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ORIGINAL RESEARCH

Dialysis Mode and Associated Outcomes in Patients With End-Stage Renal Disease and Atrial Fibrillation: A 14-Year Nationwide Cohort Study

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BACKGROUND: Benefits of patients with end-stage renal disease and atrial fibrillation undergoing peritoneal dialysis (PD) or hemodialysis are unknown.

METHODS AND RESULTS: Patients undergoing dialysis were retrieved from Taiwan National Health Insurance Research Database during 2001 to 2013 and separated into PD or hemodialysis. Primary outcomes were ischemic stroke/systemic embolism, major bleeding, and intracranial hemorrhage (ICH). An inverse probability of treatment weighting based on propensity score was used to reduce the confounding. The risk of outcomes between PD and hemodialysis was compared using Cox proportional hazard model for fatal outcomes or Fine and Gray subdistribution hazard model which considered death a competing risk, respectively. A total of 7916 patients with end-stage renal disease with atrial fibrillation undergoing PD or hemodialysis during 2001 to 2013 were identified. After exclusion criteria, 363 patients receiving PD and 5302 patients receiving hemodialysis were analyzed. At 1-year follow-up, the risk of ICH was significantly lower in the PD group compared with the hemodialysis group (0.2% versus 0.9%; subdistribution hazard ratio [SHR], 0.31; 95% CI, 0.17–0.57). At 3-year follow-up, the risks of major bleeding and ICH were significantly lower in the PD group compared with the hemodialysis group (major bleeding: 1.8% versus 3.2%; SHR, 0.68; 95% CI, 0.53–0.87; ICH: 0.5% versus 2%; SHR, 0.32; 95% CI, 0.21–0.48). At 5-year follow-up, ischemic stroke/systemic embolism, major bleeding, and ICH were significantly lower in the PD group compared with the hemodialysis group (ischemic stroke/systemic embolism: 12.4% versus 17.7%, SHR, 0.87; 95% CI, 0.79–0.96; major bleeding: 2.6% versus 4.1%; SHR, 0.79; 95% CI, 0.64–0.97; ICH: 0.5% versus 2.6%; SHR, 0.25; 95% CI, 0.17–0.37).

CONCLUSIONS: In patients with end-stage renal disease and atrial fibrillation, dialytic modalities by PD or hemodialysis impacted these patients differently. There were overall reduced ischemic stroke/systemic embolism, major bleeding, and ICH at 5-year follow-up in patients undergoing PD compared with hemodialysis.

Key Words: atrial fibrillation ■ end-stage renal disease ■ hemodialysis ■ peritoneal dialysis ■ outcome

Atrial fibrillation (AF) is the most frequently encountered arrhythmia resulting in significant risk for stroke and systemic embolism. AF has an increasing prevalence secondary to growing age. In clinical practice, the association of AF in patients with chronic kidney disease (CKD) is noticeably high.[1] The incidence of AF increases with deterioration in the kidney function, and the prevalence of AF was found in

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CLINICAL PERSPECTIVE

What Is New?

- In patients receiving dialysis with atrial fibrillation, peritoneal dialysis or hemodialysis could impact these patients differently.
- Compared with hemodialysis, peritoneal dialysis was associated with overall reduced rates of ischemic stroke/systemic embolism, major bleeding, and intracranial hemorrhage at 5-year follow-up.

What Are the Clinical Implications?

- In patients receiving dialysis with atrial fibrillation, event rates of ischemic stroke/systemic embolism, major bleeding, and intracranial hemorrhage are related to dialysis modalities.
- Peritoneal dialysis should be considered for patients with end-stage renal disease and atrial fibrillation.

Nonstandard Abbreviations and Acronyms

NHI	National Health Institute
NHIRD	National Health Institute Research Database
NOAC	non-vitamin K antagonist oral anticoagulant

up to 32% elder patients undergoing hemodialysis.[2] Patients with CKD are associated with considerable mortality, with up to 3.7-fold in cardiovascular death and up to 5-fold in all-cause death compared with those without CKD.[3] It is conceivably that patients with end-stage renal disease (ESRD) are associated with accelerated cardiovascular morbidity and high mortality.[4] Together the combination of AF in patients with ESRD adversely affects the clinical outcome.[5] An increased prevalence and incidence of AF was noted in patients who commence dialysis, with incidence of AF in hemodialysis higher than peritoneal dialysis (PD).[6,7]

The pathophysiology of AF in ESRD is multitude. It is well recognized that ESRD is associated with volume overloading and offloading. The subsequent neurohormonal alterations via sympathetic system and the renin—angiotensin—aldosterone system can cause ventricular hypertrophy and dilation as well as increased atrial pressure and size.[8,9] The structural and electrical remodeling of the atria begets electrical instability and AF.[10] Previous studies have shown that several factors are independently associated with the development of AF in ESRD, including increasing age, coronary artery disease, left and right atrial dilatation, duration of dialysis therapy, Karnofsky index performance status, pre-dialysis systolic blood pressure, and type of dialysis.[11] However, once AF developed during the course of dialysis, little is known whether the dialysis should be maintained on PD or hemodialysis to decrease incidence of AF or AF-associated events. Therefore in this study, we aimed to investigate the dialysis mode and associated outcomes in patients with ESRD and AF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

The National Health Institute (NHI) Program of Taiwan was initiated in March 1995 and offers >99.8% coverage for the 23 million residents in Taiwan. The NHI Research Database (NHIRD) provides all dates of inpatient and outpatient services, diagnosis, prescriptions, examinations, operations, and expenditures, and data are updated biannually. With >95% of Taiwan's population consists of Han Chinese, our study is considered of uniform ethnic background. The NHI system offers detailed follow-up information on medication, intervention, admission, outpatient clinic, and emergency visit of patients. In addition, accurate records of health reimbursement is ensured by prescription of medications and arrangement of interventions that are followed by appropriate examinations and indications, otherwise false reimbursement claims results in magnified penalty. Further information about NHI and NHIRD have been described in previous publications.[12–14] Since the hospital identification number of each patient was encrypted and de-identified to protect their privacy within NHIRD, informed consent was waived for this study. The study was approved by Chang Gung Memorial Hospital Institutional Review Board (No. 201801354B0).

Study Patients

The study population was those who received permanent dialysis with AF from January 1, 2001 to December 31, 2013. The permanent dialysis was determined by both the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code of 585 with a registration in the Registry for Catastrophic Illness Patient Database, a subsection of the NHIRD. The date of applying for the catastrophic illness certificate was defined as the index date. The existence of AF occurrence was verified using at least 2 outpatient

diagnoses or any one inpatient diagnosis. The accuracy of the diagnosis of AF based on *ICD-9-CM* coding in the NHIRD has been confirmed in previous studies.[15,16] We excluded patients with age <20 years, previous kidney transplant, or patients who had malignancy. To obtain patients with stable dialysis, we excluded patients who died within first 90-day follow-up, had <90 days of follow up, discontinued dialysis, had kidney transplant, or switched dialysis modality. At last, we separated the remaining patients into patients who underwent PD and patients who underwent hemodialysis (Figure 1).

Covariates

Covariates were age at the index date, sex, 12 comorbid conditions (diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, chronic obstructive pulmonary disease, anemia, alcoholism, drug abuse, venous thromboembolism, valvular heart disease or surgery, rheumatic heart disease and hyperthyroidism), Charlson Comorbidity Index score, history of events (heart failure, ischemic stroke, systemic embolism, hemorrhage stroke, history of myocardial infarction, gastrointestinal bleeding, and major bleeding), CHA_2DS_2-VASc score, hypertension, abnormal liver or renal function, stroke, bleeding, labile INR, elderly (age >65), drugs or alcohol (HAS-BELD) score, and 8 kinds of medication within 3 months prior and after the index date. All disease was detected using *ICD-9-CM* diagnostic codes. The comorbidity was defined as having at least 2 outpatient diagnoses or any one inpatient diagnosis in the previous year. The history of event was detected using any one inpatient diagnosis before the index date which can be tracked up to year 1997. Many of the diagnoses of these diseases in the NHIRD have been validated in previous studies.[11,17–20] The *ICD-9-CM* diagnostic codes of the diseases were listed in the Table S1. All the information about medications were extracted from the claims data of outpatient visits or the refill for chronic illness in the pharmacy by using the Anatomical Therapeutic Chemical codes or the Taiwan NHI reimbursement code.

Ascertainment of Outcomes

Outcomes were detected and analyzed using *ICD-9-CM* diagnostic code. Outcomes in this study were ischemic stroke (IS)/systemic embolism (SE), major bleeding, and intracranial hemorrhagic (ICH). The IS and ICH were defined according to the principal diagnosis on admission based on *ICD-9-CM* codes which have also been validated.[12,19–23] The SE was defined as the vascular thromboembolic occlusion of an extremity or extracranial vital organ by using principal or secondary diagnoses on admission. The major bleeding was defined according to principle or secondary discharge diagnosis of hospitalization, including required blood transfusion >2 units, life-threatening bleeding or vital organ hemorrhage

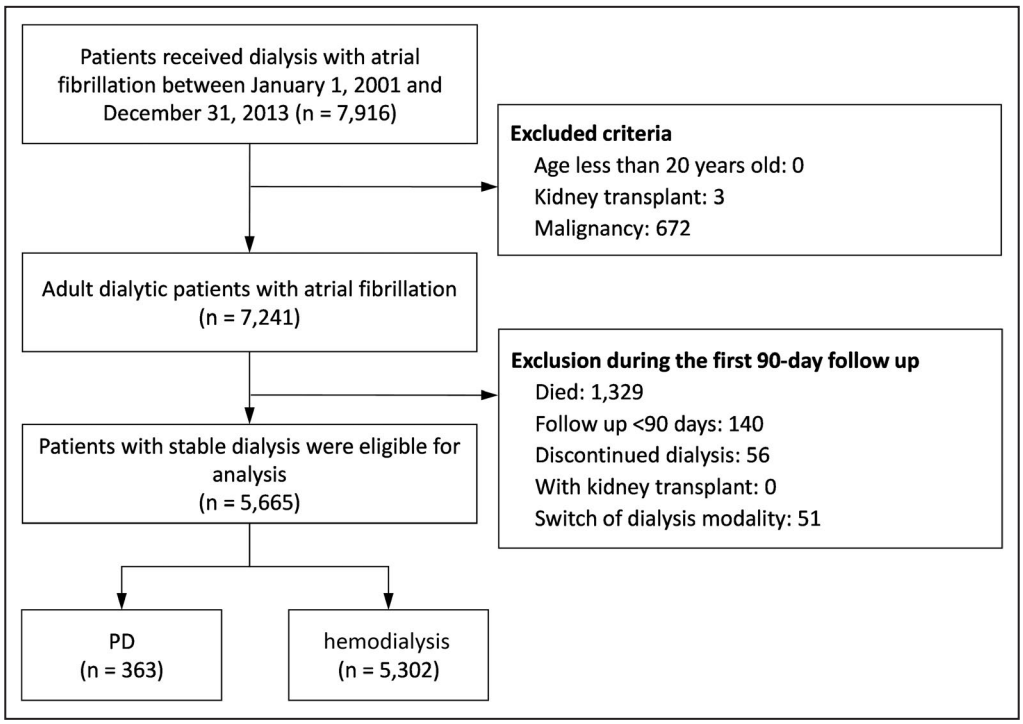

Figure 1. Study design and flowchart for the inclusion of the patients.
HD indicates hemodialysis; and PD, peritoneal dialysis.

which included ICH and gastrointestinal bleeding.[24] The outcomes were assessed in the follow-up periods of 1 year, 3 years, and 5 years, respectively. Each patient was followed until the day that developed the outcome, a modality switch 90 days after the index date, a withdrawal from the NHI program or December 31, 2013, whichever came first.

Statistical Analysis

To reduce the potential confounding when comparing outcomes between the study groups (PD versus hemodialysis), we used the inverse probability of treatment weighting (IPTW) method based on the propensity scores. The propensity score was estimated using a multivariable logistic regression model in which the study group (1=PD, 0=hemodialysis) was regressed on the selected covariates (all covariates in the aforementioned "Covariates" subsection and listed in Table 1) where the follow-up duration was replaced with the index date. We used a stabilized weight to mitigate the impact of extreme value of estimated propensity score. The balance of covariates between the groups before and after IPTW was checked using the absolute value of standardized difference between the groups, where a value <0.1 was considered a negligible difference and a value ranged 0.1 to 0.2 was considered a small difference.

The risk of time-to-event outcomes between groups was compared using a subdistribution hazard model which considered death during the follow-up a competing risk in the IPTW-adjusted cohort. We generated the plot of cumulative incidence rate using subdistribution cumulative incidence function for time-to-event outcomes. The study group (PD versus hemodialysis) was the only explanatory variable in the subdistribution hazard models. We further conducted a subgroup analysis of comparing PD with hemodialysis on risk of IS/SE in the IPTW-adjusted cohort. The predefined subgroup variables were age (dichotomized by 65), sex, diabetes mellitus, hypertension, dyslipidemia, previous stroke, vascular disease history, CHA_2DS_2-VASc score (dichotomized by 3), and the use of anticoagulation. A sensitivity analysis by using propensity-score matching was further conducted to evaluate the robustness of the results from IPTW. Each patient in the PD group was matched with 4 patients in the hemodialysis group. The paired nature of matching was accounted for by using robust standard error which was incepted from generalized estimating equation. A *P* value <0.05 was considered to be statistically significant. No adjustment of multiple testing (multiplicity) was made because the nature of this study was more exploratory rather than confirmatory. In addition, the assumption of proportional hazard in the analysis using IPTW cohort was evaluated using the Schoenfeld residual method. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), including the procedures of *"phreg"* for conducting survival analyses and the macro of "*%CIF*" for generating IPTW-adjusted cumulative incidence function under the Fine and Gray subdistribution hazard method.

RESULTS

Study Population

A total of 7916 patients with ESRD on permanent dialysis with coexisting AF between January 1, 2001 and December 31, 2013 were identified in the NHIRD. After exclusion criteria, a total of 5665 AF patients with ESRD undergoing dialysis were eligible for analysis. Among these patients, 363 patients received PD and 5302 patients received hemodialysis (Figure 1).

Before IPTW, patients in the PD group were younger, had lower prevalence of diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, heart failure, ischemic stroke, gastrointestinal bleeding, lower Charlson comorbidity index score, and lower CHA2DS-VASC and HAS-BLED scores. In contrast, the PD patients had a higher prevalence of dyslipidemia and were more likely to use angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, beta-blockers, dihydropyridine calcium channel blockers, and statins. After IPTW, the covariates were not substantially different between groups with all the absolute standardized difference values <0.1 (Table 1).

Comparing Dialysis Mode in Associated Outcomes

At 1-year follow-up, there were no significant difference in the outcomes of IS/SE and major bleeding. However, the risk of ICH was significantly lower in the PD group compared with the hemodialysis group (0.2% versus 0.9%, subdistribution hazard ratio [SHR], 0.31; 95% CI, 0.17–0.57). At 3-year follow-up, there was still no significant difference in the outcome of IS/SE. However, the risks of major bleeding and ICH were significantly lower in the PD group compared with the hemodialysis group (major bleeding: 1.8% versus 3.2%; SHR, 0.68; 95% CI, 0.53–0.87; and ICH: 0.5% versus 2%; SHR, 0.32; 95% CI, 0.21–0.48). At 5-year follow-up, the risks of all major outcomes were significantly lower in the PD group compared with the hemodialysis group (IS/SE: 12.4% versus 17.7%; SHR, 0.87; 95% CI, 0.79–0.96; major bleeding: 2.6% versus 4.1%; SHR, 0.79; 95% CI, 0.64–0.97; and ICH: 0.5% versus 2.6%; SHR, 0.25; 95% CI, 0.17–0.37) (Table 2, Figure 2A through 2C). In

Table 1. Baseline Characteristics of Patients With Atrial Fibrillation Undergoing Dialysis Who Initially Received Hemodialysis and PD

Variable	Before IPTW*			After IPTW		
	PD (n = 363)	Hemodialysis (n = 5302)	STD	PD	Hemodialysis	STD
Age, y	69.1±11.4	72.4±10.5	−0.31	72.4±10.4	72.2±10.6	0.02
Age group						
20–64 y	129 (35.5)	1194 (22.5)	0.29	23.5	23.3	<0.01
65–74 y	108 (29.8)	1698 (32.0)	−0.05	29.8	31.9	−0.05
≥75 y	126 (34.7)	2410 (45.5)	−0.22	46.7	44.8	0.04
Men	174 (47.9)	2545 (48.0)	<0.01	48.0	48.0	<0.01
Comorbid conditions						
Diabetes mellitus	184 (50.7)	3036 (57.3)	−0.13	57.4	56.9	0.01
Hypertension	306 (84.3)	4570 (86.2)	−0.05	86.8	86.1	0.02
Dyslipidemia	96 (26.4)	1136 (21.4)	0.12	22.8	21.8	0.03
Ischemic heart disease	153 (42.1)	2604 (49.1)	−0.14	48.7	48.7	<0.01
Chronic obstructive pulmonary disease	34 (9.4)	770 (14.5)	−0.16	11.2	14.2	−0.09
Anemia	54 (14.9)	647 (12.2)	0.08	12.5	12.4	<0.01
Alcoholism	3 (0.8)	36 (0.7)	0.02	0.5	0.7	−0.03
Drug abuse	1 (0.3)	3 (0.1)	0.05	0.1	0.1	0.01
Venous thromboembolism	13 (3.6)	184 (3.5)	0.01	2.1	3.5	−0.08
Valvular heart disease or surgery	15 (4.1)	154 (2.9)	0.07	3.3	3.0	0.02
Rheumatic heart disease	31 (8.5)	356 (6.7)	0.07	7.7	6.8	0.03
Hyperthyroidism	17 (4.7)	238 (4.5)	0.01	4.5	4.5	<0.01
Charlson Comorbidity Index score	4.4±1.8	5.1±2.0	−0.36	5.0±1.8	5.0±2.0	−0.03
History of event						
Heart failure	154 (42.4)	3005 (56.7)	−0.29	53.6	55.7	−0.04
Ischemic stroke	64 (17.6)	1514 (28.6)	−0.26	27.9	27.9	<0.01
Systemic embolism	20 (5.5)	347 (6.5)	−0.04	4.9	6.5	−0.07
Hemorrhage stroke	9 (2.5)	185 (3.5)	−0.06	3.5	3.4	0.01
History of myocardial infarction	44 (12.1)	701 (13.2)	−0.03	10.4	13.1	−0.08
Gastrointestinal bleeding	124 (34.2)	2384 (45.0)	−0.22	43.9	44.3	−0.01
Major bleeding	35 (9.6)	607 (11.4)	−0.06	12.4	11.3	0.03
CHA_2DS_2-VASc score	4.2±1.8	5.0±1.9	−0.40	4.9±1.9	4.9±1.9	−0.01
HAS-BLED score	3.4±1.0	3.7±1.0	−0.30	3.7±0.9	3.7±1.0	0.01
Medication						
Antiplatelet	151 (41.6)	2160 (40.7)	0.02	44.3	40.8	0.07
Anticoagulant	33 (9.1)	463 (8.7)	0.01	8.3	8.8	−0.02
ACEi/ARB	185 (51.0)	2070 (39.0)	0.24	42.5	39.8	0.06
Beta blockers	200 (55.1)	2251 (42.5)	0.25	45.5	43.3	0.04
NDCCB	53 (14.6)	789 (14.9)	−0.01	14.8	14.9	<0.01
DCCB	229 (63.1)	2891 (54.5)	0.17	59.1	55.1	0.08
OHA	83 (22.9)	1460 (27.5)	−0.11	31.6	27.3	0.095
Statin	114 (31.4)	857 (16.2)	0.36	15.9	17.1	−0.03
Follow-up year	3.0±2.6	2.8±2.7	0.04	2.4±2.2	2.9±2.7	−0.21

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCCB, dihydropyridine calcium channel blockers; HAS-BLED, hypertension, abnormal liver or renal function, stroke, bleeding, labile INR, elderly (age >65), drugs or alcohol; IPTW, inverse probability of treatment weighting; NDCCB, non-dihydropyridine calcium channel blockers; OHA, oral hypoglycemic agent; PD, peritoneal dialysis; and STD, standardized difference.

*Data are presented as frequency (percentage) or mean±SD.

†Data were presented as percentage or mean±SD.

Table 2. Follow-up Outcome in Patients With Atrial Fibrillation Who Received Hemodialysis and PD

Follow-up/Outcome‡	Data before IPTW*		Data after IPTW†			
	PD (n = 363)	Hemodialysis (n = 5302)	PD	Hemodialysis	SHR of PD (95% CI)	*P*
1-y follow-up						
Ischemic stroke/systemic embolism	18 (5.0)	374 (7.1)	5.3	7.0	0.92 (0.79–1.07)	0.287
Major bleeding	4 (1.1)	80 (1.5)	1.1	1.5	0.88 (0.63–1.22)	0.437
Intracranial hemorrhage	2 (0.6)	50 (0.9)	0.2	0.9	0.31 (0.17–0.57)	<0.001
3-y follow-up						
Ischemic stroke/systemic embolism	31 (8.5)	777 (14.7)	10.7	14.7	0.92 (0.83–1.02)	0.098
Major bleeding	9 (2.5)	170 (3.2)	1.8	3.2	0.68 (0.53–0.87)	0.002
Intracranial hemorrhage	4 (1.1)	105 (2.0)	0.5	2.0	0.32 (0.21–0.48)	<0.001
5-y follow-up						
Ischemic stroke/systemic embolism	41 (11.3)	937 (17.7)	12.4	17.7	0.87 (0.79–0.96)	0.005
Major bleeding	10 (2.8)	215 (4.1)	2.6	4.1	0.79 (0.64–0.97)	0.026
Intracranial hemorrhage	4 (1.1)	135 (2.5)	0.5	2.6	0.25 (0.17–0.37)	<0.001

IPTW indicates inverse probability of treatment weighting; PD, peritoneal dialysis; and SHR, subdistribution hazard ratio.
*Data were presented as frequency (percentage).
†Data were presented as percentage.
‡Patients who switched between peritoneal dialysis and hemodialysis were censored.

addition, the assumption of proportional hazard was not violated with the insignificance of IS/SE (*P*=0.905), major bleeding (*P*=0.492) and ICH (*P*=0.212), respectively (data not shown).

The sensitivity analysis by using propensity- score matching showed that the risks of IS/SE, major bleeding, and ICH were lower in the PD patients than that in the hemodialysis patients, though not statistically significant because of smaller sample size after matching (Table S2).

Subgroup Analysis of Primary Outcomes

Figure 3 presents the subgroup analysis of comparing PD with hemodialysis on the risk of IS/SE in the IPTW-adjusted cohort. The observed beneficial effect of PD over hemodialysis on IS/SE was more apparent in patients who were younger, with dyslipidemia, previous stroke, and vascular disease (*P* for interaction <0.05). We have provided Table S3 to demonstrate an additional subgroup analysis 5-year follow-up of 3 main outcomes by baseline medication usage, including beta-blockers and non-dihydropyridine calcium channel blockers. The use of beta-blocker and non-dihydropyridine calcium channel blockers did not affect the outcome of ischemic stroke/systemic embolism in PD group compared with hemodialysis group. However, the use of beta-blocker seemed to have beneficial effects in major bleeding in PD group compared with hemodialysis group. And whether or not patients were taking beta-blockers, there seemed to be a decreased number of events of intracranial hemorrhage in PD group compared with hemodialysis group, although the effects were more significantly pronounced in patients not taking beta-blocker.

In addition, we also provided Table S4 to demonstrate an additional subgroup analysis on the 3 main outcomes by baseline medication usage, including antiplatelet, anticoagulant. The use of antiplatelet and anticoagulant did not affect the outcome of ischemic stroke/systemic embolism. However, the use of antiplatelet seemed to have significantly decreased major bleeding event rate in PD group compared with hemodialysis group. In addition, the non-use of anticoagulant seemed to have significant decreased intracranial hemorrhage event rate in PD group compared with hemodialysis group.

DISCUSSION

In patients with ESRD on dialysis with coexisting AF, our study has the following findings. Compared with patients undergoing hemodialysis, (1) a significant decreased rate of ICH was found throughout 5-year follow-up, (2) a significant decreased rate of major bleeding was found in the 3-year and 5-year follow-up, and (3) a significantly decreased rate of IS/SE was found at 5-year follow-up in patients undergoing PD.

Previous Studies

AF is frequently observed in patients undergoing dialysis and the associated IS/SE increases both morbidity and mortality.[25] Previous study has shown that the dialysis per se was found to be a trigger of AF, in

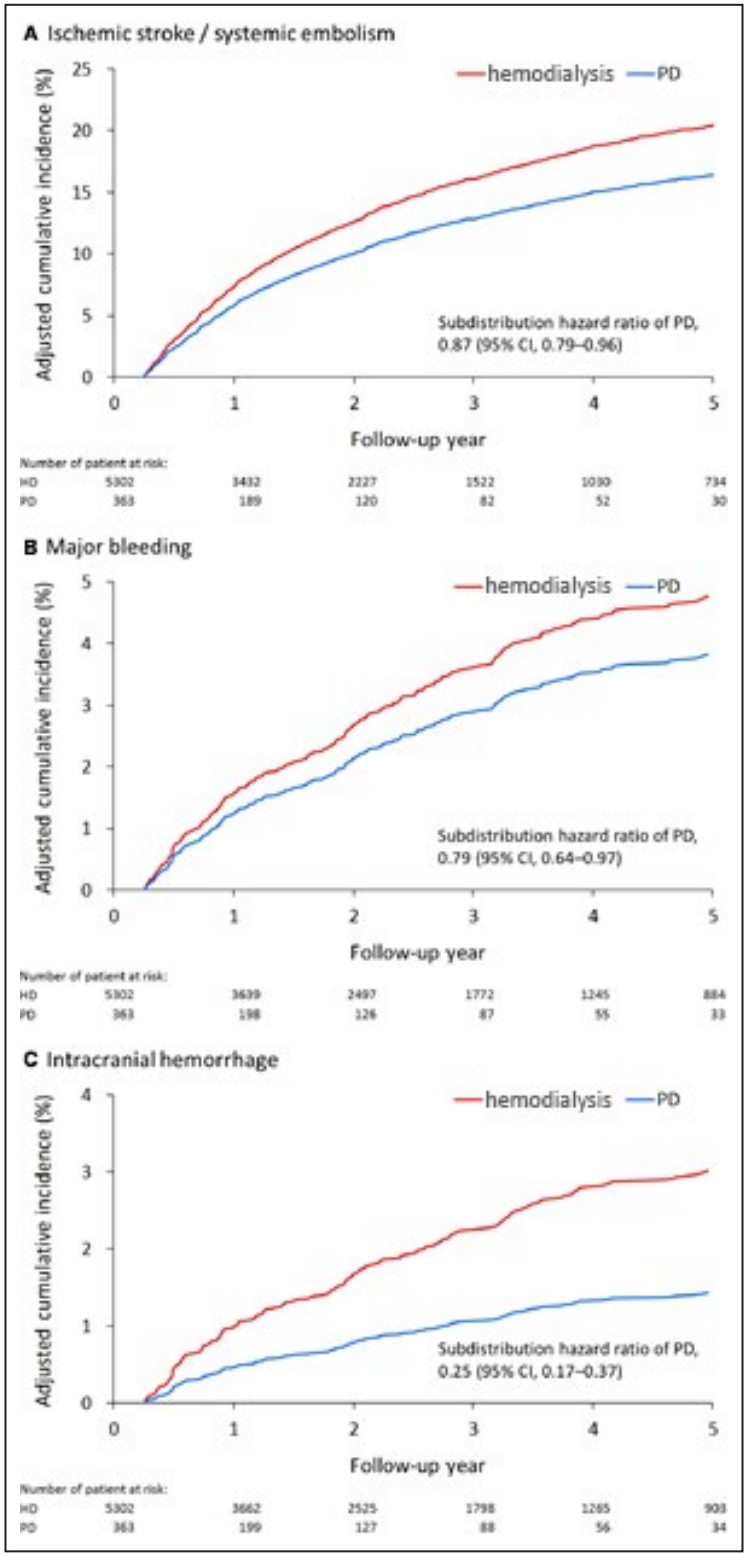

Figure 2. Cumulative incidence function of ischemic stroke/systemic embolism (A), major bleeding (B), and intracranial hemorrhage (C) in patients with end-stage renal disease and atrial fibrillation undergoing peritoneal dialysis or hemodialysis in the inverse probability of treatment weighting cohort.

The number of patients at risk was the original data before weighting. HD indicates hemodialysis; PD, peritoneal dialysis.

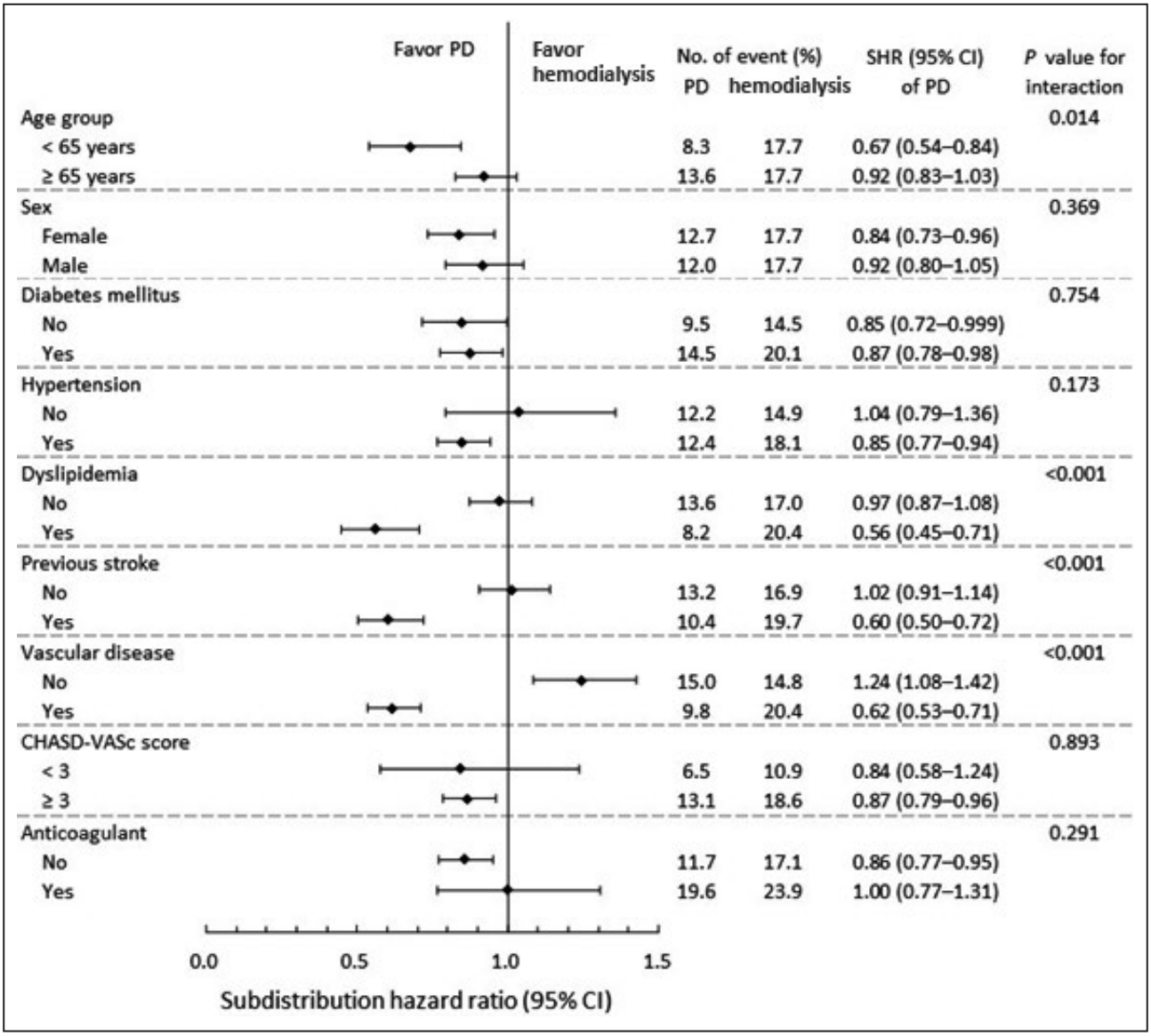

Figure 3. Subgroup analysis comparing peritoneal dialysis with hemodialysis on the risk of ischemic stroke/systemic embolism at 5-year follow-up in the inverse probability of treatment weighting cohort.
HD indicates hemodialysis; PD, peritoneal dialysis; and SHR, subdistribution hazard ratio.

both dialysis days (P<0.001) and specifically during the dialysis procedure itself (P=0.04).[26] In addition, dialysis modality was investigated with regard to the first occurrence of AF. The authors reported that PD had initially lower incidence compared with hemodialysis, however there was no difference in AF incidence after 90 days.[27] Notwithstanding, once AF occurred in patients undergoing dialysis, there had been no study conducted to examine the differences and outcomes between PD and hemodialysis. In addition, whether to prescribe anticoagulation therapy in these patients has been a subject of debate because of inherent coagulopathy in ESRD patients. Warfarin was previously used to prevent IS/SE in ESRD patients with AF. However, the difficulty in maintaining prothrombin time level constantly within therapeutic range poses clinical dilemma. Although a certain study noted non-vitamin K antagonist oral anticoagulant (NOAC) can have benefit over warfarin in these CKD patients,[28] our group also showed the use of NOACs or warfarin is not more effective than using no anticoagulants at all in reducing the risk of ischemic stroke or systemic embolism in stages 4–5 CKD.[29] In this scenario, the dialysis mode that results in the least number of AF-associated IS/SE and/or bleeding events should be used.

Current Study

In this study, we used national administrative claim-based insurance database to assess the risk of primary

outcomes, defined by IS/SE, major bleeding, and ICH by dialysis modality in patients with and AF. Patients undergoing PD were 3.3 years younger compared with patients undergoing hemodialysis (mean age, 69.1 versus 72.4 years). Several comorbid conditions, Charlson comorbidity index score, history of event, CHA2DS2-VASc, and HAS-BLED scores, and medications were different between groups. However, after IPTW-adjustment, the PD and hemodialysis cohort were not significantly different.

Since patients undergoing hemodialysis require administration of heparin at the time of dialysis, ICH occurred with significantly higher rate in the hemodialysis group compared with PD group at 1-year, 3-year, and 5-year follow-up. Even with much frequent heparinization in patients undergoing hemodialysis, patients undergoing PD were observed with significantly decreased rate of IS/SE. Our results showed that PD as the dialysis modality benefited patients with ESRD favorably compared with hemodialysis. As mentioned earlier, the pathophysiology of AF in ESRD is multifaceted. The large volume loading and offloading in patients undergoing hemodialysis activate neurohormonal responses through both sympathetic system and the renin–angiotensin–aldosterone system than PD. The changes in volume can induce ventricular and atrial wall stretch as well as electrical remodeling in the atria, resulting in increased incidence and duration of AF. In turn, AF-associated outcomes such as IS/SE can be reasonably expected in hemodialysis, despite exposure to heparin in this modality, compared with PD.

Despite guideline recommendation of warfarin as anticoagulation in patients with ESRD and AF, there are difficulties implementing this suggestion in clinical practice. Clinicians are faced with challenges of increased bleeding events in patients with ESRD because of coagulopathy, and increased incidence of major bleeding and ICH are frequently observed and reported in literature in patients with ESRD and AF undergoing anticoagulation therapy. In fact, different findings have been reported in recent literature that NOAC rivaroxaban showed better results than warfarin in severe kidney disease undergoing dialysis, while we showed NOACs as a group was not better than warfarin in chronic kidney disease stage 4–5. These findings confirmed the controversial nature of using anticoagulants in patients with ESRD and AF undergoing regular dialysis. Therefore, our findings offered an important message that bridged the knowledge gap. Our study showed that patients undergoing PD rather than hemodialysis may decrease AF-associated outcomes, including IS/SE, major bleeding, and ICH. And in subgroup analysis of risk of IS/SE once AF occurred in the IPTW-adjusted cohort, we found IS/SE was decreased in patients undergoing PD in patients age <65 years, had dyslipidemia, previous stroke, and vascular disease.

In summary, AF is prevalent among ESRD patients, and presents a dilemma to clinicians whether anticoagulation should be implemented. Therapeutic choices of dialytic modalities by PD or hemodialysis may offer impact these patients in the ischemic and embolic as well as bleeding and hemorrhagic events. This is the first study to investigate and offer answers to these questions. Our study showed benefits in ESRD patients with AF underwent PD, compared with hemodialysis, and therefore PD should be considered when dialysis patients had AF.

Limitations

There are several limitations in epidemiologic data from NHIRD. First, using *ICD-9-CM* codes for patient diagnosis and screening may miss some cases for conditions not coded correctly. However, *ICD-9-CM* codes against hospital electronic medical records have been performed in the validation studies for NHIRD, the *ICD* codes have as sensitivity up to 99% for positive predictive value against the gold standard electronic medical records. Fourth, differences in patients' personality, social characteristics, ability, social status of individuals in PD and hemodialysis groups could lead to differences in the main outcomes of ischemic stroke/systemic embolism, major bleeding, and intracranial hemorrhage. In addition, social factors such as income, resident area (urban, suburban area, countryside), occupation, education history, family configuration, housemate, and marriage status were supposedly inherently different between the 2 groups PD group and hemodialysis group as well. Since these detailed information are not recorded in Taiwan's NHIRD, the lacking data of social risk factors might contribute to uncertainness of results. Last, since our study consisted of homogeneous ethnic background, application of the results to other populations requires further studies in other regions of the world.

CONCLUSIONS

In patients with ESRD and AF, dialysis mode by PD or hemodialysis may impact these patients differently. Our study showed that ESRD patients with AF undergoing PD had overall reduced ischemic stroke/systemic embolism, major bleeding, and ICH at 5-year follow-up, compared with hemodialysis.

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Disclosures

None.

Supplementary Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 CM diagnostic codes.

Variable	ICD-9 CM Code
Dialysis	585.xx (Catastrophic illness card)
Malignancy	140.xx – 208.xx (Catastrophic illness card)
Atrial fibrillation	427.31
Diabetes mellitus	250.xx
Hypertension	401.xx-405.xx
Dyslipidemia	272.xx
Ischemic heart disease	410.xx – 414.xx
Chronic obstructive pulmonary disease	491.xx, 492.xx, 496.xx
Anemia	280.xx – 284.xx
Alcoholism	V113, 291.xx, 305.0x, 357.5, 425.5, 303.xx, 571.0, 571.1, 571.2, 571.3, 980.0
Drug abuse	304.xx, 305.xx
Venous thromboembolism	453.xx, 415.1x
Rheumatic Heart Disease	394.0, 394.1, 394.2, 395.xx, 398.9x
Hyperthyroidism	242.xx
Heart failure	428.xx
Ischemic stroke	433.xx – 437.xx
Systemic embolism	415.1x, 444.22, 444.81, 444.21, 362.30, 362.34, 593.81, 444.89, 557.0, 557.9, 557.1, 444.9x, 430.xx – 432.xx
Hemorrhage stroke	430.xx – 432.xx
Myocardial infarction	410.xx, 412.xx
Gastrointestinal bleeding	530.21, 530.7, 530.82, 531.xx – 535.xx, 537.83, 537.84, 578.xx
Major bleeding	3361, 3636, 37272, 37632, 37742, 37923, 4230, 430, 431, 4320, 4321, 4329, 531, 5312, 5314, 5316, 532, 5322, 5324, 5326, 5307, 533, 5332, 5334, 5336, 534, 5342, 5344, 5346, 5693, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53571, 53783, 53784, 56202, 56203, 56212, 56213, 56985, 578, 59381, 7191, 72992, 7725, 8520, 8522, 8524, 8530, 86601, 86602, 86611, 86612,

ICD-9 CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table S2. Follow up outcome in patients with atrial fibrillation who received hemodialysis and peritoneal dialysis in the propensity score matched cohort.

	Data before matching		Data after matching			
Follow up / Outcome‡	PD (*n* = 363)	HD (*n* = 5,302)	PD (n = 331)	HD (n = 1,324)	HR/SHR of PD (95% CI)	*P*
1 year						
Ischemic stroke / systemic embolism	18 (5.0)	374 (7.1)	18 (5.4)	89 (6.7)	0.99 (0.60–1.63)	0.953
Major bleeding	4 (1.1)	80 (1.5)	4 (1.2)	22 (1.7)	0.88 (0.30–2.56)	0.811
Intracranial hemorrhage	2 (0.6)	50 (0.9)	2 (0.6)	14 (1.1)	0.69 (0.16–3.07)	0.627
3 year						
Ischemic stroke / systemic embolism	31 (8.5)	777 (14.7)	28 (8.5)	190 (14.4)	0.75 (0.50–1.12)	0.158
Major bleeding	9 (2.5)	170 (3.2)	9 (2.7)	46 (3.5)	0.99 (0.48–2.04)	0.983
Intracranial hemorrhage	4 (1.1)	105 (2.0)	4 (1.2)	29 (2.2)	0.70 (0.25–2.00)	0.507
5 year						
Ischemic stroke / systemic embolism	41 (11.3)	937 (17.7)	35 (10.6)	234 (17.7)	0.76 (0.53–1.09)	0.140
Major bleeding	10 (2.8)	215 (4.1)	10 (3.0)	58 (4.4)	0.88 (0.44–1.73)	0.700
Intracranial hemorrhage	4 (1.1)	135 (2.5)	4 (1.2)	36 (2.7)	0.56 (0.20–1.60)	0.281

PD, peritoneal dialysis; HD, hemodialysis; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval; Data were presented as frequency (percentage).

‡ Patients who switched between PD and HD were censored.

Table S3. Additional subgroup analysis of 5-year outcome in the cohort after inverse probability of treatment weighting on whether or not patients were taking beta-blocker and non-dihydropyridine calcium channel blockers.

5-year outcome‡ / subgroup	Number of event (%)		SHR (95% CI) of PD	*P* for interaction
	PD	HD		
Ischemic stroke / systemic embolism				
Beta blockers				0.441
No	12.4	16.3	0.84 (0.73–0.96)	
Yes	15.5	19.8	0.90 (0.79–1.04)	
NDCCB				0.681
No	14.2	17.6	0.87 (0.78–0.96)	
Yes	11.6	18.9	0.92 (0.71–1.18)	
Major bleeding				
Beta blockers				<0.001
No	3.5	3.6	1.20 (0.92–1.56)	
Yes	1.7	4.8	0.39 (0.27–0.57)	
NDCCB				0.558
No	2.8	4.0	0.81 (0.65–1.01)	
Yes	2.1	4.5	0.68 (0.38–1.19)	
Intracranial hemorrhage				
Beta blockers				0.026
No	0.2	2.2	0.13 (0.06–0.28)	
Yes	0.8	3.0	0.36 (0.22–0.59)	
NDCCB				NA
No	0.6	2.6	0.28 (0.19–0.42)	
Yes	0.0	2.3	NA	

PD, peritoneal dialysis; HD, hemodialysis; NDCCB, non-dihydropyridine calcium channel blockers; SHR, subdistribution hazard ratio; HR, hazard ratio; CI, confidence interval, NA, not applicable.

‡ Patients who switched between PD and HD were censored.

Table S4. Additional subgroup analysis of 5-year outcome in the cohort after inverse probability of treatment weighting on whether or not patients were taking antiplatelet and anticoagulant.

5-year outcome‡ / subgroup	Number of event (%)		SHR (95% CI) of PD	*P* for interaction
	PD	HD		
Ischemic stroke / systemic embolism				
Antiplatelet				0.344
No	11.1	15.5	0.90 (0.78–1.03)	
Yes	17.2	21.1	0.82 (0.71–0.94)	
Anticoagulant				0.291
No	13.3	17.2	0.86 (0.77–0.95)	
Yes	19.6	24.5	1.00 (0.77–1.31)	
Major bleeding				
Antiplatelet				<0.001
No	4.0	4.3	1.22 (0.96–1.54)	
Yes	1.0	3.8	0.22 (0.13–0.37)	
Anticoagulant				0.895
No	2.6	3.9	0.79 (0.64–0.99)	
Yes	3.5	5.6	0.76 (0.41–1.40)	
Intracranial hemorrhage				
Antiplatelet				NA
No	0.9	2.6	0.45 (0.30–0.69)	
Yes	0.0	2.6	NA	
Anticoagulant				<0.001
No	0.2	2.4	0.12 (0.07–0.22)	
Yes	3.5	4.1	1.05 (0.54–2.01)	

PD, peritoneal dialysis; HD, hemodialysis; SHR, subdistribution hazard ratio; HR, hazard ratio; CI, confidence interval, NA, not applicable.

‡ Patients who switched between PD and HD were censored.