P < 0.05$). In conclusion, this observational study showed that CKD patients with AF treated with warfarin to maintain an INR between 2.0 and 3.0 had a significant reduction in thromboembolic stroke and an insignificant increase in major bleeding.

Keywords: chronic kidney disease, atrial fibrillation, anticoagulants, thromboembolic stroke, major bleeding

Introduction

Chronic kidney disease (CKD) is associated with an increased prevalence and incidence of atrial fibrillation (AF).[1–6] The prevalence of AF in persons with CKD was 7%,[1] 11%,[2] 14%,[3] 19%,[4] 23%,[5] and 27%.[6] Vazquez and colleagues reported that 26 of 190 hemodialysis patients (14%) had AF at baseline.[3] At one-year follow-up, AF was the only independent predictor of thromboembolic events (odds ratio [OR], 8.03; 95% confidence interval [CI]: 2.35–27.4).[3] During the 50-month follow-up, Vazquez and colleagues reported that 11 of the 26 patients (42.3%) with AF had 14 thromboembolic events while thromboembolic events occurred in 9.7% of the 164 patients with sinus rhythm at baseline (relative risk [RR], 4.6; 95% CI: 2.4–8.6) in unadjusted analyses.[7] During a mean follow-up period of 47 months, 20 of the 164 hemodialysis patients (12%) without AF at baseline developed AF. Those who developed AF had a significant increase in subsequent thromboembolic events (RR, 5.2; 95% CI: 2.1–12.4).[8]

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In the general population, numerous prospective, randomized, double-blind, placebo-controlled trials[9–18] and prospective, nonrandomized observational data[19–21] have shown that high-risk patients with nonvalvular AF treated with warfarin to maintain an international normalized ratio (INR) between 2.0 and 3.0 have a significant decrease in thromboembolic stroke with an acceptable risk of bleeding.[9–21] At 1.1-year follow-up in the Stroke Prevention and Atrial Fibrillation (SPAF) Study III, patients with AF considered to be at high risk for developing new thromboembolic stroke who were randomized to treatment with oral warfarin to achieve an INR between 2.0 and 3.0 had a 72% significant decrease in ischemic stroke or systemic embolism compared with patients randomized to treatment with oral aspirin 325 mg daily plus oral warfarin to achieve an INR between 1.2 and 1.5.[11] Adjusted-dose warfarin caused an absolute decrease in ischemic stroke or systemic embolism of 6.0% per year.[11]

However, all of these clinical trials[8–21] have excluded patients with late-stage CKD. It is essential that prospective, double-blind, placebo-controlled trials be performed in patients with late-stage CKD and AF to determine the efficacy of oral anticoagulant therapy in preventing thromboembolic events and the incidence and type of hemorrhagic events.[22] The present study reports a retrospective analysis of the incidence of thromboembolic stroke and of major bleeding in 399 patients with CKD and AF treated with warfarin to maintain an INR between 2.0 and 3.0 (232 patients) versus no warfarin (167 patients) by the nephrologists at Westchester Medical Center/New York Medical College.

Methods

In an observational retrospective study, we reviewed all charts for the incidence of thromboembolic events and of major bleeding in all patients with CKD and nonvalvular AF treated with and without warfarin by the nephrologists at Westchester Medical Center/New York Medical College. No patients were excluded from the analysis. Of the 399 patients with CKD, 93 (23%) were receiving hemodialysis, 132 (33%) had an estimated glomerular filtration rate (GFR) $<$ 15 mL/min/1.73 m^2, 67 (17%) had an estimated GFR between 15–29 mL/min/1.73 m^2, and 200 (50%) had an estimated GFR between 30–59 mL/min/1.73 m^2. The estimated GFR was calculated by the Modification of Diet in Renal Disease study equation.[23,24] The charts were also analyzed for all of the variables listed in Table 1.

The dose of warfarin used was adjusted to maintain an INR between 2.0 and 3.0. The dose of aspirin used was 81 mg daily.

Table 1 Baseline characteristics for patients with chronic kidney disease and atrial fibrillation treated with and without warfarin

Variable	Warfarin (N = 232)	No warfarin (N = 167)	*P* value
Women	67 (29%)	61 (37%)	Not significant
Men	165 (71%)	106 (63%)	Not significant
Age (years)	73 ± 12	77 ± 11	<0.001
GFR 30–59 mL/min/1.73 m^2	115 (50%)	85 (51%)	Not significant
GFR 15–29 mL/min/1.73 m^2	39 (17%)	28 (17%)	Not significant
GFR < 15 mL/min/1.73 m^2	78 (34%)	54 (32%)	Not significant
Hemodialysis	51 (22%)	42 (25%)	Not significant
Renal transplant	15 (6%)	5 (3%)	Not significant
Aspirin	92 (40%)	73 (44%)	Not significant
Prior stroke or TIA	19 (8%)	13 (8%)	Not significant
Coronary artery disease	145 (63%)	103 (62%)	Not significant
Valvular heart disease	46 (20%)	23 (14%)	Not significant
Peripheral arterial disease	15 (6%)	19 (11%)	Not significant
Smoking	64 (28%)	42 (25%)	Not significant
Hypertension	148 (64%)	114 (68%)	Not significant
Diabetes mellitus	108 (47%)	66 (40%)	Not significant
Dyslipidemia	156 (67%)	109 (65%)	Not significant
Follow-up (months)	31 ± 34	23 ± 30	<0.01

Abbreviations: GFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

Student's *t*-tests were used to analyze continuous variables between the warfarin and no warfarin groups. Chi-squared tests and Fisher's exact tests were used to analyze dichotomous variables between the warfarin and no warfarin groups. Stepwise Cox regression analysis was performed for thromboembolic stroke using all of the variables listed in Table 1.

The institutional review boards of Westchester Medical Center and of New York Medical College approved this study.

Results

Table 1 lists 18 variables for patients treated with and without warfarin. Table 1 also lists levels of statistical significance.

Table 2 shows the incidence of thromboembolic stroke and of major bleeding in patients treated with and without warfarin. Table 2 also lists levels of statistical significance. No thromboembolic events other than thromboembolic stroke were observed during this study. Of the 21 thromboembolic strokes that occurred on warfarin, nine (43%) occurred when the INR was <2.0. Computed tomographic brain scans or magnetic resonance imaging were performed in 60 of the 64 thromboembolic strokes (94%) diagnosed clinically and confirmed the presence of thromboembolic stroke in 60 of 60 patients (100%). Computed tomographic brain scans or magnetic resonance imaging also showed that 14 other patients had intracerebral bleeding.

Table 3 shows the stepwise Cox regression analysis for thromboembolic stroke. Significant independent predictors of thromboembolic stroke were prior stroke or transient ischemic attack (OR = 2.9) and use of warfarin (OR = 0.28).

Table 4 shows the incidence of thromboembolic stroke for patients treated with and without warfarin who were receiving hemodialysis, who had an estimated GFR < 15 mL/min/1.73 m^2, who had an estimated GFR between 15–29 mL/min/1.73 m^2, and who had an estimated GFR between 30–59 mL/min/1.73 m^2. Table 4 also lists levels of statistical significance.

Table 2 Incidence of thromboembolic stroke and of major bleeding during follow-up of patients with chronic kidney disease with atrial fibrillation treated with and without warfarin

Variable	Warfarin (N = 232)	No warfarin (N = 167)	*P* value
New stroke	21 (9%)	43 (26%)	<0.001
Major bleeding	32 (14%)	15 (9%)	Not significant

Table 5 shows the types of major bleeding episodes in patients treated with and without warfarin. No significant differences were found between the two groups.

Discussion

In an observational study of patients with AF and a high proportion of CKD undergoing percutaneous coronary intervention with stent implantation, age ($P < 0.01$) and nonanticoagulation ($P = 0.02$) were independent predictors of death, acute myocardial infarction, or target vessel revascularization in patients with AF.[25] However, there was a borderline significant finding that persons with chronic renal failure (undefined by the authors) were less likely to be anticoagulated at discharge, making it difficult to draw any conclusions regarding patients with CKD from this paper.[25]

In an observational study analyzing US Renal Data Service DMMS Wave (Dialysis Morbidity and Mortality Wave 2 Study) data, 123 persons were hospitalized for AF, and 90 (73%) died by the 2.92-year follow-up.[26] Among these persons, only use of warfarin and systolic blood pressure higher than 130 mm Hg were associated with increased survival.

Many physicians consider CKD a condition that causes a high risk of bleeding complications in patients given warfarin for AF and are unwilling to prescribe warfarin for this indication.[27] However, this viewpoint has been challenged.[28–30] In a small study of hemodialysis patients followed for 20 months, hemorrhagic events occurred in 31% of 29 patients (seven with AF) receiving oral anticoagulants and 14% of 211 patients not receiving oral anticoagulants.[29] None of the patients receiving oral

Table 3 Stepwise cox regression analysis for thromboembolic stroke

Parameter	Coefficient	Standard error	*P* value	Odds ratio	95% Confidence interval
Warfarin	−1.2765	0.2927	<0.0001	0.2790	0.1572, 0.4952
Prior stroke or TIA	1.0566	0.4277	<0.05	2.8766	1.2439, 6.6520

Abbreviation: TIA, transient ischemic attack.

Table 4 Incidence of thromboembolic stroke for different glomerular filtration rates and for hemodialysis patients treated with and without warfarin

Variable	Warfarin	No warfarin	*P* value
Hemodialysis patients	5/51 (10%)	16/42 (38%)	<0.005
GFR < 15 mL/min/1.73 m^2	8/78 (10%)	20/54 (37%)	<0.001
GFR 15–29 mL/min/1.73 m^2	2/39 (5%)	6/28 (21%)	<0.05
GFR 30–59 mL/min/1.73 m^2	11/115 (10%)	17/85 (20%)	<0.05

Abbreviation: GFR, estimated glomerular filtration rate.

anticoagulants developed a fatal hemorrhage, intracranial hemorrhage, or serious clinical sequelae.[29] In a review of warfarin use in hemodialysis patients, Elliott and colleagues noted major bleeding rates varying from 0.1 to 0.54 events per patient-year of warfarin exposure and stressed that the true bleeding risk associated with the use of warfarin in hemodialysis patients remains unknown, given the reliance on small observational studies with potential confounding by comorbid conditions.[31]

Quinn and colleagues examined the issue of anticoagulation for AF of hemodialysis patients in a cost–utility analysis.[32] At a threshold of $100,000 per quality-adjusted life-year, the probabilities that no therapy, aspirin, or warfarin was the most efficient therapy were 20%, 23%, and 58%, respectively.[32] An editorial accompanying this paper recommended that until more data are available, anticoagulation should be considered in hemodialysis patients with AF, adhering to screening and monitoring as in the general population.[33]

The data from the present observational study of 399 unselected patients with CKD and AF including 93 patients on hemodialysis and 132 with an estimated GFR < 15 mL/min/1.73 m^2 showed that the incidence of new thromboembolic stroke was 9% at 31-month follow-up for 232 patients treated with warfarin and 26% at 23-month follow-up for 167 patients not treated with warfarin ($P < 0.001$). Stepwise Cox regression analysis showed that significant independent predictors of new thromboembolic stroke were prior stroke or transient ischemic attack (OR, 2.9; 95% CI: 1.2–6.6) and use of warfarin (OR, 0.28; 95% CI: 0.16–0.50). Warfarin significantly reduced the incidence of new thromboembolic stroke in patients receiving hemodialysis (10% versus 38%) ($P < 0.005$), in patients with an estimated GFR < 15 mL/min/1.73 m^2 (10% versus 37%) ($P < 0.001$), in patients with an estimated GFR of 15–29 mL/min/1.73 m^2 (5% versus 21%) ($P < 0.05$), and in patients with an estimated GFR of 30–59 mL/min/1.73 m^2 (10% versus 20%) ($P < 0.05$).

The data from the present study also showed that episodes of major bleeding occurred in 32 of 232 patients (14%) treated with warfarin versus 15 of 167 patients (9%) not treated with warfarin (*P* not significant). The types of major bleeding episodes were not significantly different between patients treated with and without warfarin.

The major limitation of this study is that it was not a prospective, randomized, double-blind, placebo-controlled study investigating the incidence of thromboembolic stroke and of major bleeding in patients with CKD and AF treated with warfarin versus placebo. Because of the high prevalence of AF and its association with an increased incidence of thromboembolic events in patients with late-stage CKD, it is essential that prospective, randomized, double-blind, placebo-controlled trials be performed in these patients to determine the efficacy of oral anticoagulant therapy in preventing thromboembolic events and the incidence and type of hemorrhagic events. Data from the present observational study favor treating patients with CKD and AF including those with late-stage CKD with warfarin on an individual basis, taking into account both the thromboembolism risk as well as the hemorrhagic risk.

Table 5 Types of major bleeding episodes in patients treated with and without warfarin

Major bleeding episode	Warfarin (N = 32)	No warfarin (N = 15)	*P* value
Transfusion for gastrointestinal bleeding	11 (34%)	6 (40%)	Not significant
Intracerebral bleeding	11 (34%)	3 (20%)	Not significant
Transfusion for hemoptysis	3 (9%)	0 (0%)	Not significant
Transfusion for retroperitoneal hematoma	3 (9%)	1 (7%)	Not significant
Transfusion for intraperitoneal bleeding	2 (6%)	0 (0%)	Not significant
Transfusion for bleeding of unknown cause	2 (6%)	3 (20%)	Not significant
Transfusion for abdominal wall hematoma	0 (0%)	1 (7%)	Not significant
Transfusion for pelvic hemorrhage	0 (0%)	1 (7%)	Not significant

Disclosures

None of the authors have any conflicts of interest pertaining to this article.

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