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Research Article

Anticoagulation Status in Maintenance Dialyzed Patients with Nonvalvular Atrial Fibrillation - Single Polish Center Report

Żaneta Jankowska[2], Marta Zaborowska[2], Katarzyna Klejna[1], Beata Naumnik[1*]

[1]The 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Poland

[2]Students' Scientific Group at the 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Poland

[*]**Corresponding Author:** Prof. Beata Naumnik, The 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Poland, Tel: + 48 85 74 09 458, E-mail: bnaumnik@poczta.onet.pl

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Abstract

Background: Atrial fibrillation is the most common cardiac arrhythmia among patients with chronic kidney disease. Patients with both, atrial fibrillation and renal failure, have a significantly higher risk of thromboembolism and bleeding at the same time. Our aim was to determine whether end-stage renal disease-atrial fibrillation patients were treated with oral anticoagulants according to the current recommendations.

Methods and Results: This is a retrospective non-randomized study based on data from the 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, comprising of 148 patients with end-stage renal disease (105 patients on hemodialysis, 43 patients on peritoneal dialysis), of whom 29 (24 on hemodialysis and 5 on peritoneal dialysis) had a diagnosis of nonvalvular atrial fibrillation. Currently, only 2 patients (6.9% of all study group) on peritoneal dialysis were treated with anticoagulants from Vitamin K antagonists group and 1 of them had double therapy-oral anticoagulant plus antiplatelet drug. Direct oral anticoagulants were not used by any patient. Vitamin K antagonists were withdrawn in 10 individuals. Bleeding was the main reason of resigning from anticoagulants during treatment.

Conclusions: Not only did all the dialyzed patients fulfill the criteria to introduce oral anticoagulation (according to the CHA_2DS_2-VASc scale) in the observed cohort, but also they had a high risk of bleeding in HAS-BLED score.

There is no data to confirm safety and effectiveness of oral anticoagulants in European population treated with dialysis so far. The warfarin therapy involves increased risk of mortality, stroke, major bleeding and calciphylaxis among patients with end stage renal disease. The benefits from using direct oral anticoagulants remain unproven, so left atrial appendage occlusion may be the best alternative to oral anticoagulation in the above group.

Keywords: Vitamin K antagonists; Direct oral anticoagulants; End-stage renal disease; Hemodialysis; Peritoneal dialysis

1. Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia among the patients with chronic kidney disease (CKD). According to Soliman, patients with eGFR < 45 ml/min/1.73m^2 had a higher prevalence of AF compared with eGFR ≥ 45 ml/min/1.73m^2 (eGFR; estimated Glomerular Filtration Rate) [1]. According to the REGARDS study, the occurrence of AF in CKD was the highest in G4 and G5 groups after further multivariable adjustment and has been reported to be between 13 and 23% [2-7]. The end-stage renal disease (ESRD) patients on dialysis are especially prone to reveal AF. Atrial fibrillation occurrence in the group of patients treated with maintenance hemodialysis is higher compared to peritoneal dialysis.

AF is associated with 5-fold increase in the risk of stroke [8]. Patients with AF and CKD have not only significantly higher risk of thrombotic complications, particularly ischemic stroke, but simultaneously a higher bleeding risk (proportionally to the grade of renal failure) [9]. The most common scales to predict thromboembolic risk in the group of patients with nonvalvular atrial fibrillation are $CHADS_2$ and CHA_2DS_2-VASc score (Table 1). According to the Nakagawa et al., the patients with eGFR less than 60 ml/min/1.73m^2 and CHADS2 score 2 and higher had almost 11-fold higher risk of ischemic stroke [10]. Oral anticoagulation is recommended in AF group of patients with CHA_2DS_2-VASc score ≥ 2 for men and ≥ 3 for women and should be considered if there is score 1 for men and 2 for women [11]. According the ESC 2016 guidelines, it is obliged to assess modifiable and non-modifiable risk factors for bleeding including the parameters from the HAS-BLED score before the inclusion of oral anticoagulants (OAC) to the therapy (Table 2). Most of AF patients on dialysis have high score in the CHA_2DS_2-VASC score but, simultaneously, have high HAS-BLED score.

There is a dilemma for nephrologists and the question if oral anticoagulants should be introduced to the treatment despite the presence of high risk of bleeding. Anticoagulation can be safely used in AF patients with moderate or moderate-to-severe CKD (eGFR ≥ 15 mL/min/1.73m^2). The patients with ESRD are usually excluded from all trials with oral anticoagulation. There is still lack of definite evidence about the effectiveness and safety of oral anticoagulants, such as vitamin K antagonists (VKAs) as well as direct oral anticoagulants (DOACs) among the patients undergoing dialysis. However, there are some reports about the benefits of introducing DOACs rather than

VKAs to the therapy for end-stage renal disease-atrial fibrillation (ESRD-AF) patients. The trials assessing OAC, both VKAs and DOACs, are urgently needed for these specific population [12].

CHA_2DS_2-VASC[I] risk factor	**Score**
Congestive heart failure Signs and symptoms of the heart failure or objective evidence of reduced left ventricular ejection fracture	+1
Hypertension Resting blood pressure >140/90 mm Hg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose>125 mg/dl (7 mmol/L) or treatment with oral hypoglycemic agent and/or insulin	+1
Previous stroke, transient ischemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65-74 years	+1
Sex category (female)	+1

[I]$CHAD_2DS_2$-VASC: C - Congestive heart failure, H - Hypertension, A - Age ≥ 75 (doubled), D - Diabetes, S - Stroke (doubled), V - Vascular disease, A - Age 65-74 and S - Sex (female)

Table 1: Clinical risk factors for stroke, transient ischemic attack, and systemic embolism in the CHA_2DS_2-VASc score.

HAS- BLED[II] Score for Risk of Bleeding	**Score**
Hypertension	+1
Abnormal renal/liver function	+1/+2
Stroke	+1
Bleeding history or predisposition	+1
Labile INR[III]	+1
Age > 65	+1
Drugs/alcohol concomitantly	+1/+2

[II]The name of the score is derived from the first letter of each risk factor ; [III]INR= international normalized ratio

Table 2 : HAS-BLED Score for Risk of Bleeding.

2. Material and Methods

Data were extracted from the 1st Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Poland. The ESRD-AF cohort was selected from the population of patients treated with peritoneal dialysis and maintenance hemodialysis. Among the group of 105 patients on hemodialysis and 43 individuals on peritoneal dialysis, we included to the study 24 (22.86%) patients on hemodialysis (16 men, 8 women) and 5 (11.61%) on peritoneal dialysis (2 men, 3 women) according to the presence of atrial fibrillation. The type of AF was evaluated according to the medical history. The data of the ESRD-AF cohort was analyzed between September and December 2018.

In selected group we assessed the treatment of OACs: vitamin K antagonists as well as non-vitamin K oral anticoagulants. In this study, we also evaluated the time when the OACs was withdrawn. We also analyzed: the reasons of OACs withdrawal, comorbidity and co-pharmacotherapy (aspirin, other antiplatelet medications including clopidogrel, statins, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-blocking agents, diuretics, insulin and anti-diabetic drugs). The CHA2DS2-VASc score was calculated for each patient according to the indication for using oral anticoagulation therapy. Simultaneously, HAS-BLED score was established as a simply method to validate the stratification of hemorrhagic complications.

For variable distribution Shapiro-Wilk W test was used. Continuous data are expressed as mean and standard deviation. Categorical data are presented as absolute values and percentages.

3. Results

All of studied AF-ESRD population had the indications for oral anticoagulation according to the CHA_2DS_2-VASc score and, simultaneously, 100% of patients have a high risk of bleeding according to the HAS-BLED score. At present, only 2 patients (6.9% of all study group) on peritoneal dialysis were treated with anticoagulants from VKAs group and 1 patient had double therapy: oral anticoagulant + antiplatelet drug. The 18 patients (62.1%) took only antiplatelet drugs. The 9 patients (31%) didn't use any anticoagulants and any antiplatelet drugs. No one in ESRD-AF cohort was treated with DOACs (Table 3). VKAs was laid off in 10 individuals. The 7 dialysis patients (5 on hemodialysis and 2 on peritoneal dialysis) couldn't continue VKAs therapy because of bleeding occurring during the dialysis. Main source of bleeding was gastrointestinal system (Table 4).

Drugs (N^{VI}, %)	**All studied group (N = 29, 100%)**	**Hemodialysis (N = 24, 100%)**	**Peritoneal dialysis (N = 5, 100%)**
VKA^{VII}	1 (3.45%)	0	1 (20%)
ASA^{VIII} 75mg	16 (55.17%)	13 (54.17%)	3 (60%)
VKA + ASA	1 (3.45%)	0	1 (20%)

Double antiplatelet therapy (ASA+clopidogrel)	2 (6.9 %)	2 (8.33%)	0
Without anticoagulants and antiplatelet drugs	9 (31 %)	9 (37.5%)	0

[IV] hemodialysis; [V] peritoneal dialysis; [VI] number of patients; [VII] vitamin K antagonists; [VIII] acetylsalicylic acid

Table 3: Anticoagulants and antiplatelet drugs therapy in ESRD-AF group (24 HD[IV], 5 PD[V]).

Cause of laying off VKAs	**Number of patients (10)**
Bleeding from:	
Gastrointestinal system	3
Pulmonary system	1
Subcutaneous hematoma	2
Female genital system	1
Starting of dialysis procedures	1
Lack of cooperation with patient	1
Unknown cause	1

Table 4: Causes of laying off VKAs.

Left atrial appendage (LAA) occlusion was performed only in one case from thirty dialysis patients, so it's still unpopular method of treatment in Poland. In the time period of our analysis 4 ESRD-FA patients died - 3 men (2 during acetylsalicylic acid therapy and 1 without OACs and antiplatelet therapy) and 1 woman during double antiplatelet therapy. The reason of death was: undefined bacterial pneumonia in 1 patient, ruptured abdominal aortic aneurysm in 1 patient, life-threatening arrhythmia in 1 patient with ischemic heart disease and unknown in 1 case.

4. Discussion

In this retrospective observational study, we have found that the criteria to introduce the oral anticoagulation assessed with the CHA2DS2-VASc scale were fulfilled in the whole ESRD-AF observed cohort. At the same time, all patients had a high risk of bleeding (3 points and more) in HAS-BLED score. One of the main consequences of ESRD is the effect on hemostasis [13]. The severity of hemostatic disorders correlate with the stage of CKD. Impaired hemostasis in chronic renal failure result either in a recurrent thrombosis or episodes of bleeding [14]. However, the risk of thromboembolism is especially related with the presence of atrial fibrillation and the lower grade of eGFR. Among the AF patients, the decreased eGRF is an independent risk factor of ischemic stroke. Prophylactic using of oral anticoagulants can be the most effective treatment to reduce the risk of stroke and other thrombotic complications in the ESRD-AF group. Treating both, vitamin-K antagonist and non-vitamin K antagonist is not approved in maintenance dialysis patients by the European Society of Cardiology (ESC) guidelines because

there is no data to confess the safety and effectiveness of this therapy in European population. According to the Kidney Disease: Improving Global Outcomes (KDIGO) recommendations, using warfarin is contraindicated in the patients treating with dialysis. There are evidences that chronic kidney disease patients suffer from subclinical vitamin K deficiency [15]. Olesen et al. have demonstrated that warfarin reduced the risk of stroke or systemic thromboembolism in the ESRD-AF patients and increased the risk of bleeding [16]. In the most studies warfarin treatment is related with the increased mortality, hemorrhagic stroke and major bleeding [17]. The increased risk of developing calciphylaxis among dialysis patients is related to the treatment of VKA-antagonist. According to the McCabe et al., in CKD rats' model, the intake of warfarin increased cardiovascular calcification [18]. The patients treated with oral anticoagulants had a rapid calcification of the femoral artery and significantly increased coronary calcification. In the case report described by Hristova et al., the transplant recipient presented the massive arterial calcification after the treatment of warfarin [19]. Vitamin K antagonists have detrimental effects on arteriovenous fistula remodeling inducing calcification and neointimal hyperplasia [20]. As for negative aspects of VKA antagonist, the hemodialysis patients treated with warfarin for longer than 1 year had an increased risk of vertebral fractures compared to those without warfarin treatment [21]. However, in the US (but not in Europe) in AF patients with a CHA2DS2-VASc score ≥ 2 in men or ≥ 3 in women and a creatinine clearance <15 ml/min or who are on dialysis, it is reasonable to use warfarin (INR 2.0-3.0) or apixaban for oral anticoagulation [22].

The using of DOACs could be an alternative option for the patient with ESRD-AF, but there is an urgent need to confess the safety of this treatment. However, according to some researchers, in the absence of clinical data or experience of DOAC therapy in Europe, vitamin K antagonists may be a more suitable alternative although their benefit is not unequivocally proven [23]. Left atrial appendage occlusion occurs to be a good option for prevention of AF-related thromboembolic stroke in ESRD patients, especially for those who need long anticoagulation and are prone to life-threatening hemorrhage. There is a study which indicate the reduction of hemorrhagic stroke in patients after LAA occlusion in comparison to warfarin [24]. Another STOP-HARM randomized pilot trial will compare reduced dose of DOAC therapy versus LAA occlusion with the Watchman device in patients with AF and ESRD. Left atrial appendage occlusion may be the best alternative to oral anticoagulation in this ESRD-AF patient, but now the knowledge of LAA occlusion efficiency and availability of this method must be better [25].

5. Conclusion

First of all, the study showed that there is a clear discrepancy between United States and European recommendations, as DOACs are approved in treatment of ESRD-AF patients in the United States but not in Europe. Secondly, in those patients using of generally accepted risk scales for thromboembolic as well as hemorrhagic events seems to be senseless, because the study confirms that patients, who have indications for anticoagulant treatment, have also a high risk of bleeding. Due to the high risk of complications of oral anticoagulation in patients on dialysis, surgical treatment such as LAA occlusion seems to be a good alternative, however currently there is no hard evidence for benefits of this method.

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