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Oral Anticoagulation Therapy in Atrial Fibrillation Patients with Advanced Chronic Kidney Disease: CODE-AF Registry

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Purpose: Advanced chronic kidney disease (CKD), including end-stage renal disease (ESRD) on dialysis, increases thromboembolic risk among patients with atrial fibrillation (AF). This study examined the comparative safety and efficacy of direct-acting oral anticoagulant (DOAC) compared to warfarin or no oral anticoagulant (OAC) in AF patients with advanced CKD or ESRD on dialysis.

Materials and Methods: Using data from the COmparison study of Drugs for symptom control and complication prEvention of AF (CODE-AF) registry, 260 non-valvular AF patients with advanced CKD (defined as estimated glomerular filtration rate <30 mL/min per 1.73/m^2) or ESRD on dialysis were enrolled from June 2016 to July 2020. The study population was categorized into DOAC, warfarin, and no OAC groups; and differences in major or clinically relevant non-major (CRNM) bleeding, stroke/systemic embolism (SE), myocardial infarction/critical limb ischemia (CLI), and death were assessed.

Results: During a median 24 months of follow-up, major or CRNM bleeding risk was significantly reduced in the DOAC group compared to the warfarin group [hazard ratio (HR) 0.11, 95% confidence interval (CI) 0.01 to 0.93, p=0.043]. In addition, the risk of composite adverse clinical outcomes (major or CRNM bleeding, stroke/SE, myocardial infarction/CLI, and death) was significantly reduced in the DOAC group compared to the no OAC group (HR 0.16, 95% CI 0.03 to 0.91, p=0.039).

Conclusion: Among AF patients with advanced CKD or ESRD on dialysis, DOAC was associated with a lower risk of major or CRNM bleeding compared to warfarin and a lower risk of composite adverse clinical outcomes compared to no OAC.
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Key Words: Anticoagulant, atrial fibrillation, dialysis, stroke, bleeding

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INTRODUCTION

Atrial fibrillation (AF) is associated with a five-fold increase in the risk of stroke, and chronic kidney disease (CKD) increases the risk by 3.7 times compared to the general population.[1,2] Patients with CKD have a 10-fold increased prevalence of AF, with which kidney function deteriorates over time.[3,4] AF and CKD are closely interrelated conditions that are additively associated with an increased risk of stroke, and this is particularly true in those with severe renal impairment.[5,6] Although warfarin has been recommended for stroke prevention in AF patients with advanced CKD, antithrombotic therapy in these patients is complex. Increased bleeding risk due to uremia-induced platelet dysfunction complicates clinical decision-making,[7] and several studies have questioned its overall effectiveness in stroke prevention.[8,9] Recently, direct-acting oral anticoagulants (DOACs) have changed the landscape of antithrombotic therapy in AF patients with normal or near-normal renal function. Compared to warfarin, DOAC has shown non-inferior efficacy in stroke prevention and significant reduction in major bleeding.[10-13] However, DOAC relies on some degree of renal excretion, and advanced CKD or ESRD on dialysis patients have largely been excluded from clinical trials.[10-13] The objective of this study was to assess the comparable safety and effectiveness of DOAC compared to warfarin or no oral anticoagulant (OAC) among AF patients with advanced CKD or ESRD on dialysis.

MATERIALS AND METHODS

Data source and study population

The COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) registry is an ongoing prospective observational registry at 18 tertiary hospitals representing all geographical regions of South Korea. Detailed descriptions are available in previous studies.[14] In brief, the aim of this registry is to assess the clinical epidemiology of patients with AF and to determine the diagnostic and therapeutic processes applied in these patients, along with their clinical outcomes. All patients provided informed consent. The registry was designed by the Korea Heart Rhythm Society, approved by the ethics committee of each center (4-2016-0105).

A total of 11527 AF patients were enrolled in the CODE-AF registry from June 2016 to July 2020. Eligible patients from the registry were >18 years old with non-valvular AF, and did not have transient AF with reversible causes or need for chronic anticoagulation to treat conditions other than AF, such as valve prosthesis, deep venous thrombosis, or pulmonary thromboembolism. After enrollment, each patient was scheduled to be followed up every 6 months, either by outpatient clinic or telephone contact. Each patient was assessed at enrollment for demographics, medical history, and laboratory measures. In our study, advanced CKD was defined as previous diagnosis of CKD and baseline estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2, as calculated by the MDRD equation. Advanced CKD was further classified as CKD stage 4 (eGFR ≥15 to <30 mL/min per 1.73 m^2), stage 5 (eGFR <15 mL/min per 1.73 m^2), or ESRD on dialysis. Of 11527 patients in the registry, we excluded those without previous diagnosis of CKD (n=10446), baseline eGFR (MDRD) ≥30 mL/min per 1.73 m^2 (n=820), or OAC use for less than 30 days after the start of follow-up (n=1). Finally, a total of 260 patients were included in this study, and they were categorized into warfarin (n=114), DOAC (n=48), and no OAC (n=98) groups. Since DOAC use in patients with severe renal impairment has not been fully established, careful explanation about its pros and cons was conducted, and consent was obtained from the patient and their caregivers.

Outcome definition and follow-up

The primary outcome was defined as a composite of major or clinically relevant non-major (CRNM) bleeding, stroke/systemic embolism (SE), myocardial infarction/critical limb ischemia (CLI), and all-cause death. The definition of major bleeding was based on the International Society on Thrombosis and Hemostasis criteria for major bleeding or CRNM bleeding. Stroke/SE included cerebrovascular accident, transient ischemic attack, and acute loss of blood flow to a peripheral artery confirmed by magnetic resonance imaging or computed tomography. Myocardial infarction was defined based on the clinical evidence of myocardial ischemia with myocardial necrosis on laboratory findings. CLI was defined as the presence of ischemic resting pain, ulcer, or gangrene with lower extremity peripheral artery disease. Patients were followed until the end of the study period (July 2020), or until death or censoring. Patients were censored for any of the following reasons: discontinuing OAC for any reason, switching from DOAC to warfarin or vice versa, and kidney function recovery or dialysis discontinuation due to kidney transplantation.

Statistical analysis

We summarized baseline characteristics as counts and percentages for categorical variables, and medians with 25th to 75th percentiles for continuous variables. Categorical variables were compared using the χ^2 test, and continuous variables were compared using the Student's t-test. Event rate was presented as number of events per 100 person-years. Survival free of adverse events in each group was presented using the Kaplan-Meier method, and compared by the log-rank test. For each adverse clinical outcome, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards regression models to show the association between the warfarin, DOAC, and no OAC groups. HRs were adjusted by components of the baseline characteristics, and p-values<0.05 were considered statistically significant. All statistical analyses were performed using the SPSS software (The Statistical Package for Social Sciences, version 25.0; IBM Corp., Armonk, NY, USA).

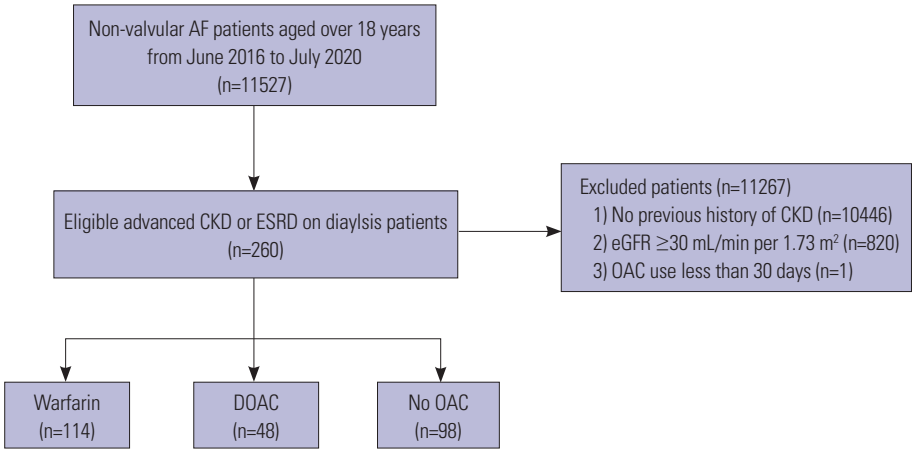

Fig. 1. Flow chart of the study population. AF, atrial fibrillation; CKD, chronic kidney disease; DOAC, direct-acting oral anticoagulant; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulant.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Warfarin (n=114)	DOAC (n=48)	No OAC (n=98)	*p* value
Age, yr	70 (64–76)	77 (70–81)	65 (58–74)	<0.001
Sex, female	50 (43.9)	24 (50.0)	38 (38.8)	0.432
Paroxysmal AF	73 (64.0)	32 (66.7)	75 (76.5)	0.137
Systolic BP, mm Hg	131 (120–143)	121 (109–126)	132 (119–143)	0.431
Diastolic BP, mm Hg	75 (68–82)	67 (60–69)	76 (68–83)	0.741
CHA_2DS_2-VASc	3 (2–5)	5 (3–6)	3 (2–4)	<0.001
1–2	32 (28.1)	6 (12.5)	44 (44.9)	
3–5	68 (59.6)	26 (54.2)	51 (52.0)	
≥6	14 (12.3)	16 (33.3)	3 (3.1)	
HAS-BLED	3 (2–5)	5 (3–6)	3 (2–4)	0.028
0–2	24 (21.1)	19 (39.6)	36 (36.7)	
3–4	79 (69.3)	28 (58.3)	52 (53.1)	
≥5	11 (9.6)	1 (2.1)	10 (10.2)	
Chronic conditions				
Hypertension	99 (86.8)	43 (89.6)	81 (82.7)	0.488
Diabetes mellitus	59 (51.8)	28 (58.3)	39 (39.8)	0.074
Dyslipidemia	38 (33.3)	22 (45.8)	36 (36.7)	0.328
Myocardial infarction	8 (7.0)	3 (6.2)	4 (4.1)	0.655
Heart failure	12 (10.5)	7 (14.6)	11 (11.2)	0.759
Stroke	20 (17.5)	17 (35.4)	9 (9.2)	0.001
PAOD	12 (10.5)	3 (6.2)	15 (15.3)	0.254
CKD, stage 4	33 (28.9)	27 (57.2)	19 (19.4)	<0.001
Medications				
RAAS inhibitor	40 (35.1)	29 (60.4)	26 (26.5)	<0.001
Beta-blocker	50 (43.9)	28 (58.3)	42 (42.9)	0.176
Statin	36 (31.6)	22 (45.8)	33 (33.7)	0.214
Anti-platelet drug	13 (11.4)	11 (22.9)	54 (55.1)	<0.001
Anti-arrhythmic drugs	46 (40.4)	17 (35.4)	28 (28.6)	0.206
Dabigatran		5 (10.4)		
Rivaroxaban		14 (29.2)		
Apixaban		25 (52.1)		
Edoxaban		4 (8.3)		

AF, atrial fibrillation; BP, blood pressure; CKD, chronic kidney disease; DOAC, direct-acting oral anticoagulant; OAC, oral anticoagulant; PAOD, peripheral artery occlusive disease; RAAS, renin-angiotensin-aldosterone-system.
Values are presented as the median (1st quartile, 3rd quartile) or n (%).

RESULTS

Study population

The flow chart and baseline characteristics of the study population are presented in Fig. 1 and Table 1, respectively. Among 260 AF patients with advanced CKD, 114 (43.8%) were in the warfarin group, 48 (18.5%) in the DOAC group, and 98 (37.7%) in the no OAC group. Compared with the warfarin group, the DOAC group had higher CHA_2DS_2VASc and HAS-BLED scores, and was more likely to have a history of stroke and CKD stage 4. Meanwhile, compared to the no OAC group, the DOAC group had a higher CHA_2DS_2-VASc score, and was more likely to have stroke and CKD stage 4 but less likely to have paroxysmal AF or use anti-platelet drugs.

Among the 48 DOAC users, 25 (52.1%) were on apixaban, 14 (29.2%) on rivaroxaban, 5 (10.4%) on dabigatran, and 4 (8.3%) on edoxaban. Among the 25 apixaban users, 22 were prescribed a 2.5-mg twice daily dose and three a 1.25-mg twice daily dose. Among the 14 rivaroxaban users, 12 were prescribed a 15-mg once daily dose and two a 10-mg once daily dose. All dabigatran and edoxaban users were prescribed a 110-mg twice daily dose and a 30-mg once daily dose, respectively. Baseline characteristics of the DOAC group by the specific types of DOAC are presented in Supplementary Table 1 (only online).

Clinical outcomes

The event numbers and ratios of adverse clinical outcomes for the three groups, including specific type of DOAC, are presented in Supplementary Table 2 (only online).

During a median 24 months (interquartile range, 12 to 36 months) of follow-up, the event rates of composite adverse clinical outcomes were 5.5 and 10.5 per 100 person-years in the DOAC and warfarin groups, respectively. No statistically significant difference in the risk of composite adverse clinical outcomes between DOAC and warfarin groups was found (HR 0.54, 95% CI 0.18 to 1.65, p=0.278). In contrast, the event rates of major or CRNM bleeding were 1.8 and 7.9 per 100 person-years for the

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DOAC and warfarin groups, respectively. Compared to the warfarin group, the DOAC group had a significantly reduced risk of major or CRNM bleeding (HR 0.11, 95% CI 0.01 to 0.93, p=0.043) (Fig. 2). Although the event rates of stroke/SE, all-cause death, and myocardial infarction/CLI showed similar trends, there were no statistically significant differences in the risks of any of these adverse clinical outcomes between the two groups (Fig. 2).

The event rates of the composite adverse clinical outcome were 5.5 and 8.4 per 100 person-years in the DOAC group and the no OAC group, respectively. Compared to the no OAC group, the DOAC group had a significantly reduced risk of composite adverse clinical outcomes (HR 0.16, 95% CI 0.03 to 0.91, p=0.039). In addition, major or CRNM bleeding risk between the two groups was not significantly different (HR 0.28, 95% CI 0.05 to 1.69, p=0.165). There were no significant differences in any of other adverse clinical outcomes (stroke/SE, all-cause death, and myocardial infarction/CLI) between the two groups (Fig. 3). In addition, there was no significant difference in composite and each of the adverse clinical outcomes in the no OAC group compared to the warfarin group (Supplementary Fig. 1, only online).

The survival curve of composite and each of the adverse clinical outcomes is presented as Kaplan-Meier curve in Fig. 4.

	Event	Event rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P-value
Major or CRNM bleeding					0.043
Warfarin	16	7.9	Reference	Reference	
DOAC	2	1.8	0.23 (0.05-0.98)	0.11 (0.01-0.93)	
Stroke/systemic embolism					0.468
Warfarin	3	1.5	Reference	Reference	
DOAC	1	0.9	0.61 (0.06-5.91)	0.33 (0.02-6.60)	
Death					0.935
Warfarin	4	1.9	Reference	Reference	
DOAC	2	1.8	0.91 (0.17-4.99)	1.12 (0.08-1.67)	
Myocardial infarction/CLI					0.908
Warfarin	2	1.1	reference	Reference	
DOAC	1	1.0	1.08 (0.10-12.0)	1.17 (0.09-15.7)	
Composite adverse outcomes					
Warfarin	21	10.5	Reference	Reference	0.278
DOAC	6	5.5	0.54 (0.22-1.35)	0.54 (0.18-1.65)	

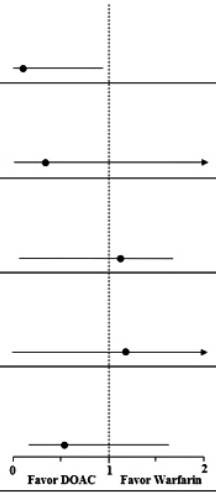

Fig. 2. Event rates and HRs of adverse clinical outcomes for DOAC versus warfarin in AF patients with advanced CKD or ESRD on dialysis. Event rate is calculated for 100 person-years. AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; CLI, critical limb ischemia; CRNM, clinically relevant non-major; DOAC, direct-acting oral anticoagulant; ESRD, end-stage renal disease; HR, hazard ratio.

	Event	Event Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P-value
Major or CRNM bleeding					0.165
No OAC	6	3.1	Reference	Reference	
DOAC	2	1.8	0.58 (0.12-2.90)	0.28 (0.05-1.69)	
Stroke/systemic embolism					0.501
No OAC	2	1.0	Reference	Reference	
DOAC	1	0.9	0.94 (0.08-10.4)	0.42 (0.03-5.27)	
Death					0.227
No OAC	6	3.1	Reference	Reference	
DOAC	2	1.8	0.62 (0.12-3.06)	0.33 (0.06-1.98)	
Myocardial infarction/CLI					0.130
No OAC	5	2.6	reference	Reference	
DOAC	1	0.9	0.32 (0.04-2.76)	0.17 (0.02-1.69)	
Composite adverse outcomes					
No OAC	16	8.4	Reference	Reference	0.039
DOAC	6	5.5	0.68 (0.27-1.74)	0.16 (0.03-0.91)	

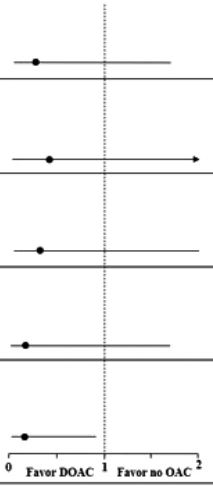

Fig. 3. Event rates and HRs of adverse clinical outcomes for DOAC versus no OAC in AF patients with advanced CKD or ESRD on dialysis. Event rate is calculated for 100 person-years. AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; CLI, critical limb ischemia; CRNM, clinically relevant non-major; DOAC, direct-acting oral anticoagulant; ESRD, end-stage renal disease; HR, hazard ratio; OAC, oral anticoagulant.

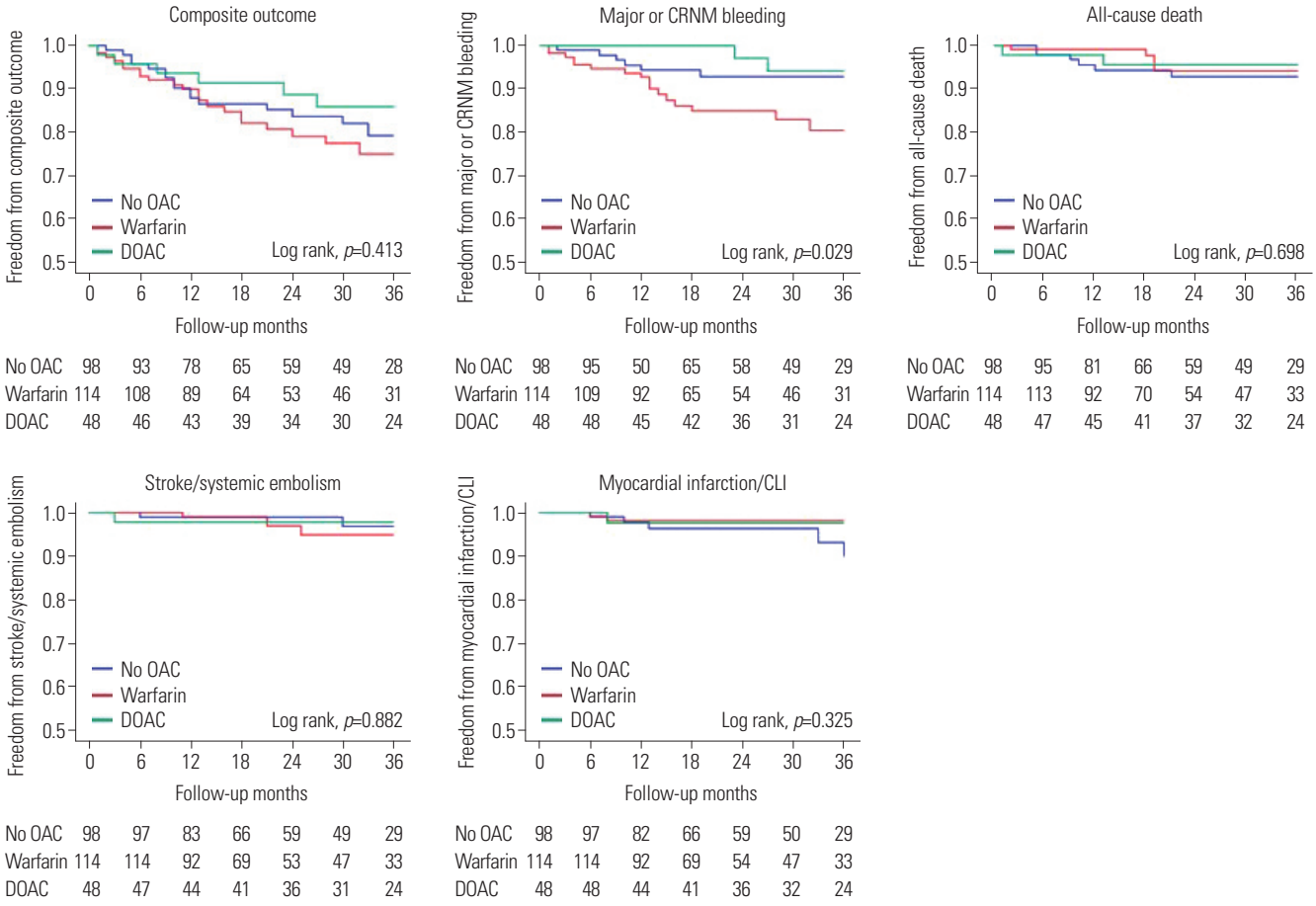

Fig. 4. Survival curves for adverse clinical outcomes in the DOAC, warfarin, and no OAC groups in AF patients with advanced CKD or ESRD on dialysis. AF, atrial fibrillation; CKD, chronic kidney disease; CLI, critical limb ischemia; CRNM, clinically relevant non-major; DOAC, direct-acting oral anticoagulant; ESRD, end-stage renal disease; OAC, oral anticoagulant.

Significant differences in major or CRNM bleeding among DOAC, warfarin, and no OAC groups were identified (log rank, p=0.029).

Subgroup analysis

Since dabigatran is not recommended in patients with advanced CKD (creatinine clearance of <30 mL/min) or ESRD on dialysis according to the U.S. and European guidelines,[3,15] we conducted a subgroup analysis after excluding those prescribed with dabigatran in the DOAC group. The results were similar to the main analysis (Supplementary Figs. 2 and 3, only online).

DISCUSSION

In this prospective observational study of 260 non-valvular AF patients with advanced CKD or ESRD on dialysis, DOAC was associated with reduced major or CRNM bleeding compared to warfarin, and with reduced composite adverse clinical outcomes compared to no OAC.

Given the non-inferior efficacy in stroke prevention and major bleeding risk reduction compared to warfarin, DOAC has become the mainstay of stroke prevention in AF patients with normal or near-normal renal function.[10-13] Despite the clinical benefits of DOACs compared to warfarin, advanced CKD patients have largely been excluded from major clinical trials, since DOACs produce varying degrees of renal excretion. Dabigatran is 80% renally excreted, while edoxaban is 50%, rivaroxaban is 35%, and apixaban is 27%.[16-18] Due to concerns regarding increased plasma concentration, as well as the lack of clinical trials in this population, the U.S. and European guidelines make tentative recommendations for the use of DOACs in patients with severe renal impairment.[3,15]

However, pharmacokinetic data for apixaban in patients with advanced CKD or ESRD on dialysis have suggested that apixaban dosing in these patients had limited impact on apixaban plasma concentration.[18] Thus, there are reasons to anticipate apixaban use in patients with severe renal impairment, and some studies have shown favorable outcomes with apixaban in AF patients with advanced CKD compared to warfarin.[19,20] Siontis, et al.[19] showed that apixaban 2.5-mg twice a day resulted in decreased major bleeding risk compared to warfarin, and apixaban 5-mg twice a day resulted in not only decreased major bleeding risk, but also decreased risk of stroke and death

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in patients on chronic dialysis. On the other hand, another study by Chan, et al.[16] showed that dabigatran and rivaroxaban in chronic dialysis patients were associated with increased major bleeding and death compared to warfarin, despite dose reductions. In our study, among the 48 DOAC users, 25 (52.1%) were on apixaban, 14 (29.2%) were on rivaroxaban, 5 (10.4%) were on dabigatran, and 4 (8.3%) were on edoxaban. All incidences of major or CRNM bleeding occurred in those who were prescribed rivaroxaban and dabigatran (Supplementary Table 2, only online), and reductions in major or CRNM bleeding were predominant in apixaban or edoxaban users, which was in line with the findings of previous studies.[19-23] There were too few stroke/SE events in either the DOAC group or the warfarin group in our study to draw any meaningful associations between the two.

Evidence that OAC therapy leads to clinical benefits in AF patients with advanced CKD or ESRD on dialysis is scarce. Although warfarin has been conventionally recommended for antithrombotic therapy in these populations, no established conclusion about its overall effectiveness in stroke prevention has been suggested.[1,8,9,24] Bonde, et al.[24] showed that advanced CKD patients on warfarin had a reduced risk of composite stroke/fatal bleeding as well as death; whereas Shah, et al.[8] found no benefit of warfarin in stroke prevention, but only an increased bleeding risk compared to no OAC. Uremia-induced platelet dysfunction and coagulopathy, as well as vascular calcification associated with warfarin use, have been suggested as a possible explanation for the differing results;[7,25] and we also found no evidence of benefit from warfarin use compared to no OAC in patients with advanced CKD or ESRD on dialysis.

In the current study, DOAC was associated with reduced composite adverse clinical outcomes without increased risk of major or CRNM bleeding compared to no OAC. Advanced CKD patients have accelerated atherosclerosis and increased risk of cardiovascular disease,[26,27] and more than 50% of CKD stage 5 patients at initiation of renal replacement therapy have angiographically significant coronary artery stenosis. One possible explanation of our result is that the benefit of the antithrombotic property, translated into secondary cardiovascular protection under OAC treatment,[28,29] was offset by the increased bleeding risk under warfarin use but remained under DOAC use. The benefit of DOAC in secondary prevention of stable cardiovascular disease patients was suggested in the COMPASS trial.[28] In this trial, composite myocardial infarction, stroke, and cardiovascular death were significantly reduced in the rivaroxaban 2.5-mg twice daily plus aspirin group, and there was a non-significant trend toward reduced risk in the rivaroxaban 5-mg twice daily group compared to the aspirin only group. Although the trial did not enroll patients with severe renal impairment, advanced CKD patients in our study might have benefitted from DOAC use, considering the increased risk of cardiovascular disease in these patients.

Our study had several limitations. First, although we found some clinical benefit of DOAC compared to warfarin or no OAC, our results require careful interpretation due to the small sample size and few number of adverse clinical events. Second, significantly different baseline characteristics between the DOAC, warfarin, and no OAC groups complicates the interpretation of our results. For example, DOAC users had better residual renal function compared to the warfarin group or no OAC group. This could have resulted in favorable cardiovascular outcomes and translated into reduced composite adverse clinical outcomes in the DOAC group. In addition, there were more users of aspirin, which is the first-line therapy in cardiovascular disease, in the no OAC group than in the DOAC or warfarin groups, and this might have translated into a smaller number of composite adverse clinical outcomes in the no OAC group. Third, the DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were not separately analyzed, since there were too few events in each of the subgroups to draw meaningful results. Although rivaroxaban (29.2%) and apixaban (47.9%) users comprised the majority of the DOAC group, the results of our study cannot confirm which drug among the DOACs represented is most favorable.

In conclusion, among AF patients with advanced CKD or ESRD on dialysis, DOAC use was associated with a lower risk of major or CRNM bleeding compared to warfarin, and a lower risk of composite adverse clinical outcomes compared to no OAC.

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AUTHOR CONTRIBUTIONS

Conceptualization: Boyoung Joung. Data curation: Hanjin Park and Hee Tae Yu. Formal analysis: Tae-Hoon Kim. Funding acquisition: Boyoung Joung. Investigation: Junbeom Park. Methodology: Jin-Kyu Park. Project administration: Ki-Woon Kang and Jaemin Shim. Resources: Jin-Bae Kim. Software: Jun Kim. Supervision: Eue-Keun Choi. Validation: Hyung Wook Park. Visualization: Young Soo Lee. Writing—original draft: Hanjin Park. Writing—review & editing: Hee Tae Yu. Approval of final manuscript: all authors.

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