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Original Investigation

Risk of Stroke in Long-term Dialysis Patients Compared With the General Population

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Background: Patients undergoing maintenance dialysis are at increased risk of stroke.

Study Design: We performed a nationwide retrospective cohort study to determine the risks for ischemic stroke and hemorrhagic stroke among incident hemodialysis (HD) and peritoneal dialysis (PD) patients in comparison to a reference group in Taiwan.

Setting & Participants: Data for 74,192 HD patients, 5,974 PD patients, and 669,773 nondialysis individuals who were older than 18 years and had no history of stroke or cancer were retrieved from the National Health Insurance Research Database for 1998-2009.

Predictors: Patient demographics, comorbid conditions.

Outcome: First hospitalization for stroke, defined as a diagnosis at discharge (either primary or 1 of 4 secondary diagnoses) of ischemic or hemorrhagic stroke using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

Results: HD and PD patients had higher incidences of hospitalized ischemic stroke (102.6 and 100.1/10,000 person-years) and hemorrhagic stroke (74.7 and 59.4/10,000 person-years) in comparison to the age- and sex-matched reference cohort (42.4 and 13.0/10,000 person-years, respectively). In addition to HD and PD therapy, older age, male sex, diabetes, and hypertension were found to be independent risk factors for both ischemic and hemorrhagic strokes. Using the HD group as the comparison group, we found that PD patients had a lower risk of hemorrhagic stroke (HR, 0.75; 95% CI, 0.58-0.96), and there was no significant difference in risks of ischemic stroke between PD and HD patients after adjusting for all potential confounders and competing risk of death, and matched by propensity scores.

Limitations: This was a retrospective study, and some important variables were not available.

Conclusions: Patients undergoing dialysis are at elevated risk of stroke. Patients undergoing PD appear to be less likely to develop hemorrhagic stroke than those undergoing HD. Comprehensive control of hypertension and diabetes is necessary when delivering dialysis treatment.

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INDEX WORDS: Hemodialysis; peritoneal dialysis; stroke; cerebrovascular disease; end-stage renal disease (ESRD); ischemic stroke; hemorrhagic stroke; renal replacement therapy (RRT).

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Stroke is the second and third leading cause of death in the United States and Taiwan, respectively.[1,2] Patients with chronic kidney disease appear to be the highest risk group for subsequent cardiovascular disease (CVD).[3,4] Patients undergoing long-term dialysis have a 10- to 20-times higher risk of CVD-related mortality than the general population.[5] Stroke represents one of the main causes of cardiovascular mortality in patients with end-stage renal disease (ESRD).[6] Previous studies in the United States and Japan reported 2- to 10-fold increased risks of stroke in dialysis patients compared with the general population.[7,8] The mortality rate of stroke in dialysis patients was found to be nearly 3 times higher than that in patients not receiving dialysis.[9] Most studies of patients with ESRD have focused on hemodialysis (HD) patients, and less is known about the incidence, relative risks, and subtypes of stroke in peritoneal dialysis (PD) patients.

We designed the present study using a nationwide database to estimate incidence rates for different subtypes of stroke in patients undergoing HD and PD, and compared these with a reference cohort.

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METHODS

Data Source

This nationwide cohort study was based on data obtained from the National Health Insurance Research Database (NHIRD),[10] which is abstracted from the reimbursement data of the National Health Insurance in Taiwan. The National Health Insurance program is a mandatory single-payer social health insurance launched on March 1, 1995, and 99.48% of citizens (23 million) were enrolled in the program by the end of 2008. This system covers most forms of treatment and the related expenses. Most importantly, it has comprehensive coverage for catastrophic illnesses, of which ESRD is one, and all such patients can have all copayments waived. Thus, the registry for ESRD is very comprehensive and includes all patients receiving maintenance dialysis. The National Health Research Institutes, Taiwan, encrypts the personal identification data and transforms and maintains the NHIRD for research purposes.

Study Participants, Stroke, and Comorbid Conditions

From this database, patients who were older than 18 years and had received maintenance dialysis for more than 3 months during the study period from January 1, 1998, to December 31, 2009, were enrolled in the dialysis cohort. Patients who had ever received a kidney transplant prior to dialysis, had a history of cancer, or had a stroke before dialysis therapy were excluded. The dialysis cohort then was divided into HD and PD groups. Patients who changed dialysis modality were classified as HD or PD according to their initial treatment modality.

The reference cohort was selected from a randomly sampled data set of 1,000,000 from January 1, 1998, to December 31, 2009, released by the NHIRD. To ensure comparability, we excluded individuals who were younger than 18 years, those who had ever received dialysis treatment, and those who had a history of cancer or stroke prior to being enrolled in the study.

For each individual in both cohorts, baseline demographic data and clinical conditions were obtained from the NHIRD. The major outcome of the study was the first hospitalization because of stroke, which was defined as a diagnosis at discharge (either primary or up to 4 secondary diagnoses) of ischemic or hemorrhagic stroke, namely, the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes of 433.xx, 434.xx, and 436.xx for infarction and 430.xx, 431.xx, and 432.xx for hemorrhage. In addition to an in-hospital diagnosis of stroke, more than 84% of patients underwent one or more imaging studies of the brain by computed tomography or magnetic resonance imaging within 30 days of stroke onset. The diagnoses quality achieved the criteria of the ideal stroke incidence study suggested by Sudlow and Warlow.[11] Other clinical conditions, including hypertension (*ICD-9-CM* codes 401-402, 405, and A codes 260 and 269), diabetes (*ICD-9-CM* codes 250, 357.2, 362.0X, and 366.41), hyperlipidemia (*ICD-9-CM* codes 272.0-272.4 and A code 189), congestive heart failure (*ICD-9-CM* codes 398.91, 425, 428, 402.X1, 404.X1, and 404.X3), coronary artery disease (*ICD-9-CM* codes 414.8 and 414.9), acute myocardial infarction (*ICD-9-CM* code 410.X), arrhythmia (*ICD-9-CM* codes 426-427, V45.0, and V53.3), peripheral vascular disease (*ICD-9-CM* codes 440-444, 447, and 557), anemia (*ICD-9-CM* codes 280-285), chronic obstructive lung disease (*ICD-9-CM* codes 491-494 and 496), gastrointestinal bleeding (*ICD-9-CM* codes 456.0-456.2, 530.7, 531-534, 569.84, 569.85, and 578), and liver disease (*ICD-9-CM* codes 070, 570, 571, 572.2, 572.3, 572.4, and 573.1-573.3), were obtained from both inpatient and outpatient reimbursement data.

Because accidental inclusion of miscoded patients may be ineludible in outpatient claims, the diagnosis from outpatient encounters should fulfill the following rules. First, individuals were classified as having any kind of comorbid condition if they had a diagnosis of the comorbid condition at any time in outpatient claims and then experienced another one or more diagnoses within the subsequent 12-month follow-up period. Second, the first and last outpatient visits within 1 year had to be more than 30 days apart.[12] Comorbid conditions were recorded during 2 different periods in this study. The first period was the medical record within 1 year prior to an individual being enrolled in the study and implied the clinical conditions before the beginning of the study. All variables in this period, in addition to age and sex, were applied in logistic regression models of propensity scores. The second period was abstracted from the beginning to the time of being censored or the end of the study. The CVD-related comorbid conditions during this period were used as covariates in multivariable Cox models and competing-risk analyses (Fig 1).

Statistical Analyses

Baseline descriptive data are described as mean ± standard deviation for continuous variables and frequency and percentage for categorical variables. One-way analysis of variance, χ^2 test, and standardized differences[13] were used to compare baseline characteristics of the 3 groups, ie, HD patients, PD patients, and the reference cohort. Because matching of propensity score (the probability of being on dialysis therapy relative to not) in the dialysis and reference populations shows a C statistic value of 0.96, indicating little overlap,[14] we applied simple age- and sex-matched referents for comparison. To compare risk of stroke in groups with different dialysis modalities, we used propensity score (for receiving HD as the initial treatment) matching by a greedy algorithm in order to ensure better comparability among the 2 dialysis groups and minimize possible selection bias in choosing PD or HD. Then, the impact of different dialysis modalities on stroke was analyzed using multivariable Cox proportional hazard models. Survival time was censored if the patient changed dialysis modality from one to another for more than 3 months, received a kidney transplant, died, or came to the end of the study period. Because we treated mortality other than stroke as censored, our model had to be adjusted for the competing risk. Thus, we re-ran the Cox model and conditional on competing risk of death (Fine and Gray[15] competing-risk models) to validate the previous models. The proportional hazard assumption of the Cox models was assessed by a graphical method.

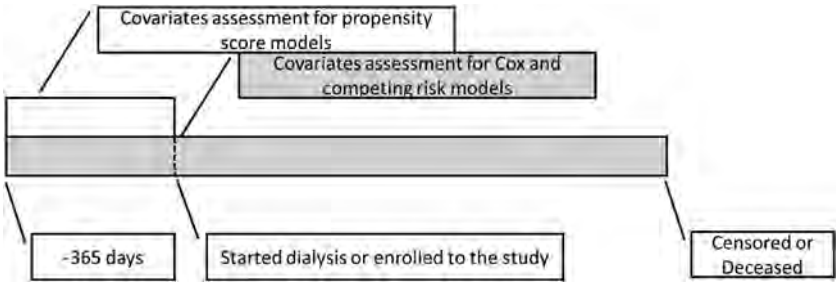

Figure 1. Periods of covariate ascertainment.

Statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc), and R statistical software, version 2.15.3 (R Foundation for Statistical Computing). A 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

For January 1, 1998, to December 31, 2009, there were 73,630 (91.8%) incident HD patients and 4,364 (5.4%) incident PD patients; another 1,610 (2.0%) switched from PD to HD, and 562 (0.7%) switched from HD to PD. Because patients were grouped according to incident modality, overall, there were 74,192 HD patients and 5,974 PD patients included in this analysis. Within the same study period, 669,773 nondialysis patients were recruited into the reference cohort.

Before matching processes, mean ages of HD patients, PD patients, and the reference cohort were 60.5 ± 14.1, 52.2 ± 15.0, and 40.0 ± 16.0 years, respectively, indicating that the dialysis patients generally were older than the reference cohort. There was a higher proportion of women in the PD group than in the HD group. Patients undergoing dialysis had higher prevalence rates of all comorbid conditions compared with those in the reference cohort. In general, PD patients had lower proportions of comorbid conditions than HD patients, with the exceptions of hypertension, anemia, and hyperlipidemia.

After the age- and sex-matching process, 5,974 PD patients, 28,940 HD patients, and 29,870 reference individuals were selected, creating a ratio of 1:4.8:5 (Table 1). Dialysis patients still had significantly higher proportions of comorbid conditions than the age- and sex-matched reference cohort, with the exception of chronic obstructive pulmonary disease. After balanced matching with predialysis conditions by the propensity score, HD patients had slightly higher proportions of comorbid conditions than PD patients during follow-up, with the exception of significantly lower proportions of anemia and hyperlipidemia (Table 1).

Because PD patients had better baseline parameters than HD patients, we applied a propensity score (probability of receiving HD as the initial treatment relative to PD) to match the differences in predialysis conditions in the selection of treatment modality in further construction of the Cox models and competing-risk analyses in dialysis patients. The distribution of propensity score before matching processes seems to reflect a tendency with a higher proportion of PD shifted to the left (Fig 2).

Risk of Hospitalization for Stroke and Mortality

After being matched by age and sex, the reference cohort had 1,742 stroke events, with the lowest incidence rate of the groups (55.4/10,000 person-years), while the HD and PD groups had 2,134 and 290

Table 1. Age- and Sex-Matched Frequency Distributions of Demographic Characteristics and Clinical Comorbid Conditions During Follow-up

	Age and Sex Matched						Propensity Score Matched		
				d_i (%)			d_i (%)		
Characteristic	HD (n = 28,940)	PD (n = 5,974)	RC (n = 29,870)	PD vs HD	PD vs RC	HD vs RC	HD (n = 5,974)	PD (n = 5,974)	PD vs HD
Male sex	45.7	44.9	44.9	−1.6	0.0	1.6	45.0	44.9	−0.2
Age (y)	52.2 ± 15.0	52.2 ± 15.0	53.0 ± 14.6	−5.2	0.0	5.2	52.2 ± 15.0	52.0 ±15.0	−0.1
Comorbid condition									
DM	47.2	35.9	15.7	−23.1	47.5	72.2	35.9	36.2	0.6
Hypertension	79.6	83.5	31.3	10.1	124.3	111.1	80.1	83.5	9.1
Hyperlipidemia	35.6	41.8	20.6	12.1	46.8	34.2	36.4	41.8	10.1
Acute MI	4.1	3.4	1.3	−3.7	14.0	17.4	3.4	2.9	−2.9
CAD	18.6	13.9	9.1	−12.8	15.1	27.8	16.8	13.9	−8.0
CHF	27.0	18.5	6.9	−20.4	35.4	55.6	21.6	18.5	−7.8
Arrhythmia	11.0	9.4	8.4	−5.3	3.5	8.8	10.3	9.4	−3.0
PVD	15.0	8.7	4.7	−19.6	16.1	35.1	13.4	8.7	−15.0
Anemia	35.0	56.7	4.9	44.4	135.2	81.3	39.1	56.7	35.8
COPD	15.2	13.2	17.4	−5.1	−11.1	−6.0	13.4	13.2	−0.6
GI bleeding	34.4	26.9	23.0	−16.3	9.0	25.4	31.3	26.9	−9.7
Liver disease	21.7	18.1	15.8	−9.0	6.1	15.2	20.8	18.1	−6.8

Note: Unless otherwise indicated, values for categorical variables are given as percentages; values for continuous variables, as mean ± standard deviation.

Abbreviations and definitions: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; d_i, standardized differences with absolute values > 10% considered as residual imbalance; DM, diabetes mellitus; GI, gastrointestinal; HD, hemodialysis; MI, myocardial infarction; PD, peritoneal dialysis; PVD, peripheral vascular disease; RC, reference cohort.

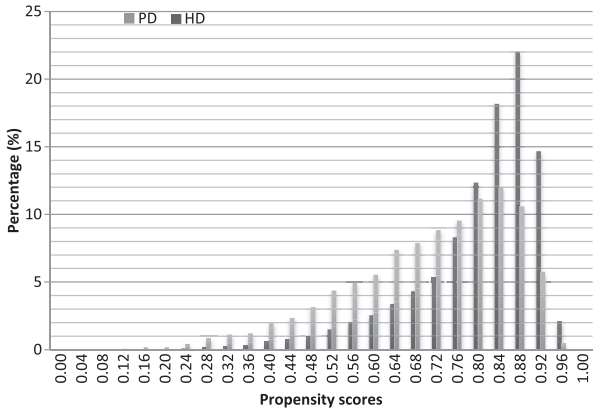

Figure 2. Distribution of propensity scores for receiving hemodialysis (HD) as the initial treatment in 74,192 HD patients and 5,974 peritoneal dialysis (PD) patients.

stroke events (incidence rates of 177.4 and 159.5/10,000 person-years, respectively). Dialysis patients had a 4- to 5-times higher mortality rate than the age- and sex-matched reference cohort, and patients undergoing PD had the highest crude mortality rate of 730.8/10,000 person-years (Table 2). The proportion of ischemic subtype of stroke was higher than that of hemorrhagic subtype in the 3 groups.

After matching dialysis patients by propensity score, PD patients had a higher incidence rate of ischemic stroke and higher mortality than HD patients. Although crude incidence rates of ischemic stroke were correlated positively with increasing age, crude incidence rates of hemorrhagic stroke were higher in middle age (45-64 years) in HD and PD patients (Fig 3). In addition, male patients or those with a diagnosis of diabetes or hypertension had an elevated risk of ischemic stroke and the same trend was observed in hemorrhagic stroke (Table 3). After adjustments, dialysis patients had higher risks of hemorrhagic (hazard ratios [HRs] of 6.83 [95% confidence interval (CI), 5.89-7.92] and 6.15 [95% CI, 4.83-7.84] for HD and PD, respectively) and ischemic strokes (HRs of 2.88 [95% CI, 2.60-3.19] and 3.21 [95% CI, 2.69-3.83] for HD and PD, respectively) than those of the age- and sex-matched reference cohort, as summarized in Table 3.

Validation of Risk Factors by Competing-Risk Model Using HD Patients as Comparison Cohort

Death may have an important role in competing risk in this study because approximately 22%-27% of dialysis patients were censored for death (Table 2). Further validation analysis by the competing-risk model comparing propensity score–matched patients undergoing PD and HD showed that PD patients had a lower risk of hemorrhagic stroke (HR, 0.75; 95% CI, 0.58-0.96) and no significantly different risk of ischemic stroke (HR, 0.94; 95% CI, 0.77-1.15) compared with HD patients after adjustment for potential confounders and the competing risk of death (Table 4). Diabetes and hypertension were the major predictive factors for both ischemic stroke and hemorrhagic stroke in dialysis patients. Age appears to be a consistent risk factor for ischemic stroke; the older the age, the higher the risk. However, the age trend appears to be less consistent for hemorrhagic stroke.

Table 2. Age- and Sex-Matched Accumulated Person-Years, Mean Follow-up Time, Frequency and Crude Incidence Rates of Stroke and Death

	Age and Sex Matched			Propensity Score Matched	
	HD (n = 28,940)	PD (n = 5,974)	RC (n = 29,870)	HD (n = 5,974)	PD (n = 5,974)
Person-years	120,327	18,186	314,501	25,368	18,186
Follow-up time (y)	4.2 ± 3.2	3.0 ± 2.3	10.5 ± 3.1	4.2 ± 3.2	3.0 ± 2.3
Stroke					
Overall					
Frequency[a]	2,134 (7.4)	290 (4.9)	1,742 (5.8)	400 (6.7)	290 (4.9)
Incidence rate[b]	177.4	159.5	55.4	157.7	159.5
Ischemic					
Frequency[a]	1,235 (4.3)	182 (3.1)	1,332 (4.5)	225 (3.8)	182 (3.1)
Incidence rate[b]	102.6	100.1	42.4	88.7	100.1
Hemorrhagic					
Frequency[a]	899 (3.1)	108 (1.8)	410 (1.4)	175 (2.9)	108 (1.8)
Incidence rate[b]	74.7	59.4	13.0	69.0	59.4
Death					
Frequency[a]	7,689 (26.6)	1,329 (22.3)	5,049 (16.9)	1,389 (23.3)	1,329 (22.3)
Incidence rate[b]	639.0	730.8	160.5	547.5	730.8

Note: Follow-up time is given as mean ± standard deviation.
Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; RC, reference cohort.
[a]Given as number of events (percentage of group with event).
[b]Per 10,000 person-years.

DISCUSSION

To our knowledge, our study is the first nationwide population-based cohort study to quantify incidence rates of ischemic and hemorrhagic strokes in patients undergoing HD and PD in comparison to a reference cohort drawn from the general population. Although we found a 3-fold increased incidence rate in patients undergoing dialysis, it does not necessarily follow that such an increased risk is causally linked. However, we provide the following evidence to argue in support of such a hypothesis. First, because we have adjusted and/or matched the propensity to receive different modalities of dialysis and excluded all individuals with cancer or history of stroke, this observational study attempted to accommodate the concept of comparability in randomized controlled trials and minimized the selection bias. Second, because all major potential confounding factors for stroke, including age, hypertension, and diabetes, were adjusted for in the Cox proportional hazard model (Tables 3 and 4) and the competing-risk model (Table 4), they would not be explanatory of the increased risks. Third, there were increased adjusted HRs for ischemic stroke in individuals with hypertension, the aged, and those with diabetes, which corroborates results from previous studies[16-19] (Table 3). The same trend was found for hemorrhagic stroke.[19] These findings could be considered as validation of our models. Thus, we tentatively conclude that patients undergoing dialysis appear to be at higher risk of stroke hospitalization than those in the reference cohort, independent of diabetes, hypertension, and the aging process, and that HD patients seem to be at greater risk of hemorrhagic stroke in comparison to propensity score–matched PD patients (Table 4).

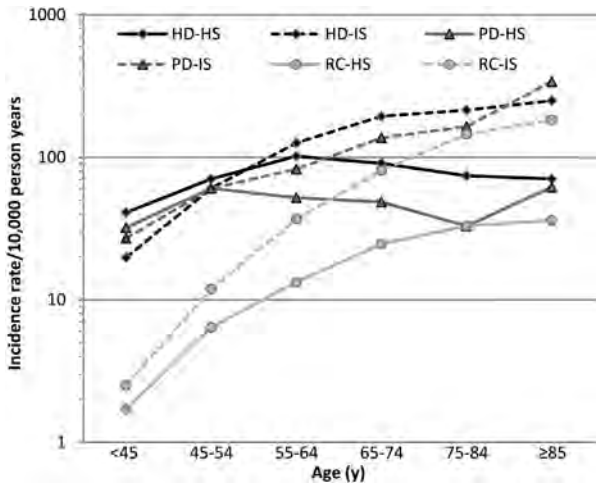

Figure 3. Age- and sex-matched incidence rates of hemorrhagic (HS) and ischemic stroke (IS) stratified by age in hemodialysis (HD) patients, peritoneal dialysis (PD) patients, and the reference cohort (RC).

It may be surprising that some cardiovascular conditions in our study had significantly lower adjusted HRs from the results of the construction of Cox models and competing-risk models (Tables 3 and 4). The following are possible reasons. First, there is the competing effect of CVD-related mortality. Because this study treated all causes of death other than stroke as censored, patients with comorbid CVDs were expected to have a higher mortality rate and were censored upon death. Almost all regression coefficients adjusted for the competing-risk model in Table 4 showed a consistent trend of being closer to the null effect (or, adjusted HR of 1) compared with those in the Cox model. A second explanation might be the characteristics of the reimbursement data, in which a patient's special examinations and/or treatments usually must be accompanied by a clinical diagnosis to be legitimate for such claims. Namely, a diagnosis in the NHIRD may imply that it is either a clinically suspected diagnosis only or a diagnosed disease for which treatment is ongoing. Moreover, almost all clinical interventions for CVDs usually reduce or modify the risk of stroke. Thus, we anticipated such potential overadjustments by these factors (Tables 3 and 4).

Several possible explanations have been proposed for the increased risk of stroke in dialysis patients. Both conventional and uremia-related cardiovascular risks have been proposed.[6,19] As listed in Table 1, dialysis patients had significantly higher prevalences of hypertension, diabetes, and hyperlipidemia than those in the reference cohort. Together with higher prevalence rates of the 3 mentioned conventional risk factors for atherosclerosis, our data also showed that prevalence rates of CVDs in dialysis patients were all significantly higher than those in the reference cohort (Table 1), which corroborates the findings of the CHOICE (Choices for Healthy Outcomes in Caring for ESRD) Study.[20]

There is still debate regarding anemia and the consequence of stroke in patients with ESRD. Seliger et al[17] reported that dialysis patients with anemia (hemoglobin < 9 g/dL) had an increased risk of stroke, but Tripepi et al[21] found that dialysis patients have a 27% increase in stroke risk with a 1-g/dL increase in hemoglobin level. Our data also suggested a protective effect of anemia for stroke. Anemia control is an important quality index of dialysis therapy worldwide.[22] The Taiwan Society of Nephrology has recommended that a dialysis center should have $<10\%$ of patients with a hematocrit $< 26\%$ in order to fulfill the accreditation criteria for high quality. Because a diagnosis of anemia is required for the prescription of erythropoietin and patients with ESRD

Table 3. Major Determinants and HRs of Ischemic and Hemorrhagic Stroke in Age- and Sex-Matched Multivariable Cox Models

Variable	Ischemic Stroke	Hemorrhagic Stroke
HD[a]	2.88 (2.60-3.19)	6.83 (5.89-7.92)
PD[a]	3.21 (2.69-3.83)	6.15 (4.83-7.84)
Male sex	1.24 (1.15-1.34)	1.34 (1.23-1.52)
Age (per 1-y greater)	1.07 (1.06-1.07)	1.03 (1.03-1.03)
DM	1.84 (1.69-2.00)	1.46 (1.29-1.64)
HTN	1.15 (1.05-1.26)	1.20 (0.92-1.58)
Hyperlipidemia	0.83 (0.77-0.91)	0.70 (0.62-0.79)
Anemia	0.70 (0.63-0.77)	0.76 (0.67-0.87)
CHF	0.88 (0.79-0.97)	0.97 (0.84-1.11)
CAD	0.96 (0.87-1.06)	0.74 (0.63-0.86)
Arrhythmia	0.77 (0.68-0.87)	0.57 (0.47-0.70)
PVD	0.64 (0.56-0.73)	0.75 (0.64-0.89)

Note: Values given as adjusted HR (95% confidence interval).

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HD, hemodialysis; HR, hazard ratio; HTN, hypertension; PD, peritoneal dialysis; PVD, peripheral vascular disease.

[a]General population used as reference cohort.

are waived copayment, severe anemia, as Seliger et al[17] reported, may not be commonly seen in Taiwan.

The aging process is an important risk factor for stroke in the general population. Iseki and Fukiyama[23] and Power et al[24] reported that the mean age at hemorrhagic stroke onset was younger than that of ischemic stroke onset in dialysis patients. Earlier onset of hypertension and comorbid conditions and frequent exposure to anticoagulation therapy during dialysis may explain the different trends of hemorrhagic stroke in dialysis patients and the general population.

There are some risk factors distinct to the uremic process.[25] Disturbances in mineral metabolism[26-31] are associated with the consequences of vascular calcification and CVD. In addition, hyperhomocysteinemia,[32,33] endothelial dysfunction,[34-37] and chronic inflammation[38,39] also predispose dialysis patients to accelerated atherosclerosis.

Patients undergoing intermittent HD experience more intradialysis hemodynamic change, fluctuations in body fluid content, and electrolyte and acid-base homeostasis than patients undergoing PD and the reference cohort. These disturbances may induce a higher risk of brain injury and consequent ischemic stroke. In addition, routine heparin use in HD may have an important role in the difference in risk of hemorrhagic stroke when comparing HD patients with PD patients and the reference cohort.[8,40]

Most patients undergoing PD use a glucose-based dialysate, which might increase the burden of glucose and result in more metabolic side effects, including obesity, dyslipidemia, hyperinsulinemia, and peripheral insulin resistance, than in those undergoing HD and the general population.[41-45]

Thus, although different dialysis modalities may have varied clinical effects in terms of the development of stroke, comprehensive control over hypertension and diabetes remains the basic strategy for control of the aforementioned risk factors.

There are several limitations in our study. First, some important variables and information that might affect the risk of stroke, such as body mass index,

Table 4. Major Determinants and HRs of Ischemic and Hemorrhagic Stroke in Propensity Score–Matched Multivariable-Adjusted Cox Regression Models and Multivariable-Adjusted Competing-Risk Regression Models of Dialysis Patients

	Ischemic Stroke		Hemorrhagic Stroke	
Variable	Cox Model	CRR Model	Cox Model	CRR Model
PD	1.14 (0.93-1.41)	0.94 (0.77-1.15)	0.88 (0.69-1.14)	0.75 (0.58-0.96)
Male sex	1.15 (0.95-1.41)	1.12 (0.92-1.37)	1.43 (1.12-1.81)	1.38 (1.09-1.76)
Age (per 1-y greater)	1.05 (1.04-1.06)	1.03 (1.02-1.04)	1.02 (1.01-1.03)	1.00 (1.00-1.01)
DM	2.25 (1.82-2.77)	1.85 (1.47-2.31)	1.76 (1.36-2.28)	1.45 (1.11-1.88)
HTN	1.41 (1.03-1.93)	1.45 (1.06-1.99)	1.71 (1.17-2.50)	1.76 (1.20-2.58)
Hyperlipidemia	1.05 (0.86-1.28)	1.16 (0.95-1.41)	0.85 (0.66-1.08)	0.93 (0.73-1.18)
Anemia	0.74 (0.60-0.91)	0.82 (0.66-1.00)	0.96 (0.75-1.23)	1.04 (0.81-1.34)
CHF	0.81 (0.63-1.03)	0.76 (0.59-0.98)	0.95 (0.71-1.28)	0.92 (0.67-1.25)
CAD	0.90 (0.70-1.15)	0.92 (0.71-1.19)	0.82 (0.59-1.14)	0.84 (0.60-1.17)
Arrhythmia	0.78 (0.57-1.08)	0.83 (0.61-1.14)	0.43 (0.26-0.72)	0.45 (0.27-0.75)
PVD	0.56 (0.40-0.77)	0.64 (0.46-0.88)	0.58 (0.39-0.87)	0.66 (0.44-0.97)

Note: Hemodialysis patients used as reference cohort. Values given as adjusted HR (95% confidence interval).

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CRR, Fine and Gray competing-risk regression; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; PD, peritoneal dialysis; PVD, peripheral vascular disease.

waist to hip ratio, physical activity, nutrition status, psychosocial stress, smoking, and alcohol consumption, were not available in the NHIRD. However, because these factors usually lead to increased risks of cardiovascular-related comorbid conditions and were controlled in our model construction, they did not seem to contribute to any differential bias in this study. Second, to gain a more accurate diagnosis of stroke in the reimbursement data, we defined stroke hospitalization as our outcome of interest. Thus, we might have overlooked patients with minor stroke who sought only ambulatory care, and our estimation of the incidence of stroke may too low. However, because stroke is considered a catastrophic illness and for all patients, copayments are waived for the first month, we believe that the underestimation is minimal. Third, although we adjusted for potential confounders, the duration of risk-factor exposure before stroke and the severity of the diseases were not taken into consideration in our study due to data limitations. Generally, dialysis patients have a longer history and greater severity of the major risk factors for stroke, such as diabetes and hypertension. Therefore, we may have overestimated the true risk of stroke when comparing dialysis patients and the reference cohort. Fourth, ideally, a prospective randomized controlled clinical trial usually would be the gold standard to compare outcomes. However, it is difficult to randomize dialysis treatments because of the complicated clinical conditions, nonclinical conditions, and ethical issues. Thus, we applied the propensity score method in multivariate analyses to minimize selection bias as much as possible. Because we were looking for only adverse outcomes of both subtypes of stroke, our estimates reflected the real conditions of dialysis treatment in Taiwan and are useful for the development of a prevention strategy.

In conclusion, we found that patients undergoing dialysis have significantly greater risks of both subtypes of stroke, with approximate adjusted HRs of 2.88-3.21 for infarction and 6.83-6.15 for hemorrhage (Table 3). Moreover, patients undergoing PD seemed to have a lower risk of hemorrhagic stroke than those undergoing HD in Taiwan (Table 4). Although different dialysis modalities involve different mechanisms of pathophysiology, comprehensive control of hypertension and diabetes may still be the fundamental preventive strategy for stroke in these patients.

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