



Atrial fibrillation and chronic kidney disease requiring hemodialysis — Does warfarin therapy improve the risks of this lethal combination?

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ABSTRACT

Introduction: Warfarin therapy for stroke prevention is recommended for patients with AF, but its value in patients with chronic kidney disease on HD is unknown.

Methods: The anticoagulation regimens of patients with a prior history of AF hospitalized for initiation of chronic HD, and of patients receiving chronic HD who had a new diagnosis of AF between 2009 and 2012 were reviewed. Exclusions were renal transplant, peritoneal dialysis, rheumatic valve disease, prosthetic heart valve, GI bleeding, malignancy with chemotherapy in last 6 months or still undergoing treatment, a history of AF ablation, a history of ICD implantation, or those receiving warfarin for non-AF indications.

Results: Among 302 patients included in the study, 119 (39%) were prescribed warfarin and 183 (61%) were not. The two groups were similar regarding demographics, and prevalence of comorbidities including diabetes, heart failure, coronary artery disease, hypertension, use of antiplatelet agents and prior stroke. Warfarin use did not lower risk for ischemic stroke (HR 0.93; 95% CI 0.49–1.82, $P = 0.88$) or improve overall survival (HR 1.02; 95% CI 0.91–1.15, $P = 0.62$), but trended toward higher risk of bleeding complications (HR 1.53; 95% CI 0.94–2.51, $P = 0.086$) after adjusting for potential confounders.

Conclusion: Warfarin use was not associated with reduction in stroke risk or mortality in patients with AF on chronic HD, but trended toward greater bleeding risk. The benefit of warfarin therapy in these patients may be outweighed by its risks.

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the elderly population [1], and is an independent risk factor for stroke and mortality [2]. The risk of atrial fibrillation is associated with older age, non-African race, and underlying cardiovascular diseases. Atrial fibrillation is also more common in patients with renal disease compared to the general population, and risk increases to as much as ten times in population on hemodialysis compared to their healthy counterparts [3, 4]. Prevalence of atrial fibrillation in patients on hemodialysis has been reported to be between 7 and 24% in various studies [3–6]. Intermittent hemodialysis has been associated with remodeling of cardiac structure and has been found to cause left atrial enlargement [7]. Left atrial

hypertrophy and enlargement is an independent risk factor to develop atrial fibrillation [7,8]. The hemodialysis procedure may be a trigger for atrial fibrillation. It has been reported that AF occurred significantly more on hemodialysis days, with highest rate reported during the procedure itself. [8].

Warfarin has been the chosen anticoagulant for stroke prevention in many patients with AF and is associated with reduction in mortality and morbidity due to stroke [9–12]. However, the current observational evidence on use of warfarin in hemodialysis patients has conflicting results [6,13–20]. Some of the studies in the past have postulated that warfarin use in chronic hemodialysis accelerates vascular calcification and aortic stiffness by inhibiting the enzyme Matrix G1a and Gas-6 protein responsible for preventing calcification in vascular smooth muscle, thereby increasing the risk of ischemic stroke [13,21,22]. Whether or not warfarin confers the same protection against stroke to patients on hemodialysis is still not answered, as reflected in discordant recommendations from current guidelines [23,24].

The patients with advanced kidney disease requiring hemodialysis have high mortality rate and those with concomitant diagnosis of AF have worse prognosis [26,27]. We hypothesized that worse survival in patients with concomitant AF is partially due to thromboembolic events

Abbreviations: AF, atrial fibrillation; ESRD, end stage renal disease; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; DAPT, dual antiplatelet therapy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Warf+, patients receiving warfarin; Warf–, patients receiving no oral anticoagulation.

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and warfarin use might mitigate this risk somewhat. Current evidence on warfarin use in patients with atrial fibrillation and on hemodialysis is unclear and has conflicting results [6,13–20]. The use of CHADS₂/CHA₂DS₂-VASc score to predict stroke risk is not validated in patients on chronic hemodialysis. There is often hesitation among clinicians to prescribe warfarin in hemodialysis patients due to several limitations, including frequent blood monitoring, drug interactions, uncertainty regarding benefit, and possible increased risk of bleeding. To better understand this equipoise, we retrospectively examined the outcomes of patients with atrial fibrillation undergoing hemodialysis with and without warfarin therapy.

2. Methods

2.1. Study design and population

A cohort of patients >65 year old was assembled by including all patients hospitalized to Beaumont Health System between January 2009 and December 2012 for initiation of chronic hemodialysis who had a prior history of AF, and all patients receiving chronic hemodialysis who had a new diagnosis of AF. Patients were identified using the ICD 9 code for atrial fibrillation (435.0) and ESRD on hemodialysis (V451, V560, V561, V568). Patients with renal transplant, peritoneal dialysis, rheumatic valve disease, prosthetic heart valve, gastrointestinal (GI) bleeding requiring hospitalization or blood transfusion, malignancy with chemotherapy in the last 6 months or still undergoing treatment, a history of AF ablation, a history of ICD implantation, or those receiving warfarin for non-AF indications were excluded.

Baseline characteristics were recorded including age, gender, cause of renal failure when available, and history of high blood pressure, diabetes, coronary artery disease, cerebrovascular disease, and liver disease. Baseline medication use including aspirin, clopidogrel, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins was also recorded. Use of anticoagulant medication was documented and patients were designated as receiving chronic oral warfarin or not. Decisions about initiation of anticoagulation were left to the discretion of the physicians caring for the patients. Echocardiographic parameters were collected when available including left ventricular systolic function, and parameters for diastolic dysfunction (left atrial pressure, E/A ratio and E/e' ratio). Hypertension was defined as blood pressure >140/90 mm Hg at time of enrollment or a history of use of antihypertensive medication. Diabetes mellitus was defined as fasting blood sugar more than 126 mg/dL, random blood sugar >200 mg/dL, Hb A1c >6.5, or a history of anti-diabetic medication. Coronary artery disease was defined as documented acute coronary syndrome, history of coronary artery bypass grafting, percutaneous angioplasty, or evidence of obstructive coronary artery disease on coronary angiography. The incidence of ischemic stroke, intracranial hemorrhage, major hemorrhage, acute coronary syndrome, and all-cause mortality were recorded. Ischemic stroke was considered when hospitalization was required for focal neurologic deficit and had evidence of acute ischemia on brain imaging. Major hemorrhage was characterized as bleeding from any site requiring hospitalization or blood transfusion. Intracranial hemorrhage was defined as any evidence of intracranial bleeding on brain imaging. All patients were treated according to the practice of the attending physician without specific recommendations regarding anticoagulant treatment.

2.2. Statistical analysis

All the statistical analyses were undertaken using the SAS version 9.3 and R statistical packages for Windows. Descriptive statistics were obtained for all variables; summary statistics tables were obtained for continuous variables and frequency tables were created for categorical variables. Continuous variables are described as means $\pm$ standard deviations with minimum and maximum values listed in parentheses. Categorical variables are given as the frequency and percentage of subjects in the data set with the specified condition. Statistical significance testing was conducted using unpaired Student *t*-test for continuous variables, and chi-square test and Fisher's exact test for categorical variables. A value of *p* < 0.05 was considered statistically significant. The median survival times were calculated for each group along with the corresponding 95% confidence intervals. Kaplan–Meier survival curves and plots of the estimated hazard function were obtained. A log-rank test was used to compare the Kaplan–Meier survival curves for the group on warfarin and the group not on warfarin; the test determined whether the curves were significantly different for the two groups.

3. Results

3.1. Baseline characteristics

A total of 724 patients were identified who had a primary or secondary diagnosis of atrial fibrillation and ESRD on chronic hemodialysis. Four hundred and two patients were excluded from the analysis: 144 patients were excluded because they were receiving anticoagulants

for other indications (87 for history of pulmonary embolism and 57 for prosthetic heart valves; 141 had history of GI bleeding that prevented the use of anticoagulation; and 137 were excluded for other causes (renal transplant, bleeding disorder, catheter ablation of AF, or ICD implantation). The final population was comprised of 302 patients. These patients were managed by conventional hemodialysis three times per week, 3–4 h per day. Unfractionated heparin was used for anticoagulation during hemodialysis.

The mean age of patients included was 77 ± 13 years (65–91 years), and 160 (53%) were male. Ischemic nephropathy (37%) and diabetic nephropathy (28%) were the common etiologies of renal failure. Of the 302 patients, 119 patients were prescribed warfarin for stroke prevention and 183 patients received no oral anticoagulation. Patients prescribed warfarin were similar to those not receiving this drug regarding comorbidities and other medications prescribed (Table 1). Common comorbidities were diabetes (56.6%), heart failure with preserved ejection fraction (53.6%), systolic heart failure (32%), hypertension (92%), and coronary artery disease (79.5%). A minority (22%) had a history of stroke or transient ischemic attack.

3.2. Mortality

Patients were followed for a mean of 2.1 years (range 0.2–5.3 years). Among the 302 patients included in the study, 242 patients (80%) died during follow-up with a mean survival time of 1.8 years (range 0.2–5.2 years, Fig. 1) (Tables 2, 3). The major causes for mortality were either withdrawal of care and/or hemodialysis (31%), out of hospital cardiac arrest (17%), intracranial bleed (6%), or heart failure (15%). In our cohort, 25% of patients died within 1.2 years, 50% of patients died within 2 years, and 75% of patients died within 3.6 years from their date of study entry. We found no significant association between warfarin use and mortality benefit. Ninety-seven patients (82%) taking warfarin and 145 patients (79%) not treated died (HR 1.02; 95% CI 0.9–1.15, *P* = 0.62, figure).

Table 1
Patient characteristics at recruitment.

Patient characteristics	Total, N (%)	Warf+, N (%)	Warf–, N (%)	<i>p</i> value
Total	302	119	183	
Paroxysmal AF	127 (42.0)	47 (39.5)	80 (43.7)	NS
Gender (male)	160 (53.0)	66 (55.4)	94 (51.3)	NS
Age (Median $\pm$ SD)	77 $\pm$ 7	75 $\pm$ 7	78 $\pm$ 7	
65–75	116 (38.4)	49 (41.2)	67 (36.7)	NS
>75	186 (61.6)	70 (58.8)	116 (63.3)	NS
Hypertension	262 (86.8)	101 (84.8)	161 (88)	NS
Diabetes mellitus	171 (56.6)	70 (58.8)	101 (55.1)	NS
Coronary artery disease	240 (79.5)	92 (77.3)	148 (80.9)	0.46
Heart failure	274 (90.7)	107 (89.9)	167 (91.2)	NS
HFpEF	162 (53.6)	61 (51.2)	101 (55.1)	NS
HFREF	112 (37.0)	46 (38.6)	66 (36.0)	NS
Ischemic stroke	66 (21.9)	24 (20.1)	42 (23.0)	NS
Beta blocker	277 (92.0)	106 (89.0)	171 (93.4)	NS
ACEi/ARBs	133 (44.0)	53 (44.5)	80 (43.7)	NS
Rhythm control	98 (32.4)	32 (26.9)	66 (36)	0.11
Aspirin	215 (71.2)	90 (75.6)	125 (68.3)	0.19
Plavix	65 (21.5)	22 (18.4)	43 (23.5)	0.31
DAPT	13 (4.3)	3 (2.5)	10 (5.4)	0.25
CHA ₂ DS ₂ -VASc				
2–4	176 (58.3)	63 (52.9)	113 (61.7)	0.15
5–9	126 (41.7)	56 (47.1)	70 (38.3)	0.15
HASBLED ^a				
0–1	3 (1.0)	2 (1.7)	1 (0.6)	0.56
2–3	112 (37.0)	39 (32.8)	73 (39.9)	0.22
4–9	187 (62.0)	78 (65.5)	109 (59.5)	

^a Labile INR not included (unavailable for all patients). Abbreviations: ACEi/ARBs = angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CHA₂DS₂-VASc = thromboembolic risk score (ref); DAPT = dual antiplatelet therapy; HASBLED = bleeding risk score (ref); HFpEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; Warf+ = patients receiving warfarin; Warf– = patients receiving no oral anticoagulation.

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