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ORIGINAL ARTICLE

Adequacy of Dialysis and Incidence of Atrial Fibrillation in Patients Undergoing Hemodialysis

Ga Young Heo, MD; Jung Tak Park, MD, PhD; Hyo Jeong Kim, MD; Kyung Won Kim, MD; Yong Uk Kwon, MD; Soo Hyun Kim, BSN; Gui Ok Kim, BSN; Seung Hyeok Han, MD, PhD; Tae-Hyun Yoo, MD, PhD; Shin-Wook Kang, MD, PhD; Hyung Woo Kim, MD

BACKGROUND: Atrial fibrillation (AF) can lead to stroke, heart failure, and mortality and has a greater prevalence in dialysis patients than in the general population. Several studies have suggested that uremic toxins may contribute to the development of AF. However, the association between dialysis adequacy and incident AF has not been well established.

METHODS: In this retrospective nationwide cohort study, we analyzed data from the Korean National Periodic Hemodialysis Quality Assessment from 2013 to 2015 of patients who received outpatient maintenance hemodialysis 3× a week. The main exposure was single pooled Kt/V (spKt/V), which is the dialysis adequacy index, and the primary outcome was the development of AF. For the primary analysis, patients were categorized into quartiles according to baseline spKt/V. The lowest quartile, representing the lowest adequacy, was used as the reference group. Fine-Gray subdistribution hazard models were used, treating all-cause mortality as a competing risk.

RESULTS: Of 25 173 patients, the mean age was 60 (51–69) years, and 14 772 (58.7%) were men. During a median follow-up of 5.7 years, incident AF occurred in a total of 3883 (15.4%) patients. Participants with a higher spKt/V tended to have lower AF incidence. In survival analysis, a graded association was observed between the risk of incident AF and spKt/V quartiles: subdistribution hazard ratios and 95% CIs for the second, third, and the highest quartile compared with the lowest quartile were 0.90 (95% CI, 0.82–0.98), 0.84 (95% CI, 0.77–0.93), and 0.79 (95% CI, 0.72–0.88), respectively.

CONCLUSIONS: This nationwide cohort study showed that a higher spKt/V is associated with a reduced risk of incident AF. These findings suggests that reducing uremic toxin burden through enhanced dialysis clearance may be associated with a lower risk of AF development in patients undergoing maintenance hemodialysis.

Key Words: atrial fibrillation ■ cardiovascular disease ■ dialysis ■ uremia

See Editorial by Turner and Mehta

Atrial fibrillation (AF) is the most common sustained arrhythmia and a significant risk factor for thromboembolic events in the general population.[1,2] In addition, AF is also common in patients with end-stage kidney disease (ESKD), with a significantly higher prevalence in this population compared with the general population.[3,4] Previous studies have shown that AF is associated with a higher risk of stroke and heart failure and is an independent predictor of mortality in patients with ESKD.[5,6]

Patients with ESKD have nonmodifiable risk factors for AF, such as advanced age, diabetes, and cardiovascular comorbidities. Previous studies monitoring electrocardiograms have shown a higher incidence of AF on the peridialysis or intradialysis day,[7–9] suggesting that dialysis-related factors may play a crucial role in the

Correspondence to: Hyung Woo Kim, MD, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Email drhwint@yuhs.ac
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WHAT IS KNOWN

- Uremic toxins trigger inflammatory reactions and activate the neuro-hormonal system, leading to the development of atrial fibrillation and other cardiovascular diseases.
- Adequate removal of uremic toxins during dialysis is associated with an improved prognosis in patients with end-stage kidney disease.

WHAT THE STUDY ADDS

- Dialysis adequacy was associated with the incidence of atrial fibrillation in patients undergoing maintenance hemodialysis. Increasing dialysis clearance may decrease the risk of atrial fibrillation in this patient population.
- In this study, risk factors such as advanced age, obesity, chronic obstructive lung disease, heart failure, and dialysis-specific factors such as longer dialysis vintage and larger ultrafiltration volume were found to be associated with a higher risk of atrial fibrillation.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BMI	body mass index
ESKD	end-stage kidney disease
HIRA	Health Insurance Review and Assessment Service
ICD-10	International Classification of Diseases, Tenth Revision
SBP	systolic blood pressure
sHRs	subdistribution hazard ratios
spKt/V	single pooled Kt/V
URR	urea reduction ratio

development of AF in patients with ESKD. Notably, specific dialysis-related risk factors such as higher ultrafiltration rate, lower blood pressure, and hypokalemia have been reported to be associated with an increased AF risk.[10–15]

Previous studies have suggested that uremic toxins promote the development of AF[16–19] and other cardiovascular diseases.[20] Uremic toxins generate inflammatory reactions and activate the neuro-hormonal system, leading to fibrosis and oxidative injury of cardiac tissues.[16–18] In patients with ESKD, several small and middle molecular weight substances serve as uremic toxins. Adequate removal of these toxins during dialysis has been associated with an improved prognosis in this population.[21,22] Despite the relationship between uremic toxins and poor prognosis, it is unknown whether improved dialysis adequacy is associated with AF prevention in this population. Therefore, this study aimed to investigate the association between dialysis adequacy and the development of AF in patients receiving maintenance hemodialysis, using large, nationwide data from obligatory quality assessment of hemodialysis patients.

METHODS

Data Source and Study Population

In Korea, the National Health Insurance System is a public and single-payer system that covers 98% of the population. The remaining 2% consists of lower-income individuals who are supported by the government Medical Aid program. The Health Insurance Review and Assessment Service (HIRA) is a national institution that evaluates the medical service fee and quality of health care. The HIRA has periodically conducted a nationwide obligatory quality assessment for hemodialysis patients since 2010 (Korea National Periodic Hemodialysis Quality Assessment Program). All patients aged 18 years or older who receive maintenance hemodialysis at least twice a week (8× per month) as outpatients at a single dialysis facility in Korea are enrolled for hemodialysis quality assessment. The Korea National Periodic Hemodialysis Quality Assessment excluded patients who were lost to follow-up due to hospitalization or other reasons during each assessment period of 3 to 6 months.

Patients who underwent maintenance hemodialysis 3× a week and had a single pooled Kt/V (spKt/V) measurement at baseline in the fourth and fifth Korea National Periodic Hemodialysis Quality Assessment from 2013 to 2015 were initially screened. Patients with a history of kidney transplantation or those whose dialysis duration was <3 months were excluded. We also excluded patients with the following criteria: (1) a prior diagnosis of AF before the index date, defined as the date of assessments; (2) a history of pacemaker/implantable cardioverter defibrillator insertion; (3) mitral stenosis or prosthetic valve disease; (4) missing measurement data; and (5) extremely low or high (defined as <0.25th or >99.75th percentile) measurements of dialysis adequacy, body mass index (BMI), ultrafiltration volume, hemoglobin, albumin, and calcium (Table S1). After exclusion, 25 173 patients were included in the final analysis (Figure 1). Furthermore, we constructed an additional data set screening patients with a urea reduction ratio (URR) measurement at baseline for sensitivity analysis.

This study was conducted in adherence to the Helsinki Declaration, and the research protocol received approval from the Institutional Review Board of Yonsei University Health System (4-2022-0890). The informed consent was waived because of the retrospective nature involving medical record review alone without any personally identifiable information. Data sharing is not applicable to this article as the original data is available after getting approval from HIRA. Data sets are available at https://opendata.hira.or.kr with the permission of HIRA.

Data Collection

Demographic data, including age, sex, BMI, and predialysis systolic blood pressure (SBP), were collected. Dialysis-related factors, such as the cause of ESKD, hemodialysis vintage, type of vascular access (eg, arteriovenous fistula, arteriovenous graft, or central catheter), and ultrafiltration volume, were collected.

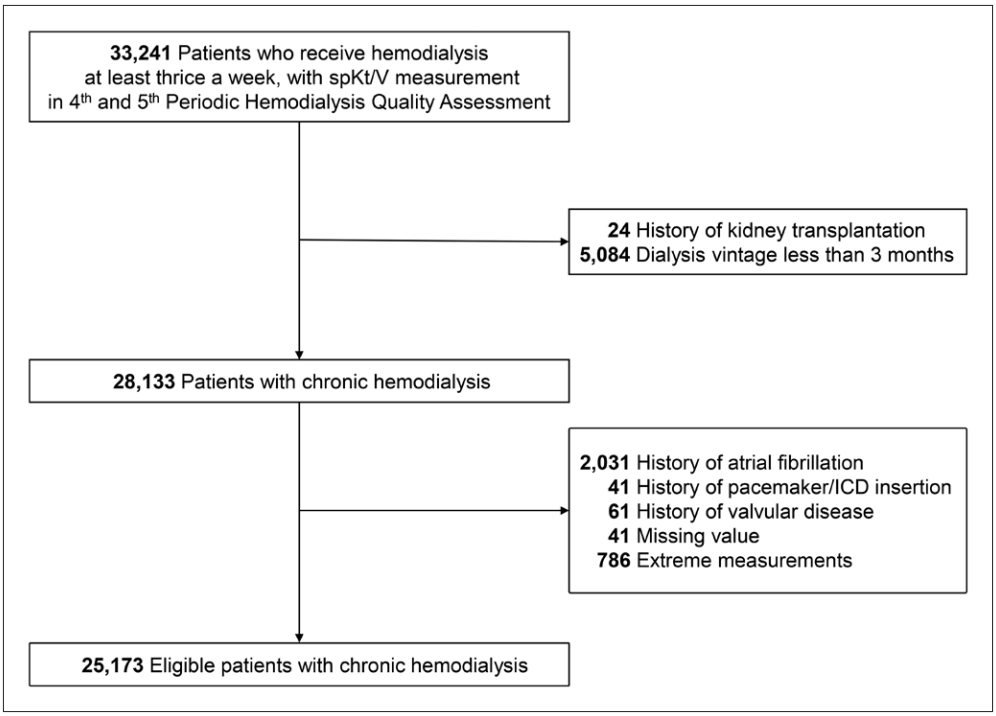

Figure 1. Study flow.
ICD indicates implantable cardioverter defibrillator; and spKt/V, single pooled Kt/V.

Economic status was classified based on the type of health care insurance coverage. The following laboratory measurements were collected: dialysis adequacy indices, hemoglobin, serum albumin, and serum calcium. Blood samples were obtained before and after the dialysis session. The use of medications, including antihypertensive drugs and statins, was defined based on prescription claim records. Comorbidities were obtained from the National Health Insurance System claims database and defined according to the *International Classification of Diseases, Tenth Revision* (ICD-10) codes (Table S2).

Primary Exposure of Interest and Study Outcome

The primary exposure of interest was the dialysis adequacy indices. Baseline dialysis adequacy was measured based on the spKt/V. spKt/V was calculated using the following formula:

$$Kt/V = -\ln(R - 0.008*t) + (4 - 3.5*R)*UF/W$$

R is the ratio of postdialysis to predialysis blood urea nitrogen levels, t is the session length in hours, UF is the filtration volume in liters, and W is the weight after dialysis in kilograms.[23]

For primary analysis, patients were categorized into quartiles according to baseline spKt/V, and the lowest quartile was used as the reference group. spKt/V was used as a continuous variable in the analysis, with a per 0.1 increase. The URR, another measurement for dialysis adequacy, was also evaluated in a sensitivity analysis. The URR was calculated by the difference in predialysis and postdialysis levels of blood urea nitrogen, dividing by the prehemodialysis levels of blood urea nitrogen, and multiplied by 100 (%).[24]

The primary outcome was the incident AF, defined using *International Classification of Diseases, Tenth Revision* from the National Health Insurance System claims database (Table S2). To ensure accuracy, the development of AF was defined as a discharge diagnosis confirmed more than twice in the outpatient department. The positive predictive value of this definition was 94.1% in previous studies.[25–27] Patients were followed up from the index date until the date of AF incidence or the end of the study period (June 30, 2021). Patients were censored at the date of kidney transplantation.

Statistical Analysis

The baseline characteristics of the study population were described based on the quartile of spKt/V level. Continuous variables were expressed as medians with interquartile ranges and compared using a one way ANOVA or Kruskal-Wallis test. The Shapiro-Wilks test was used to confirm the normality of the distribution. Categorical variables were presented as numbers with percentages and examined using the χ^2 test or Fisher exact test. To examine the relationship between dialysis adequacy and incident AF, Fine-Gray subdistribution hazard models were used. All-cause mortality was considered a competing risk, and the cumulative incidence function curve was treated as a subdistribution function.[28,29] The proportional hazards assumptions were confirmed by Schoenfeld residuals.[30] Model 1 was minimally adjusted for age and sex. Model 2 incorporated the demographic data (medical aid, dialysis vintage, and BMI), predialysis SBP, ultrafiltration volume, and comorbidities (diabetes, congestive heart failure, myocardial infarction, cerebrovascular disease, and chronic obstructive pulmonary disease) with model 1. Model 3 further included the use of medications (antihypertensive agents and statins) and laboratory measurements (hemoglobin, serum albumin, and serum calcium). The results are presented as subdistribution

hazard ratios (sHRs) and 95% CIs. Adjusted cubic spline analyses were used to assess the association between spKt/V levels and the risk of incident AF. Statistical significance was defined as $P<0.05$, and all statistical analyses were performed with R (version 3.5.1; www.r-project.org; R Foundation for Statistical Computing, Vienna) and SAS Enterprise Guide, version 6.1 (SAS Institute).

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted by stratifying the patients based on sex (men or women) and age (<65 or ≥65 years). The *P* value for interaction was estimated to investigate the consistency of the main results among subgroups.

Sensitivity analyses were performed to verify the robustness of the results. First, we repeated the primary analysis in the validation cohort using data from the fifth and sixth Korean National Periodic Hemodialysis Quality Assessment. This cohort included participants only in the fifth and sixth assessments and were not included in the primary analysis. Second, patients were categorized into spKt/V different groups: 1.2, and ≥1.2; <1.4, and ≥1.4; <1.2, 1.2 to 1.4, 1.4 to 1.6, and ≥1.6. These categories were based on the Kidney Disease Outcomes Quality Initiative guidelines, which recommend a spKt/V of 1.4 per dialysis session for patients undergoing thrice-weekly treatment, with a minimum spKt/V of 1.2. Third, we analyzed the association between the URR measurement and the risk of incident AF. In addition, the association between spKt/V levels and incident AF was investigated among patient groups as follows: patients without a history of heart failure or myocardial infarction, patients whose dialysis vintage was longer than 12 months, patients whose dialysis vintage was shorter than 12 months, and patients not receiving assistance from the medical aid program. Finally, the inverse probability of treatment weighting weighted Cox proportional hazard model was used to balance the baseline characteristics (details are described in Supplemental Methods).

RESULTS

Baseline Characteristics

Table 1 presents the baseline characteristics of the participants according to spKt/V quartiles. The mean age was 60 years, and 14 772 (58.7%) patients were men. The median spKt/V among total participants was 1.5, and the median spKt/V levels of each quartile were 1.2, 1.4, 1.6, and 1.9, respectively. Overall, patients with higher spKt/V were more often to be older and female. In addition, patients in higher spKt/V group had longer dialysis vintages, more frequent use of arteriovenous grafts, lower BMI, and lower ultrafiltration volume. Furthermore, the number of patients using antihypertensive agents was smaller in the higher spKt/V quartile. Moreover, patients with the highest spKt/V quartile showed higher serum calcium levels and lower serum albumin levels than patients with the lowest spKt/V quartile (Table 1).

Association Between Dialysis Adequacy and Incident AF

During the 5.7 years of median follow-up, there were 3883 (15.4%) AF (event rate, 32.1 per 1000 person-years). The incidence rates were 34.4, 32.8, 31.6, and 29.7 per 1000 person-years from the lowest to the highest quartiles of spKt/V, respectively (Table 2). Compared with the lowest spKt/V quartile, the risk of incident AF was significantly lower in the higher quartile in the minimally adjusted model (Table 3, model 1). The results were consistent after adjustments for demographic factors, comorbidities, medication use, and laboratory measurements: the adjusted sHRs were 0.90 (95% CI, 0.82–0.98; $P=0.017$), 0.84 (95% CI, 0.77–0.93; $P<0.001$), and 0.79 (95% CI, 0.72–0.88; $P<0.001$) from the second to the highest quartiles of spKt/V measurement compared with the lowest quartile, respectively (Table 3, model 3). When treating spKt/V as a continuous variable, the adjusted sHR per a 0.1 increase in spKt/V was 0.97 (95% CI, 0.96–0.99; $P<0.001$). The sHRs for the entire covariates are shown in Table S3. Older age, higher BMI, larger ultrafiltration volume, longer dialysis vintage, and history of congestive heart failure and chronic obstructive lung disease were associated with a higher risk of incident AF. The restricted cubic spline curve also showed that lower spKt/V was related to a higher risk of AF (Figure 2). In the validation cohort, using data from the fifth and sixth Korean National Periodic Hemodialysis Quality Assessment, the association between the risk of incident AF and spKt/V was similar to the results of the primary analysis (Table S4).

Subgroup and Sensitivity Analyses

Effect modification was evaluated for sex and age (<65 versus ≥65 years). There were no interactions between the stratified age and spKt/V for the incident AF. However, there was a significant interaction between sex and spKt/V on the risk of incident AF (*P* for interaction=0.001). The association between the risk of incident AF and spKt/V was more pronounced in men than in women (Figure 3).

The findings were consistent with the main analysis across the following sensitivity analyses. Using different categories of the spKt/V measurement, patients with spKt/V ≥1.2 had a lower risk of incident AF (sHR, 0.85 [95% CI, 0.76–0.96]; $P=0.007$), compared with patients with spKt/V <1.2. Similarly, patients with spKt/V ≥1.4 had a lower risk of incident AF compared with patients with spKt/V <1.4 (sHR, 0.91 [95% CI, 0.85–0.98]; $P=0.011$). The sHR (95% CI) for the 1.4 to 1.6, and ≥1.6 compared with spKt/V <1.2 were 0.87 (0.77–0.98; $P=0.024$), and 0.77 (0.68–0.88; $P<0.001$; Table S5). Among patients with a URR measurement, the risk of incident AF in the highest URR quartile was 0.82-fold

Table 1. Baseline Characteristics of Participants According to Quartile of spKt/V Levels

Variables*	Total (N=25 173)	Quartile of spKt/V				*P* value
		Q1 (<1.33; N=6294)	Q2 (1.33–1.49; N=6293)	Q3 (1.50–1.69; N=6293)	Q4 (≥1.70; N=6293)	
Demographic data						
Age, y	60 (51–69)	57 (49–67)	59 (51–69)	61 (51–70)	61 (52–71)	<0.001
Men, n (%)	14 772 (58.7)	5360 (85.2)	4618 (73.4)	3337 (53.0)	1457 (23.2)	<0.001
BMI, kg/m²	22.9 (20.9–25.1)	24.0 (22.0–26.4)	23.2 (21.4–25.4)	22.6 (20.8–24.8)	21.5 (19.7–23.6)	<0.001
SBP, mm Hg	140.0 (130.0–50.0)	140.0 (130.0–150.0)	140.0 (130.0–150.0)	140.0 (130.0–150.0)	140.0 (130.0–150.0)	<0.001
Medical beneficiaries, n (%)	5572 (22.2)	1475 (23.5)	1354 (21.6)	1349 (21.5)	1394 (22.2)	0.025
Primary renal disease, n (%)						
Diabetes	11367 (45.2)	3142 (49.9)	3012 (47.9)	2834 (45.0)	2379 (37.8)	<0.001
Hypertensive	6472 (25.7)	1547 (24.6)	1612 (25.6)	1592 (25.3)	1721 (27.3)	
Glomerulonephritis	2756 (10.9)	595 (9.5)	636 (10.1)	706 (11.2)	819 (13.0)	
Other	2056 (8.2)	475 (7.5)	453 (7.2)	517 (8.2)	611 (9.7)	
Unknown	2522 (10.0)	535 (8.5)	580 (9.2)	644 (10.2)	763 (12.1)	
Dialysis characteristics						
spKt/V	1.5 (1.3–1.7)	1.2 (1.2–1.3)	1.4 (1.4–1.5)	1.6 (1.5–1.6)	1.9 (1.8–2.0)	<0.001
URR	71.4 (67.3–75.7)	64.8 (62.1–66.5)	69.5 (68.2–70.9)	73.5 (72.2–74.8)	78.6 (76.9–80.8)	<0.001
Ultrafiltration volume, L	2.2 (1.6–2.9)	2.3 (1.6–3.1)	2.3 (1.6–3.0)	2.3 (1.6–2.9)	2.1 (1.5–2.7)	<0.001
Dialysis vintage, mo	41.2 (18.1–84.9)	29.8 (13.7–65.2)	37.9 (17.2–79.3)	44.9 (19.9–91.3)	54.7 (22.9–104.1)	<0.001
Vascular access, n (%)						
AVF	21 131 (83.9)	5411 (86.0)	5366 (85.3)	5264 (83.6)	5090 (80.9)	<0.001
AVG	3655 (14.5)	771 (12.2)	835 (13.3)	929 (14.8)	1120 (17.8)	
Catheter	387 (1.5)	112 (1.8)	92 (1.5)	100 (1.6)	83 (1.3)	
Comorbidity, n (%)						
Diabetes	12 988 (51.6)	2916 (46.3)	3050 (48.5)	3283 (52.2)	3739 (59.4)	<0.001
Myocardial infarction	155 (0.6)	52 (0.8)	35 (0.6)	31 (0.5)	37 (0.6)	0.087
Congestive heart failure	837 (3.3)	233 (3.7)	209 (3.3)	203 (3.2)	192 (3.1)	0.217
Cerebrovascular disease	885 (3.5)	228 (3.6)	245 (3.9)	199 (3.2)	213 (3.4)	0.139
Chronic pulmonary disease	1349 (5.4)	352 (5.6)	344 (5.5)	331 (5.3)	322 (5.1)	0.644
Medication use, n (%)						
Statin	6712 (26.7)	1618 (25.7)	1681 (26.7)	1677 (26.6)	1736 (27.6)	0.118
Antihypertensive agents	15857 (63.0)	4099 (65.1)	4037 (64.2)	3945 (62.7)	3776 (60.0)	<0.001
Laboratory findings						
Hemoglobin, g/dL	10.6 (10.1–11.2)	10.6 (10.1–11.3)	10.7 (10.1–11.3)	10.7 (10.1–11.2)	10.6 (10.1–11.2)	0.026
Calcium, mg/dL	8.9 (8.5–9.5)	8.8 (8.4–9.4)	8.9 (8.4–9.4)	9.0 (8.5–9.5)	9.0 (8.6–9.5)	<0.001
Albumin, g/dL	4.0 (3.8–4.2)	4.0 (3.8–4.2)	4.0 (3.8–4.2)	4.0 (3.8–4.2)	3.9 (3.7–4.2)	<0.001

AVF indicates arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; SBP, systolic blood pressure; spKt/V, single-pool Kt/V; and URR, urea reduction ratio.

*The values for categorical variables are given as the number (percentage); values for continuous variables are given as the median (interquartile range).

lower (sHR, 0.82 [95% CI, 0.74–0.90]; *P*<0.001) than that in the lowest quartile. Considering URR as a continuous value, a 10% higher URR level reduced the risk of incident AF by 13% (*P*<0.001; Table S6). When patients with previous heart failure or myocardial infarct were excluded, the risk of incident AF in the highest spKt/V quartile was 0.80-fold lower than that in the lowest quartile (Table S7). A similar association was found for patients with a dialysis vintage longer than 12 months (Table S8). In contrast, there was no association between dialysis adequacy and AF development in patients who had been on dialysis for <12 months (Table S9). Among patients who did not receive the medical aid program, higher dialysis adequacy was also associated with a lower risk of AF (Table S10). To substantiate our findings, an inverse probability of treatment weighting based matching weight analysis was performed. The maximum pairwise standardized difference showed that all variables were well balanced (maximum absolute standardized difference <0.2; Figure S1). Compared with the lowest quartile, the inverse probability of treatment weighting weighted sHR (95% CI) for the second,

Table 2. Incidence Rates of Atrial Fibrillation According to Quartile of spKt/V

Outcomes	Total	Quartile of spKt/V			
		Q1 (<1.34)	Q2 (1.34–1.49)	Q3 (1.50–1.69)	Q4 (≥1.70)
No. of participants, n (%)	25173	6294	6293	6293	6293
Person-year	120924	30130	29806	30390	30598
Incident atrial fibrillation					
Incidence of outcome, n (%)	3883 (15.4)	1037 (16.5)	978 (15.5)	960 (15.3)	908 (14.4)
Incidence rate per 1000 person-years	32.1	34.4	32.8	31.6	29.7
All-cause mortality					
Incidence of outcome, n (%)	8665 (34.4)	2114 (33.6)	2187 (34.7)	2122 (33.7)	2031 (32.2)
Incidence rate per 1000 person-years	71.7	70.1	73.3	69.8	66.3

spKt/V indicates single-pool Kt/V.

third, and the highest quartile were 0.94 (0.90–0.99), 0.91 (0.87–0.95), and 0.85 (0.81–0.89), respectively (Table S11).

DISCUSSION

In this cohort study using data from a nationwide dialysis quality assessment, there was a significant association between dialysis adequacy and the risk of incident AF in patients receiving maintenance hemodialysis 3× a week. After adjustment for confounding variables, higher spKt/V was associated with a lower risk of incident AF, with overwhelming evidence. This association was consistent throughout the various sensitivity analyses.

In patients with advanced chronic kidney disease or ESKD, uremic toxins are known risk factors for cardiovascular disease, and the effective removal of uremic solutes is associated with reduced adverse outcomes.[31–33] The Kidney Disease Outcomes Quality Initiative guideline recommends an spKt/V of 1.4 per dialysis session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2.[34] In this study, the restricted cubic spline curve showed that the risk of AF decreased as the dialysis adequacy increased, even when spKt/V exceeded 1.2; however, the risk did not decrease further once a certain level of spKt/V was reached. This finding suggests that adequate uremic removal through hemodialysis and increased dialysis adequacy may lower the risk of AF more than with the minimum recommendations of present guidelines. Nonetheless, further prospective intervention trials are needed to confirm this finding.

In this study, the incidence of AF and related risk factors other than dialysis clearance were similar to that in previous investigations. The prevalence of AF in patients receiving maintenance dialysis has been reported to vary from 6% to 27%.[35–38] In this study, the incidence of AF was 15.4% during a median follow-up 4.8 years. Risk factors such as advanced age, obesity, chronic obstructive pulmonary disease, and heart failure were also identified, consistent with previous investigations.[10–14,39] In addition, this study showed several dialysis-specific factors associated with the risk of AF. Longer dialysis vintage and larger ultrafiltration volume were related to a higher risk of AF. This finding is also in accordance

Table 3. Associations of spKt/V With Incident Atrial Fibrillation

spKt/V	Model 1*		Model 2†		Model 3‡	
	sHR (95% CI)	*P* value	sHR (95% CI)	*P* value	sHR (95% CI)	*P* value
Quartile						
Q1 (<1.34)	1.00 (Reference)	…	1.00 (Reference)	…	1.00 (Reference)	…
Q2 (1.34–1.49)	0.91 (0.84–1.00)	0.044	0.90 (0.82–0.98)	0.016	0.90 (0.82–0.98)	0.017
Q3 (1.50–1.69)	0.88 (0.80–0.96)	0.006	0.84 (0.77–0.92)	<0.001	0.84 (0.77–0.93)	<0.001
Q4 (≥1.70)	0.83 (0.76–0.92)	<0.001	0.79 (0.71–0.88)	<0.001	0.79 (0.72–0.88)	<0.001
Continuous						
Per 0.1 increase	0.98 (0.97–0.99)	0.002	0.97 (0.96–0.99)	<0.001	0.97 (0.96–0.99)	<0.001

sHR indicates subdistribution hazard ratio; and spKt/V, single pooled Kt/V.

*Model 1: minimally adjusted for age and sex.

†Model 2: model 1+medical aid, dialysis vintage, body mass index, predialysis systolic blood pressure, ultrafiltration, and a history of diabetes, congestive heart failure, myocardial infarction, cerebrovascular disease, and chronic obstructive pulmonary disease.

‡Model 3: model 2+the use of medications (antihypertensive drugs and statins), and laboratory measurements (hemoglobin, serum albumin, and serum calcium).

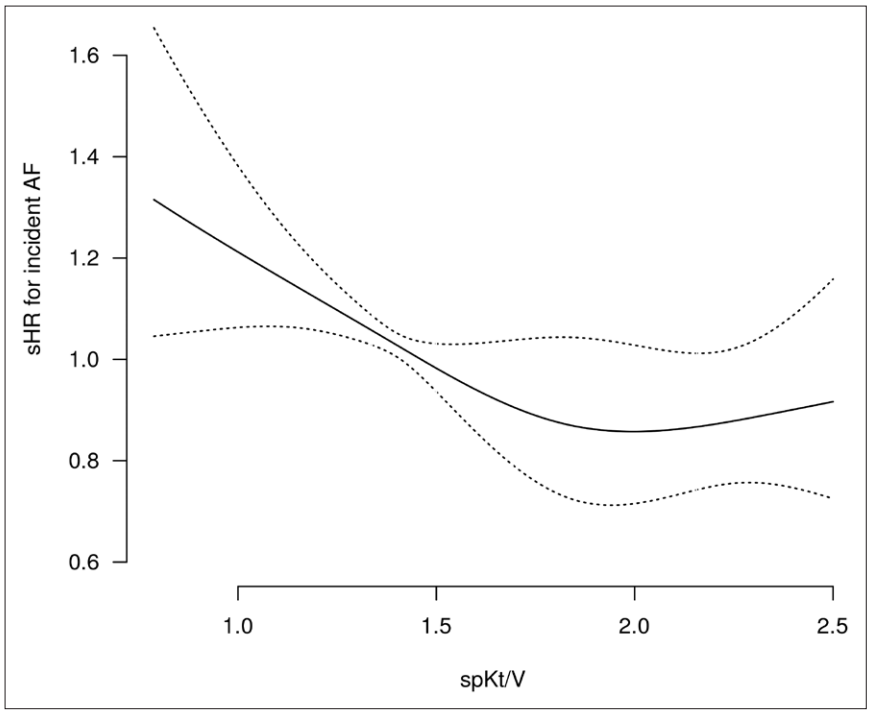

Figure 2. Restricted cubic spine plot for incident atrial fibrillation according to single pooled Kt/V (spKt/V).
AF indicates atrial fibrillation; and sHR, subdistribution hazard ratio.

with previous observational studies on older patients receiving hemodialysis.[13] However, in contrast to the previous investigation, showing a U-shaped association between predialysis SBP and incident AF,[12,40] there was no increased risk of incident AF in the lower predialysis SBP group in this study. Patients with lower predialysis

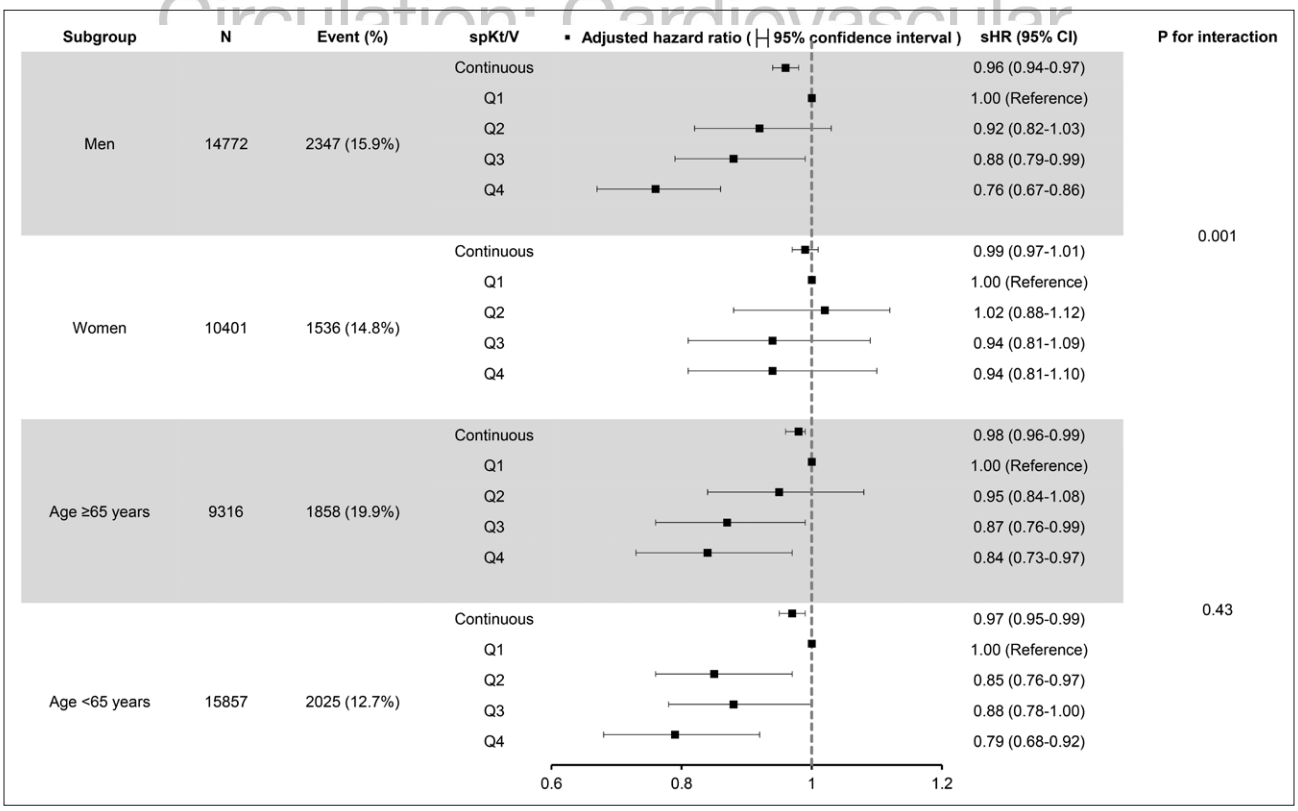

Figure 3. Subgroup analysis showing the effect of single pooled Kt/V (spKt/V) levels on the risk of incident atrial fibrillation.
Subdistribution hazard ratios (sHRs) were adjusted for age; sex; medical aid; dialysis vintage; dialysis vintage; body mass index; predialysis systolic blood pressure; ultrafiltration; a history of diabetes, congestive heart failure, myocardial infarction, cerebrovascular disease, and chronic obstructive pulmonary disease; the use of medications (antihypertensive agents, and statins); and laboratory measurements (hemoglobin, serum albumin, and serum calcium).

SBP can be interpreted as being either well-controlled or seriously ill. It should be noted that Periodic Hemodialysis Quality Assessment data excluded patients who were admitted to the hospital during the assessment period. Considering the participants had fewer comorbidities and were younger compared with those in previous studies, the possibility that there were fewer seriously ill patients in this study cannot be excluded.[12,40]

This study found a significant interaction between sex and dialysis adequacy for incident AF. The observed difference may be attributed to the fact that underdialysis occurs more frequently in women.[41] Several studies have suggested that malnourished patients exhibit higher spKt/V, and female patients undergoing hemodialysis tend to have a more malnourished status,[42] which can outweigh the benefits of relatively high Kt/V.[43] Furthermore, there are potential sex-specific differences in the underlying factors contributing to the development of AF. A previous study showed that women had a lower age-adjusted incidence and prevalence of AF than did men.[44] Sex differences in the mechanism of AF, including electrophysiology, sex hormones, cardiac structural remodeling, and function, have been reported.[45] In addition, the level of uremic toxins tends to be higher in men,[46] and study showed that kidney function decline and variability were only significantly associated with AF in men.[47] Therefore, such potential sex-specific differences in the pathophysiology of AF may have contributed to the difference in the effects of uremic burden on the development of AF.

Several animal studies have demonstrated that uremic toxins induce AF. These studies showed that indoxyl sulphate and protein-bound uremic toxin upregulated the expression of oxidative stress markers and activated inflammatory and profibrotic reactions, consequently promoting AF inducibility via structural remodeling.[16,18] In addition, it was also reported in an experiment using rabbit's heart that indoxyl sulphate induces delayed after-depolarizations and burst firings in pulmonary veins and atria.[19] Furthermore, indoxyl sulphate has been suggested as a strong and independent predictor of AF recurrence in patients undergoing catheter ablation.[48] In this study, a longer dialysis vintage was associated with a higher AF development risk. In addition, AF risk was not related to dialysis adequacy among patients with dialysis vintage shorter than 12 months. This may be because of interference with residual kidney function, which is an observation that possibly strengthens the notion that increased uremic toxin burden affects the development of AF in patients with ESKD.

This study has several limitations. First, due to the observational nature of the study, this study did not incorporate a direct intervention on hemodialysis adequacy and the cause-effect relationship between dialysis adequacy and AF could not be examined. Despite sensitivity analyses using a validation cohort showed consistent results, further prospective interventional studies would be needed to confirm the association found in this study. Second, potential confounding variables such as lifestyle factors, including diet, smoking, alcohol intake, exercise, and emotional stress, could not be considered. The data set also did not include detailed information, such as cardiac function measured by echocardiography or other cardiac markers, and did not specify whether AF occurred during hemodialysis. To mitigate potential biases resulting from this limitation, our study adjusted for potential confounding variables, including valvular heart disease and heart failure. In addition, a sensitivity analysis was conducted, which excluded participants with preexisting cardiovascular disease, and yielded consistent results. Third, the diagnoses of AF and other comorbidities relied on claims records. Although, the positive predictive value of AF definition was 94.1%.in previous studies,[25–27] there is a possibility of misclassification and underestimation of AF development and other comorbidites. Finally, other factors that may affect dialysis adequacy, including nutritional status, dialysis duration, type of dialyzer, electrolyte homeostasis, and residual kidney function, were not available for evaluation. Further investigation considering factors affecting dialysis adequacy would be warranted.

CONCLUSIONS

This study found a relationship between dialysis adequacy and the incidence of AF in patients receiving maintenance hemodialysis. Increasing dialysis clearance may lower the risk of AF occurrence in this patient population, particulary in men. Further well-designed randomized-controlled trials are needed to clarify these findings.

ARTICLE INFORMATION

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Affiliations

Department of Internal Medicine, Institute of Kidney Disease Research, Yonsei University College of Medicine, Seoul, Republic of Korea (G.Y.H., J.T.P., S.H.H., T.-H.Y., S.-W.K., H.W.K.). Division of Nephrology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul, Republic of Korea (H.J.K.). Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea (K.W.K.). Healthcare Review and Assessment Committee, Health Insurance Review and Assessment Service, Wonju, South Korea (Y.U.K.). Quality Assessment Department, Health Insurance Review and Assessment Service, Wonju, South Korea (S.H.K.). Quality Assessment Management Division, Health Insurance Review and Assessment Service, Wonju, South Korea (G.O.K.). Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Republic of Korea (H.W.K.).

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Supplemental Material

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