Comparison of Anticoagulation and no Anticoagulation in Patients with Atrial Fibrillation on Dialysis: A Single-Center Retrospective Study

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TABLE OF CONTENTS

LIST OF TABLES

ABSTRACT

Comparison of Anticoagulation and no Anticoagulation in Patients with Atrial Fibrillation on Dialysis: A Single-Center Retrospective Study

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Atrial fibrillation (AF) is a common arrhythmia in end-stage renal disease (ESRD) patients. Although the need for anticoagulation to prevent stroke and thromboembolism is increasing, there is still controversy about the efficacy of anticoagulation in patients with ESRD. Therefore, we analyzed the risk and benefit of anticoagulation in patients with ESRD with AF.

We retrospectively analyzed all data of 99 patients who received dialysis therapy and were diagnosed with AF using the medical records. Among the 99 patients who were diagnosed with AF and on dialysis, 36 received anticoagulation (17 had warfarin, and 19 had apixaban 2.5 mg twice a day), while 63 received no anticoagulation. No significant difference in baseline characteristics was noted between patients with anticoagulation and those without anticoagulation. Although the no anticoagulation group experienced more all-cause (39.7%

vs. 32.4%, $p = 0.572$) and cardiovascular (17.6% vs. 10.8%, $p = 0.197$) mortality than the anticoagulation group, the difference was not statistically significant. Compared with patients with apixaban 2.5 mg twice a day, those with warfarin exposure experienced more frequent major adverse cardiovascular events (35.3% vs. 15.8%, $p = 0.109$), but the difference was not statistically significant in the multivariate Cox regression analysis (hazard ratio, 2.80; 95% confidence interval, 0.34–23.02).

Apixaban 2.5 mg twice a day was not inferior to warfarin, considering the risk and benefit of anticoagulation in patients on dialysis. However, apixaban 2.5mg also increased risk of bleeding and did not show survival benefit to no anticoagulation in patients with AF on dialysis. Therefore, we could not recommend low dose apixaban for anticoagulation in patients with ESRD, and further large studies are needed.

Key words: Anticoagulation, Atrial fibrillation, End Stage Renal Disease (ESRD)

I. Introduction

1. Background

Atrial fibrillation (AF) belongs to the category of supraventricular arrhythmia, and the prevalence is over 7%–13% of patients on dialysis, which is 10–20-fold higher than the general population[1-2]. Patients with AF have a 4–5 times higher risk of stroke, thromboembolism, and death than the general population[2-3]. And when they are on dialysis, the risk of the stroke becomes even higher[2-3]. Although the need for anticoagulation in patients with AF on dialysis is increasing, there has been no randomized controlled trial regarding the use of anticoagulation in this population. Moreover, the use of anticoagulation in patients on dialysis is still controversial[4].

Because of the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and these do not require routine monitoring of coagulation, these are emerging as a replacement for warfarin in stroke and thromboembolism treatment[5-9]. Four NOACs are currently used: dabigatran, rivaroxaban, apixaban, and edoxaban[6-9]. However, the efficacy of NOACs was not fully proved, and several severe side effects such as bleeding were reported in patients on dialysis[10-11].

Among the four types of NOACs, only apixaban received approval from the Food–and Drug Administration (FDA) that the number of patients with AF on dialysis receiving apixaban increased[12]. However, the FDA approved apixaban based on pharmacokinetic data, not clinical outcomes[13]. Following this trend, the AHA/ACC/HRS guideline in 2019 described the use of apixaban as a feasible option in patients with AF and on dialysis[14]. Nevertheless, the efficacy, proper dose, and risk of apixaban in patients with AF on dialysis are not yet clearly documented.

2. Research Purpose

Thus, we conducted a retrospective study to clarify the effect and proper dose of apixaban in patients with AF on dialysis[15]. In addition, this study aimed to compare the risk and benefit between the low-dose apixaban (2.5 mg twice a day) group and the warfarin group among the patients with AF and on dialysis.

II. Materials and methods

1. Study Design and Subjects

We conducted a retrospective cohort study of patients diagnosed with AF or atrial flutter and on dialysis in Wonju Severance Christian Hospital. Data were collected from the electronic medical record system of Wonju Severance Christian Hospital from 2010 to 2020. This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR320114). Written consent from subjects was not necessary for this is a retrospective study. We included 182 patients who had a diagnostic code with AF or atrial flutter on electrocardiography and simultaneously had hemodialysis or peritoneal dialysis during the study period. We excluded subjects with a history of cancer (n = 37), those who received kidney transplantation (n = 4), and those who had short-term follow-up period (within 90 days) (n = 21) and missing laboratory values (n = 21). Finally, 99 patients were enrolled in this study. Whether they were taking anticoagulant medication (apixaban 2.5 mg twice a day or warfarin) or not, patients were classified into two groups (anticoagulation and no anticoagulation group). Patients receiving anticoagulant therapy were divided into two groups according to the type of drug (apixaban or warfarin).

2. Data Collection

Demographic variables including age, gender, and various medical histories, for example, history of major bleeding (gastrointestinal and cerebral), thromboembolism, major

adverse cardiovascular events (MACE), and hospitalization, were collected from the database. Baseline laboratory profiles were measured at the index date. The CHA_2DS_2-VASc (consisting of congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack, vascular disease, and sex) and HAS-BLED (consisting of hypertension, abnormal renal and liver function, stroke, bleeding history, the labile international normalized ratio [INR], elderly, and drugs or alcohol) scores and Charlson comorbidity index (CCI) were calculated at the same time[16]. Previous medication history was reviewed by researching medical records. Aspirin, clopidogrel, warfarin, and other antiplatelet medications that affect bleeding risk were reviewed. All prescribed medications, including antihypertensive medicines, were also reviewed and included. We defined index date only when the patients were on dialysis and diagnosed with AF or atrial flutter. We defined the primary outcome as cardiovascular mortality and MACE. The secondary outcome included adverse events includes major bleeding events, stroke, thromboembolism, deep vein thrombosis, and transient ischemic attack.

3. Statistical Analysis

Continuous variables are presented as means and standard deviations, and categorical variables are presented as frequencies and percentages. The Two-sample t-test, x^2 test (Fisher exact test), and Mann–Whitney test were used to compare groups as appropriate. Multivariate Cox regression was performed using age, sex, CCI, CHA_2DS_2-VASc, and HAS-BLED scores. These variables were chosen considering collinearity and clinical importance. Hazard ratios (HR), 95% confidence intervals (CI), and P values were also shown. The model's goodness of fit was assessed using the Hosmer–Lemeshow test. A P value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM Statistical Package for the Social Sciences version 25.0 (IBM Corporation, Armonk, NY, USA).

III. Results

1. Baseline Characteristics

Among the 99 patients, 36 took an anticoagulation medication (apixaban 2.5 mg twice a day or warfarin), whereas the other 63 were not. There were no patients taking apixaban 5 mg twice a day or diffenent kinds of NOACs. The baseline characteristics were similar between the anticoagulation group and non-anticoagulation groups. The follow-up durations, presence of mechanical valve, INR prolongation, frequencies of blood transfusion more than three times, and prescribed vintage of aspirin and proton pump inhibitors were significantly different between the two groups (Table 1). Among the 36 patients in the anticoagulation group, 19 had been prescribed NOACs (apixaban 2.5 mg twice a day), and 17 had been prescribed warfarin. Except for the follow-up duration, hemoglobin level, and frequency, the baseline characteristics were similar between patients taking apixaban and those taking warfarin.

Table 1. Baseline Characteristics of anticoagulation and non-anticoagulation patients.

	Anticoagulation (n=36)	**Non-anticoagulation (n=63)**	***P* value**
(1) Clinical characteristics			
Age (years)	70.2 ± 13.1	67.2 ± 11.3	0.707
Sex (male, %)	19 (51.4)	35 (51.5)	0.576
HD (N, %)	29 (78.4)	54 (79.4)	0.733
BMI	23.6 ± 3.6	22.8 ± 4.0	0.731
F/U duration (months)	464.2 ± 600.6	960.4 ± 1123.5	0.004
DM (N, %)	16 (43.2)	37 (54.4)	0.311
Dyslipidemia (N, %)	18 (48.6)	26 (38.2)	0.289
Bleeding Hx (N, %)	5 (13.5)	5 (7.4)	0.301
HF (N, %)	16 (43.2)	28 (41.2)	0.839
CAOD (N, %)	9 (24.3)	24 (35.3)	0.279
CABG (N, %)	1 (2.7)	2 (2.9)	0.283
PAOD (N, %)	1 (2.7)	7 (10.3)	0.255
Old CVA (N, %)	9 (24.3)	10 (14.7)	0.289
INR >3	15 (40.5)	0 (0)	<0.001
Transfusion, 3 units	8 (21.6)	2 (2.9)	0.002
EF (%)	53.5 ± 13.3	55.7 ± 12.8	0.85
Hb (g/dL)	10.3 ± 1.5	10.2 ± 1.4	0.718
Platelet count (E9/L)	191.5 ± 85.2	188.4 ± 58.1	0.004
LDL (mg/dL)	66.1 ± 33.1	80.5 ± 43.9	0.22
CRP (mg/dL)	3.2 ± 5.2	3.0 ± 5.4	0.84
HAS-BLED score	4.3 ± 0.7	3.6 ± 0.9	<0.001
CHAD-VAS score	4.5 ± 1.6	3.7 ± 1.7	0.261
CCI index	6.9 ± 2.4	6.2 ± 1.9	0.154
Brain infarction (N, %)	2 (5.4)	10 (14.7)	0.205
Brain hemorrhage (N, %)	3 (8.1)	4 (5.9)	0.697
GI bleeding (N, %)	6 (16.2)	5 (7.4)	0.098
Minor bleeding (N, %)	3 (8.1)	3 (4.4)	0.664
Any bleeding (N, %)	10 (27.0)	8 (11.8)	0.064
Hospitalization (N, %)	2.6 ± 3.9	2.8 ± 2.8	0.158
Admission (N, %)	2.0 ± 3.0	2.1 ± 2.0	0.974
All-cause mortality (N, %)	12 (32.4)	27 (39.7)	0.572
CV mortality (N, %)	4 (10.8)	12 (17.6)	0.197
MACE (N, %)	9 (24.3)	24 (35.3)	0.271
(2) Medication			
Aspirin (N, %)	9 (24.3)	43 (63.2)	<0.001
Clopidogrel (N, %)	5 (13.5)	18 (26.5)	0.146
Statin (N, %)	13 (35.1)	30 (44.1)	0.406
PPI (N, %)	16 (43.2)	10 (14.7)	0.004

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CAOD, coronary artery disease; CCI, Charlson comorbidity index; CRP, C-reactive protein; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; EF, ejection fraction; F/U, follow-up; Hb, hemoglobin; Hx, history; GI, gastrointestinal; HD, hemodialysis; HF, heart failure; INR, international normalized ratio; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; N, number; PAOD, peripheral arterial occlusive disease; PPI, proton pump inhibitor;

2. Cardiovascular mortality, MACE, all-cause mortality, cerebrovascular disease between anticoagulation and no anticoagulation groups

During the follow-up period, the incidences of cerebrovascular disease, MACE, and cardiovascular and all-cause mortality were higher in the non-anticoagulation group than those in the anticoagulation group; however, the difference of all these parameters were not statistically significant. In addition, the incidence of gastrointestinal bleeding was more frequent in the anticoagulation group; however, the difference was not statistically significant (Table 1).

In the subgroup analysis, compared with patients with warfarin treatment, those taking apixaban 2.5 mg twice a day had lower incidences of brain hemorrhage, any bleeding events, MACE, and cardiovascular and all-cause mortality. However, the differences were not statistically significant (Table 2).

Table 2. Baseline characteristics of NOAC and warfarin groups.

	Warfarin (n=17)	Apixaban (n=19)	*P* value
(1) Clinical characteristics			
Age	69.0 ± 11.4	71.3 ± 15.0	0.336
Male (N, %)	7(41.2)	12 (63.2)	0.330
HD (N, %)	10 (58.8)	18 (94.7)	0.014
BMI	23.5 ± 4.0	23.6 ± 3.3	0.703
Follow-up duration (months)	839.8 ± 723.3	151.3 ± 95.8	<0.001
DM (N, %)	10 (58.8)	5 (26.3)	0.104
Dyslipidemia (N, %)	7 (41.2)	11 (57.9)	0.730
Bleeding Hx (N, %)	2 (14.3)	3 (15.8)	0.649
HF (N, %)	7 (41.2)	9 (47.3)	0.540
CAOD (N, %)	4 (23.5)	5 (26.3)	0.612
CABG (N, %)	2 (14.3)	0 (0)	0.204
PAOD (N, %)	0 (0)	1 (5.3)	0.541
Old infarction (N, %)	3 (17.6)	4 (21.1)	0.596
INR >3 (N, %)	12 (70.6)	2 (10.5)	0.001
Transfusion, 3 units (N, %)	5 (29.4)	3 (15.8)	0.254
EF (%)	55.1 ± 14.2	52.3 ± 12.8	0.446
Hb (g/dL)	11.1 ± 1.5	9.7 ±1.3	0.007
Platelet count (E9/L)	188.9 ± 58.7	184.1 ± 81.3	0.667
LDL (mg/dL)	82.3 ± 37.0	52.6 ± 22.4	0.004
CRP (mg/dL)	4.1 ± 6.5	2.5 ± 3.9	0.855
HAS-BLED score	4.1 ± 0.7	4.4 ± 0.7	0.345
CHAD-VAS score	4.6 ± 1.6	4.5 ± 1.7	0.743
CCI index	6.7 ± 2.4	7.1 ± 2.5	0.739
Brain infarction (N, %)	1 (5.9)	1 (5.3)	0.715
Brain hemorrhage (N, %)	2 (11.8)	1 (5.3)	0.584
GI bleeding (N, %)	5 (29.4)	1 (5.3)	0.075
Minor bleeding (N, %)	1 (5.9)	2 10.5)	0.543
Any bleeding (N, %)	6 (35.3)	4 (21.1)	0.281
Hospitalization (N, %)	3.6 ± 4.9	1.8 ± 2.6	0.362
Admission (N, %)	2.7 ± 4.0	1.5 ± 1.8	0.655
All-cause mortality (N, %)	7 (41.2)	4 (21.1)	0.243
CV mortality (N, %)	4 (23.5)	0 (0)	0.070
MACE (N, %)	6 (35.3)	3 (15.8)	0.147
(2) Medication			
Aspirin (N, %)	6 (35.3)	3 (15.8)	0.147
Clopidogrel (N, %)	3 (17.6)	2 (10.5)	0.644
HTN med (N, %)	15 (88.2)	19 (100)	0.444
DM med (N, %)	10 (58.8)	5 (26.3)	0.104
Statin (N, %)	5 (29.4)	8 (42.1)	0.727
PPI (N, %)	4 (23.5)	12 (63.2)	0.016

Abbreviations: BMI, body mass index, CABG, coronary artery bypass graft; CAOD, coronary artery disease; CCI, Charlson comorbidity index; CRP, C-reactive protein; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; EF, ejection fraction; F/U, follow-up; Hb, hemoglobin; Hx, history; HD, hemodialysis; HF, heart failure; HTN, hypertension; INR, international normalized ratio; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; N, number; PAOD, peripheral arterial occlusive disease; PPI, proton pump inhibitor;

3. Comparison of MACE, CV mortality, All-cause mortality, and adverse events between anticoagulation and no anticoagulation group.

The univariate Cox regression analysis showed that compared with no anticoagulation treatment, anticoagulation treatment was statistically associated with increased incidences of any bleeding (HR, 4.8; 95% CI, 1.80–12.79) and cerebrovascular disease (HR, 3.61; 95% CI, 1.38–9.43). However, MACE and cardiovascular and all-cause mortality were not statistically significant (Table 3).

The multivariate-adjusted Cox regression analysis showed that compared with no anticoagulation treatment, anticoagulation treatment was associated with any bleeding (HR, 5.72; 95% CI, 1.84–17.81) and cerebrovascular disease (HR, 3.12; 95% CI, 1.04–9.35). However, MACE and cardiovascular and all-cause mortality were not significantly different between the two groups.

Table 3. Clinical outcomes of anticoagulation in dialysis patients with atrial fibrillation.

	Crude	Model 1	Model 2
All-cause mortality	1.42 (0.72–2.83)	1.47 (0.73–2.97)	0.95 (0.44–2.08)
MACE	1.18 (0.54–2.56)	1.20 (0.54–2.67)	0.94 (0.40–2.20)
Cardiovascular mortality	1.00 (0.32–3.19)	0.77 (0.20–3.02)	0.93 (0.17–5.07)
Any bleeding	4.80 (1.80–12.79)	5.43 (1.98–14.89)	5.72 (1.84–17.81)
Cerebrovascular disease	3.61 (1.38–9.43)	3.95 (1.50–10.43)	3.12 (1.04–9.35)

Abbreviation: MACE, major adverse cardiovascular events.

Model 1: adjusted for age sex.

Model 2: adjusted for Model 1 + Charlson comorbidity index and CHA_2DS_2-VASc and HAS-BLED scores.

4. Comparison of MACE, CV mortality, All-cause mortality, and adverse events between warfarin vs. NOAC.

The univariate Cox regression analysis showed that compared with apixaban 2.5 mg twice a day treatment, treatment with warfarin was associated with an increased incidence of cerebrovascular disease (HR, 19.67; 95% CI, 2.01–200.72). Any bleeding, MACE, and all-cause mortality were not statistically significant. The multivariate-adjusted Cox regression analysis also showed that compared with apixaban treatment, treatment with warfarin was associated with an increased incidence of cerebrovascular disease (HR, 15.74; 95% CI, 1.24–200.72). Because there was no cardiovascular mortality in the apixaban treatment group, it was impossible to calculate the HR about cardiovascular mortality. Any bleeding, MACE, and all-cause mortality were not statistically different between the two groups (Table 4).

Table 4. Comparison of MACE, CV mortality, All-cause mortality and adverse events between Apixaban 2.5 mg Twice a Day and Warfarin

	Crude	Model 1	Model 2
All-cause mortality	3.08 (0.72–13.21)	3.06 (0.63–14.96)	2.02 (0.38–10.61)
MACE	1.69 (0.30–9.63)	2.92 (0.41–20.87)	2.80 (0.34–23.02)
Any bleeding	3.52 (0.59–21.12)	2.63 (0.42–16.35)	1.90 (0.28–12.90)
Cerebrovascular disease	19.67 (2.01–184.53)	25.85 (2.00–355.22)	15.74 (1.24–200.72)

Abbreviation: MACE, major adverse cardiovascular events.

Model 1: adjusted for age sex.

Model 2: adjusted for Model 1 + Charlson comorbidity index and CHA_2DS_2-VASc and HAS-BLED scores.

5. Comparison of MACE, CV mortality, All-cause mortality and adverse events between NOAC vs. no-anticoagulation group.

Compared with the no anticoagulation group, the anticoagulation (apixaban 2.5 mg twice a day) group had a low incidence of mortality. However, the multivariate-adjusted Cox regression analysis showed that compared with no anticoagulation, low dose apixaban (2.5 mg twice a day) was associated with any bleeding and cerebrovascular disease (Table 5).

Table 5. Comparison of Apixaban 2.5 mg Twice a Day and No Anticoagulation

	Crude	**Model 1**	**Model 2**
All-cause mortality	5.14 (1.59–16.57)	4.55 (1.38–14.97)	2.70 (0.72–10.05)
MACE	3.79 (0.83–17.26)	3.21 (0.68–15.08)	2.28 (0.47–11.17)
Any bleeding	43.66 (4.3–443.38)	37.54 (3.65–386.44)	31.47 (3.05–325.20)
Cerebrovascular disease	15.8 (4.14–60.25)	14.46 (3.59–58.22)	12.30 (2.85–53.09)

Abbreviation: MACE, major adverse cardiovascular events.

Model 1: adjusted for age sex.

Model 2: adjusted for Model 1 + Charlson comorbidity index and CHA_2DS_2-VASc and HAS-BLED scores.

IV. **Discussion**

In our study, among patients on dialysis, the incidences of all-cause mortality and MACE were similar in the anticoagulation and no anticoagulation groups. However, compared with the no anticoagulation group, the anticoagulation group was associated with any bleeding and cerebrovascular disease. In the subgroup analysis, compared with warfarin treatment, low-dose apixaban (2.5 mg twice a day) showed no difference in all-cause mortality, MACE, and any bleeding. However, patients with low dose apixaban treatment had an increased risk of cerebrovascular disease than those with no anticoagulation treatment.

The number of non-anticoagulation group was larger than anticoagulation group in this study. More than half of the participants were already prescribed antiplatelet agents like aspirin and clopidogrel. As the benefit of anticoagulation is still in a debate in dialysis patients, concomitant use of antiplatelet agents and anti-coagulation agents seemed to be not preferred in clinicians in this study.

According to the result, the apixaban group showed a lower all-cause mortality, MACE, CV mortality than the warfarin group, but all of these parameters were not statistically significant. Probably, the number of patients prescribed with the apixaban or warfarin was not big enough to reveal the statistically significant differences.

Warfarin is currently the most widely used anticoagulation agent in patients on dialysis. It is mainly eliminated by the liver and not significantly removed by dialysis[17]. As patients on dialysis have a higher bleeding risk and warfarin may increase bleeding risk, major bleeding complications are the primary concern in administering warfarin in these patients[18]. Also, warfarin can induce adverse events like calciphylaxis and nephropathy[19-20]. Therefore, the risk and benefits of warfarin should be considered in patients with end-stage renal disease (ESRD) with AF. A meta-analysis study among the 12 observational studies that analyzed the effect of warfarin therapy in patients with ESRD showed a nonsignificant decrease in the

incidence of ischemic stroke events (HR, 0.74; 95% CI, 0.51–1.06) and a significant increase in bleeding events and increased incidence of hemorrhagic stroke events (HR, 1.93; 95% CI, 0.93–3.98)[21]. Combined with the results of our study, warfarin appears to have more side effects than benefits in patients with ESRD.

A systematic review that compared stroke and bleeding outcomes in warfarin and NOACs in 10 studies revealed no significant difference in stroke outcomes between two groups in patients on dialysis with AF[11]. At the same time, rivaroxaban and dabigatran showed a higher incidence of hospitalization and mortality than warfarin in patients with AF on dialysis[22]. In one cohort study for patients on dialysis, dabigatran showed no significant difference in stroke and thromboembolism events than warfarin (95% CI, 0.97–2.99)[23]. However, dabigatran showed higher mortality in patients with ESRD in the observational study[23]. Rivaroxaban and edoxaban are barely cleared by dialysis, and in a retrospective study, they showed higher mortality than warfarin[23, 27]. The clearance of apixaban is less dependent on kidney function, and each hemodialysis session removes only 6.7% of the drug[28]. Therefore, there is still insufficient evidence for using of ribaroxaban, dabigatran and edoxaban.

On the other hand, apixaban showed better results in clinical studies compared to rivaroxaban, dabigatran, and edoxaban. In contrast to our results, in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the administration of apixaban (mostly 5 mg twice a day) showed a lower incidence of major bleeding events and better mortality results compared with that of warfarin[22]. In the ARISTOTLE trial, patients with moderate CKD (eGFR, 25–50 mL/min) showed a lower incidence of major bleeding (3.28% per year) in the apixaban group than those in the warfarin group (6.78% per year)[25]. Moreover, apixaban revealed significantly reduced stroke outcomes compared with warfarin in patients with moderate CKD (eGFR, 25–50 mL/min)[25]. Another US retrospective cohort study showed that compared with the no anticoagulation

group, the apixaban (5 mg twice a day and 2.5 mg twice a day) group was associated with a higher incidence of fatal bleeding and no difference in the myocardial infarction and ischemic stroke[24]. Moreover, in the subgroup analysis, compared with the no anticoagulation group, the standard-dose apixaban (5 mg twice a day) group showed a higher risk of major bleeding (HR, 4.61; 95% CI, 1.91–11.15), but the reduced dose of apixaban (2.5 mg twice a day) was not increased risk of major bleeding (HR, 2.02; 95% CI, 0.58–7.04). However, the reduced-dose apixaban was associated with an increased incidence of ischemic stroke or myocardial infarction (HR, 1.56; 95% CI, 1.02–2.39). The limitation of this study was that the use of aspirin was not included in this cohort study[24]. The retrospective cohort study in the US, which compared apixaban with warfarin use in patients with AF on dialysis, revealed that the apixaban (5 mg twice a day and 2.5 mg twice a day) group showed a lower risk of major bleeding events than the warfarin group[12]. The incidences of ischemic stroke, thromboembolism events, and all-cause mortality were similar in the two groups[12]. Apixaban 5 mg twice a day and 2.5 mg twice a day showed no significant difference in bleeding outcomes compared with warfarin[12]. In the subgroup analysis, compared with reduced-dose apixaban (2.5 mg twice a day) and warfarin, standard-dose apixaban (5 mg twice a day) was associated with a lower risk of stroke, systemic embolism, and mortality[12]. Patients on dialysis showed no difference in bleeding tendency between the apixaban (mostly 5 mg twice a day) and warfarin groups[26]. In other cohort studies with patients on dialysis, the apixaban group showed no difference with the warfarin group[26]. Compared with our study, our study revealed similar results. The apixaban group did not show significant difference from the warfarin group in dialysis patients.

The ideal dose of apixaban in patients with ESRD is not fully established and still needs to be studied. The recommended dose from the US FDA is 5 mg twice daily. Either patient older than 80 years or those with a bodyweight of <60 kg are recommended to reduce the dose to 2.5 mg twice daily. In one study, 2.5 mg twice a day over eight days in patients with

ESRD was similar to the amount in healthy patients. However, the dose of 5 mg twice a day over 8 days was higher than the therapeutic level of healthy patients[29]. Currently, an ongoing randomized clinical trial compares apixaban with the reduced dose and warfarin in patients with AF and on dialysis (NCT02933697). Another randomized trial that compares the apixaban group with the standard and reduced dose, warfarin group, and no anticoagulant group is still in progress (NCT03987711).

This retrospective observational cohort study has several limitations. The selection bias could affect the results that patients with a higher risk of bleeding were more likely to be treated with no anticoagulation. As the number of patients prescribed apixaban was small, our study had limited explanatory power. In addition, compared with warfarin, apixaban was a new drug that was prescribed in our hospital after 2017 that apixaban-treated patients had a relatively short follow-up duration than warfarin-treated patients. Despite these limitations, the strength of our study is that we reviewed the medications that could affect the bleeding potency, including antiplatelet and antihypertensive agents and diabetes medications, as many as possible. These points could reduce other significant biases that could have affected cardiovascular outcomes.

V. Conclusion

For patients with ESRD with AF, anticoagulation increases the risk of bleeding, regardless of the type of medication. Our study showed that compared with warfarin, low dose apixaban reduced the incidences of all-cause mortality and MACE. Still, the the difference between the two groups was not statistically significant in the multivariate adjustment analysis. Therefore, through our results, we could not recommend low dose apixaban for anticoagulation in patients with ESRD, and further large studies are needed.

VI. References

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국 문 요 약

심방세동을 동반한 투석환자에서 항응고치료 여부에 따른 비교

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의학과

김 미 령

1. 배경

심방세동은 투석 환자에서 매우 흔하게 발견되는 상심실성 빈맥이다. 말기 신부전 환자 및 투석 환자는 질병 자체적인 특성 만으로도 출혈 위험성이 높아, 심방세동을 동반한 투석 환자에서 항응고제 치료를 시행할 지 여부에 대해서는 아직 논란이 많다.

이에 따라, 저자는 심방세동을 동반한 투석 환자에서 아픽사반 약제를 사용하는 것의 효능과 안전성을 확인하기 위해 후향적 연구를 시행하였다. 본 연구에서는 심방세동을 동반한 투석 환자에서 아픽사반 약제를 사용한 군과 와파린 약제를 사용한 군, 그리고 항응고제를 투약하지 않은 군 간의 예후를 비교하였다.

2. 연구방법

본 연구는 원주세브란스기독병원의 의무기록 자료를 사용하였다. 2010년부터 2020년까지 심방세동 혹은 심방조동을 진단받은 투석환자를 대상으로 후향적 코호트 연구를 진행하였다. 각 그룹을 비교하기 위해 T-test, 카이제곱 검정, 맨휘트니 검정을 진행하였고나이, 성별, CHA2DS2-VASc score, HAS-BLED score 비교에 다변량 Cox 회귀분석을 활용하였다.

3. 결과

총 99명의 환자가 본 연구에 포함되었고 36명의 환자가 항응고치료를 받고 63명의 환자는 항응고치료를 받고 있지 않았다. 이중 17명의 환자는 와파린 치료를 받았고 19명의 환자는 아픽사반 2.5mg 하루 2번 치료를 받았다. 항응고치료를 받은 군과 항응고치료를 받지 않은 군 사이에 기본 특성은 차이를 보이지 않았다. 항응고치료를 받지 않은 군에서 총사망률 (39.7% vs. 32.4%, p =0.572) 과 심혈관계 연관 사망률 (17.6% vs. 10.8%, p =0.197) 이 더 높았으나 통계학적으로 유의한 차이를 보이지는 않았다. 아픽사반 2.5mg 하루 2회 투여군과 비교해 보았을 때, 와파린 투여군에서 심혈관계 부작용이 좀더 높은 확률로 나타났지만 (35.3% vs. 15.8%, p =0.109) 통계학적으로 유의한 차이

를 보이지는 않았다. 다변량 콕스 회귀분석으로 항응고치료를 받지 않은 군과 비교해보았을 때, 아픽사반 2.5mg 하루 2번 투여군은 뇌혈관계 출혈 위험성 및 기타 출혈 위험성이 더 높게 나타났다. (위험비율 12.30)

4. 고찰

투석 환자군에서 아픽사반 2.5mg 하루 2회 치료는 와파린 치료와 비교해 보았을 때 이득과 위험율에 있어 큰 차이가 없었다. 그러나, 투석 환자군에서 아픽사반 2.5mg 하루 2회 치료 시 항응고치료를 하지 않은 군과 비교해 보았을 때 출혈 위험성이 더 높은 것으로 확인되어 아직은 투석 환자군에서 아픽사반의 사용이 큰 이득을 가진다고 판단하기는 어렵고, 추가적인 연구가 필요할 것으로 생각된다.