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ORIGINAL RESEARCH

Nationwide Trends in Stroke Among Patients Undergoing Hemodialysis by Sex and Race: An Analysis From the US Renal Database

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BACKGROUND: The risk of ischemic stroke hospitalization in patients with end-stage kidney disease has declined over time, but data are limited, especially for hemorrhagic stroke trends. Race- and sex-based differences have not been well studied.

METHODS AND RESULTS: We conducted a retrospective cohort study using the US Renal Data System to examine the incidence of stroke among incident patients undergoing hemodialysis from 2006 to 2016. We identified 391 195 new patients undergoing hemodialysis (mean age, 70.1 years; 44.8% women) between 2006 and 2016. The incidence of any stroke per 100 000 patients decreased from 2746 cases at 1 year and 6823 cases at 3 years during 2006 to 2009 to 1983 cases at 1 year and 5162 cases at 3 years in 2014 to 2016 (P<0.001). Women had higher stroke incidence than men (P<0.001). White adults had higher incidence compared with Black adults, Hispanic adults, and Other (Native American participants and those whose racial and ethnic identification did not align with the classifications) race (P<0.001). The risk decreased over the study period for both sexes and races, except "Other" race. Hemorrhagic stroke incidence was 409 cases at 1 year and 1125 at 3 years per 100 000. No sex difference was observed at 1 year, but women had higher 3-year rates (P=0.005). Black and Hispanic adults had higher 3-year hemorrhagic stroke rates than White adults (P<0.001). Decreases occurred only for women, Black adults, and Hispanic adults at 1 year.

CONCLUSIONS: While the overall risk of stroke remains high after hemodialysis initiation, significant reductions in stroke risk have occurred over the past decade across sexes and racial groups.

Key Words: end-stage kidney disease ■ hemodialysis ■ racial disparities ■ sex disparities ■ stroke

Stroke is the second-leading cause of death and disability worldwide and is associated with both modifiable and nonmodifiable risk factors.[1] Modifiable factors include hypertension, dyslipidemia, diabetes, smoking, atrial fibrillation, physical inactivity and high body mass,[2,3] coronary artery disease (CAD),[4] and alcohol consumption,[5] while nonmodifiable factors include age, race and ethnicity,[2,6] and sex.[7] Patients with end-stage kidney disease (ESKD) have been shown to have up to 6 times higher risk of stroke compared with those without ESKD.[8] This is likely due to a higher prevalence of risk factors like hypertension, diabetes, and accelerated atherosclerotic vascular disease related, at least in part, to uremia.[9] Noninvasive imaging studies have demonstrated that patients undergoing dialysis exhibit increased carotid

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CLINICAL PERSPECTIVE

What Is New?

- The study reveals a declining trend in overall stroke incidence from 2006 to 2016, with ischemic stroke accounting for 87% of all strokes.
- Significant differences in stroke risk were observed between sexes and racial groups, with women and White adults showing higher risk for ischemic stroke, while hemorrhagic stroke risk was higher in women and non-White adults.

What Are the Clinical Implications?

- Strategies are needed to address disparities in stroke risk for different demographic groups within the end-stage kidney disease population.
- The overall declining trend in stroke risk suggests improvements in care, but the persistently high risk emphasizes the need for continued efforts in stroke prevention among patients undergoing hemodialysis.
- The limited decrease in hemorrhagic stroke incidence and the relatively higher risk compared with the general population indicate a need for focused research and interventions for this stroke subtype in the end-stage kidney disease population.

Nonstandard Abbreviation and Acronym

USRDS United States Renal Data System

artery atherosclerosis, suggesting a significant role of accelerated atherosclerosis in their elevated stroke risk.[10] There is also some evidence that women may have a higher stroke risk than men in ESKD compared with the general population.[8]

Cardiovascular diseases, which include stroke, account for more than half (52.2%) of deaths with known causes in patient with ESKD. Specifically, stroke is responsible for ≈2.3% of deaths among patients with ESKD.[11]

A secondary analysis of the national inpatient sample data set suggested a significant trend toward decreasing ischemic stroke hospitalizations in patients undergoing dialysis, with incidence rates falling from 1390 per 100 000 in 2003 to 783 per 100 000 in 2014.[12] However, it is not known if there are sex- or race-based differences in these trends.

Prior studies have primarily focused on stroke incidence in patients undergoing hemodialysis for unknown duration,[12] but the specific risk of stroke in patients who have recently initiated hemodialysis (incident hemodialysis) remains unclear. Furthermore, prior studies have not specifically examined hemorrhagic strokes in patients with ESKD. This gap is crucial, as patients with ESKD experience a higher mortality rate from hemorrhagic strokes[13] and have a greater prevalence of atrial fibrillation.[14] The use of anticoagulation in these patients, often necessary for stroke prevention, further increases their already elevated risk of bleeding.[15]

To address this knowledge gap, we conducted an analysis of the US Renal Data system (USRDS) to evaluate sex- and race-related trends of ischemic and hemorrhagic stroke among patients with ESKD with new initiation of hemodialysis.

METHODS

The findings of this study are based on limited data from the USRDS. Due to data use restrictions, we cannot share these data files with third parties. We obtained the data under a specific agreement with the USRDS. For access to USRDS data, interested parties should contact usrds@niddk.nih.gov.

This database is supported by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases. The USRDS contains patient information, including demographics, medical conditions, treatments, and outcomes from the End-Stage Renal Disease Quality Reporting System, the Centers for Medicare and Medicaid Services, the Organ Procurement and Transplantation Network, the Centers for Disease Control and Prevention, and the End-Stage Renal Disease Networks.[16] While USRDS provides medication information for patients with Part D coverage, our study primarily focuses on stroke risk. Not all eligible participants in our study have Part D coverage. Consequently, we chose not to restrict our sample selection on the basis of Part D coverage status.

The study was reviewed and approved by the University of Kansas Medical Center's Institutional Review Board and USRDS. The Institutional Review Board approved a waiver of consent. We ensured that our reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17]

We conducted a retrospective cohort study using the USRDS[18] database between January 1, 2006, and December 31, 2016.

We included patients aged ≥18 years who were newly initiated on hemodialysis between January 1, 2006, and December 31, 2016. Patients were required to have at least 90 days of hemodialysis to be included in the study cohort (Figure 1). Patients entered the cohort after the 90th day of hemodialysis. The analysis incorporated data from cohort

entry until December 31, 2019, which served as the censoring date. The requirement of a minimum 90-day period of hemodialysis was implemented to exclude patients on temporary dialysis for acute kidney injury.

We excluded patients who had missing sex or race information, were on peritoneal dialysis, lived outside of the United States, and did not have both Medicare A and B coverage (Figure 1). We censored patients at the time of kidney transplant, death before stroke event, or loss of either Medicare Part A or Part B coverage (Figure 1).

Demographic and clinical variables relevant to our study like age, sex, race, history of hypertension, diabetes and reasons for ESKD were obtained from the Centers for Medicare and Medicaid Services Form 2728. We categorized race and ethnicity into 4 groups: White, Black, Hispanic, and Other. The Other category encompassed Native American participants and those whose racial and ethnic identification did not align with the classifications.

This categorization was based on self-reported data from patient records using form Centers for Medicare and Medicaid Services 2728. To identify cases of atrial fibrillation, we used the *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes that were submitted within 6 months of initiating dialysis. Table S1 provides additional information about relevant *ICD* codes.

The primary study outcome was 1- and 3-year occurrence of any stroke hospitalization after initiation of hemodialysis. We evaluated stroke outcome by analyzing Medicare claims, using previously validated *ICD-9* and *ICD-10* codes for both ischemic and hemorrhagic strokes. To identify ischemic stroke cases using *ICD-9* codes, we applied the codes 433, 434, and 436, and for hemorrhagic stroke, we used the codes 430 and 431.[19] For *ICD-10* coding, we identified ischemic stroke

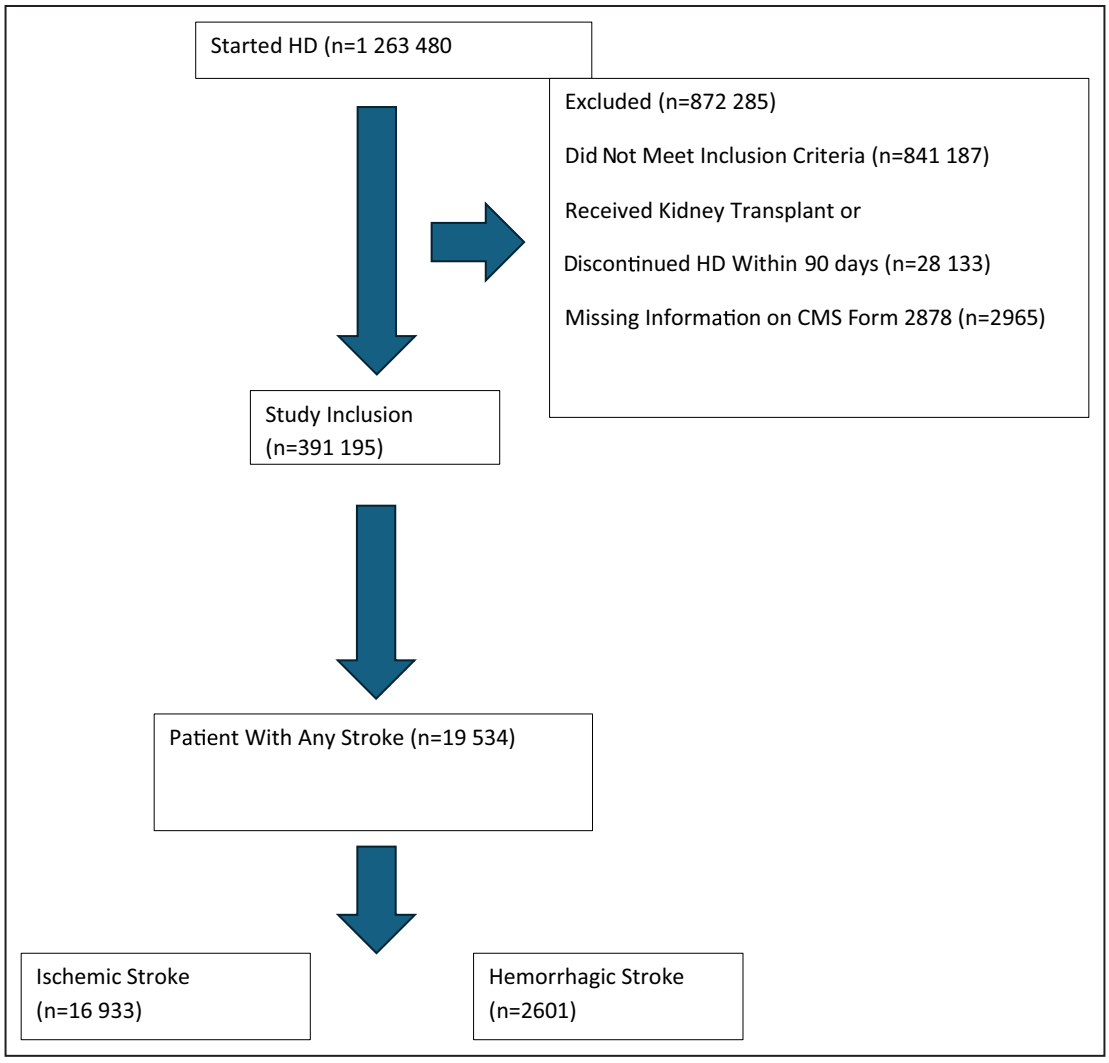

Figure 1. Patient selection and study cohort.
CMS indicates Centers for Medicare and Medicaid Services; and HD, hemodialysis.

cases by using the code I63[20] and hemorrhagic stroke cases by using the codes I61 and I60.[21]

Secondary outcomes were 1- and 3-year occurrence of ischemic and hemorrhagic stroke. Study outcomes were assessed for male and female sex as well as among different racial groups. To assess trends over time, the study population was grouped into 3 cohorts based on the year hemodialysis was initiated (2006–2009, 2010–2013, and 2014–2016). In each cohort, a 1- and 3-year risk of stroke was calculated after initiation of dialysis, with last follow-up on December 31, 2019.

Statistical Analysis

We used descriptive statistics to provide an overview of the demographic characteristics of the study population. Continuous variables were expressed as means±SD, while categorical variables were expressed as frequencies with percentages. Baseline characteristics of different cohorts were used to examine temporal trends. We used simple linear regression to analyze trends in patient age over the years. To assess changes in categorical variables such as sex, race, primary reasons for ESKD, and comorbidities across the study period, we used the Cochran–Mantel–Haenszel test. Survival analyses with the Kaplan–Meier method were used to calculate the incidence of first stroke after initiation of dialysis. The 1- and 3-year incidence of first stroke hospitalization was age-standardized to the 2006 US ESKD population using the direct standardization method and is presented as the number of stroke events per 100 000 patients.

To analyze the data, we used the Cox proportional hazards regression model, which allowed us to estimate the hazard ratio (HR) of stroke while accounting for age, sex, race, hypertension, diabetes, CAD, cerebrovascular accident (CVA), peripheral artery disease, and atrial fibrillation. To identify changes in the risk of stroke over time, we used logistic regression with occurrence of stroke as the dependent variable and year of hemodialysis initiation as the independent variable while adjusting for age. We stratified the data by sex and various racial groups to determine if the trends are consistent across both men and women, as well as different racial groups. We created separate models for different types of strokes, including ischemic, hemorrhagic, and any type of stroke.

To visually illustrate the time to stroke events, we constructed cumulative incidence curves. We created separate curves for ischemic, hemorrhagic, and all types of strokes for each cohort as described above. We used log-rank tests to compare the survival curves between different cohorts and constructed cumulative incidence curves stratified by sex and race. For all analyses in this study, we used a significance level of $P<0.01$ to determine statistical significance. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) software, and R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

While statistical tests indicated significant violations of the proportional hazards assumption, this is likely due to our large sample size. Visual inspection through β and Schoenfeld residual plots revealed a stable pattern across the follow-up period, suggesting no substantial time-dependent effects or influential outliers. These findings support the validity of our Cox regression model (Figures S1 through S3).

RESULTS

Demographics

The overall study cohort is shown in Figure 1. A total of 1 263 480 patients with ESKD who started hemodialysis between January 1, 2006, and December 31, 2016, were identified. Of these, 169 685 patients

Table 1. Baseline Characteristics

Variable, n (%)	Total patients (n=391 195)
Age, y, mean (SD)	70.1 (11.8)
Female sex	175 376 (44.8)
Race or ethnicity	
White adults	233 122 (59.6)
Black adults	99 706 (25.5)
Hispanic adults	39 124 (10.0)
Other (race)*	19 243 (4.9)
Atrial fibrillation	88 986 (22.8)
Alcohol dependence	4203 (1.1)
Unemployed	54 680 (14.0)
Hypertension	345 104 (88.2)
Diabetes	234 189 (59.9)
CAD	92 849 (23.7)
Peripheral artery disease	67 992 (17.4)
CVA	45 191 (11.6)
Cancer	34 847 (8.9)
Congestive heart failure	147 940 (37.8)
COPD	48 094 (12.3)
Primary reasons for ESKD	
Diabetes	193 922 (49.6)
Hypertension	127 290 (32.5)
Glomerulonephritis	21 148 (5.4)
Other	48 835 (12.5)

CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; and ESKD, end-stage kidney disease.

*The Other category encompassed Native American participants and those whose racial and ethnic identification did not align with the classifications.

were excluded because they did not live in the United States or were aged <18 years, were undergoing peritoneal dialysis, or had missing sex information. An additional 671 502 patients were excluded because they did not have Medicare A and B coverage during the first 90 days, and 28 133 patients were excluded because they received a kidney transplant or discontinued hemodialysis during the first 90 days. Finally, 2965 patients were excluded due to missing information on the Centers for Medicare and Medicaid Services 2728 form. After applying all exclusion criteria, a total of 391 195 patients with ESKD on maintenance hemodialysis remained eligible for inclusion in the study (Figure 1).

Table 1 presents the baseline characteristics of the study cohort. The mean age of the patients at the start of dialysis was 70.1 years±11.8. Women accounted for 44.8% of the sample. Atrial fibrillation was present in 22.8% of patients. Most patients identified as White adults (59.6%) followed by Black adults (25.5%), Hispanic adults (10.0%), and Other race (4.9%). The most common primary reason for ESKD was diabetes (49.6%) followed by hypertension (32.5%), glomerulonephritis (5.4%), and other reasons (12.5%). Hypertension was the most common comorbidity (88.2%), followed by diabetes (59.9%), coronary artery disease (23.7%), peripheral artery disease (17.4%), cerebrovascular accident (11.6%), cancer (8.9%), and congestive heart failure (37.8%).

Table S2 details the baseline characteristics for study patients grouped according to years in which hemodialysis was initiated. The percentage of women decreased from 45.4% to 43.8% (P<0.001) over the decade. The mean age decreased from 70.3 to 69 (P<0.001; Table S1). There were increases in the prevalence of atrial fibrillation (18.7% in 2006–2009 to 27.1% in 2014–2016; P<0.001), hypertension (87.3%–88.7%; P<0.001), and diabetes (58.3%–61.5%; P<0.001). However, the prevalence of CAD, peripheral artery disease, congestive heart failure, chronic obstructive pulmonary disease, and cancer decreased over time.

Table 2. Age-Standardized Stroke Risk in Men Versus Women (per 100 000 Population)

Outcome	Entire cohort	Men	Women	*P* value
1-y stroke	2385	2101	2754	<0.001
3-y stroke	5988	5255	6934	<0.001
1-y ischemic stroke	1980	1719	2329	<0.001
3-y ischemic stroke	4890	4225	5746	<0.001
1-y hemorrhagic stroke	409	390	432	0.12
3-y hemorrhagic stroke	1125	1049	1217	0.005

Any Stroke

In the overall cohort, the incidence of age-adjusted any-stroke hospitalization per 100 000 population was 2385 at 1 year and 5988 at 3 years following hemodialysis initiation. When analyzed by sex, women exhibited a higher stroke incidence per 100 000 compared with men at both 1 year (2754 versus 2101) and 3 years (6994 versus 5254.0) (P<0.001 for all comparisons; Table 2, Figure 2A). There was a decrease in the age-adjusted 1-year stroke hospitalization rate (2746.0 in 2006–2009, 2298 in 2010–2013, and 1983 in 2014–2016; P<0.001; Table 3). Similarly, the 3-year age-adjusted stroke risk was higher in the 2006–2009 period (6823) compared with the later periods (5752 in 2010–2013 and 5162 in 2014–2016), (P<0.001) (Table 3, Figure 3A). An examination of temporal trends, stratified by sex, revealed a decline in the risk of age-adjusted 1- and 3-year stroke occurrence among both men and women (Table 3).

Among racial groups, White adults had slightly higher stroke incidence per 100 000 at both time points (1 year, 2466; 3 years, 6101) compared with Black adults (1 year, 2345; 3 years, 6078), Hispanic adults (1 year, 2376; 3 years, 5665), and Other (1 year, 2079; 3 years, 5062) (P<0.001, Table 4, Figure 4A). Similarly, when considering temporal trends across various racial groups, a reduction in hospitalization rates was observed among White adults, Black adults, and Hispanic adults but not in the Other category (Table 5).

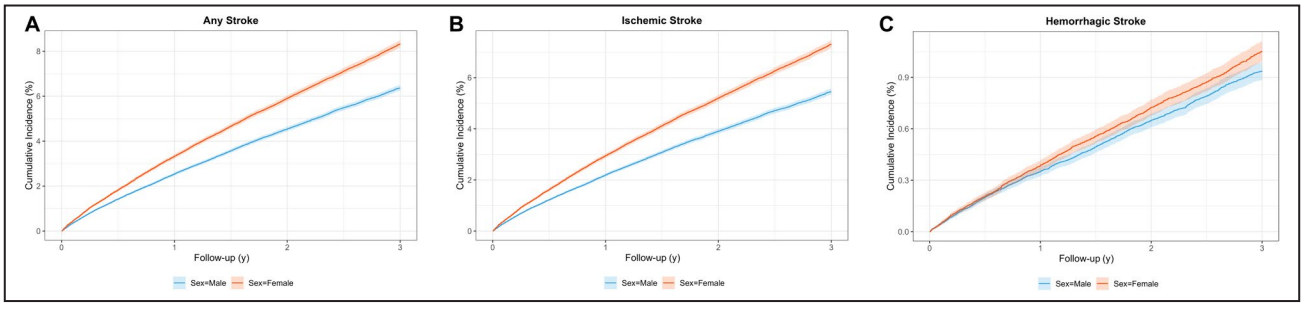

Figure 2. Sex-based comparison of cumulative stroke incidence: (A) any stroke, (B) ischemic stroke incidence, (C) hemorrhagic stroke incidence.

Table 3. Age-Standardized Stroke Incidence Trends by Sex (per 100 000 Population)

Outcome	Sex	Entire cohort	2006–2009	2010–2013	2014–2016	*P* value
1-y stroke	Entire group	2385	2746	2299	1983	<0.001
	Male (n=215 819)	2101	2332	2114	1768	<0.001
	Female (n=175 376)	2754	3288	2542	2275	<0.001
3-y stroke	Entire group	5988	6823	5752	5162	<0.001
	Male	5255	5962	5134	4478	<0.001
	Female	6934	7908	6526	6088	0.001
1-y ischemic stroke	Entire group	1980	2296	1918	1605	<0.001
	Male	1719	1923	1743	1395	<0.001
	Female	2329	2779	2171	1892	<0.001
3-y ischemic stroke	Entire group	4890	5692	4729	3983	<0.001
	Male	4225	4853	4171	3471	<0.001
	Female	5746	6749	5481	4702	<0.001
1-y hemorrhagic stroke	Entire group	409	457	380	382	<0.001
	Male	390	410	376	379	0.12
	Female	432	515	375	383	0.001
3-y hemorrhagic stroke	Entire group	1125	1156	1037	1198	0.03
	Male	1049	1130	979	1022	0.12
	Female	1217	1192	1090	1413	0.11

The crude any-stroke rates demonstrated similar trends to the age-adjusted rates, as shown in Tables S3 through S5.

Variables associated with an increased risk of stroke are given in Table 6. Notable risk factors associated with any stroke were female sex (HR, 1.32 [95% CI, 1.28–1.36]; *P*<0.001), atrial fibrillation (HR, 1.25 [95% CI, 1.21–1.30]; *P*<0.001), smoking (HR, 1.20 [95% CI, 1.13–1.27]; *P*<0.001), diabetes (HR, 1.09 [95% CI, 1.05–1.13]; *P*<0.001), peripheral artery disease (HR, 1.17 [95% CI, 1.12–1.21]; *P*<0.001), and CVA (HR, 1.62 [95% CI, 1.56–1.68]; *P*<0.001). Hypertension was not associated with stroke incidence (*P*=0.15). Compared with White adults, Hispanic adults and Other racial groups were at a lower adjusted risk of any type of stroke (HR, 0.94 [95% CI, 0.89–0.98]; *P*=0.009; and HR, 0.77 [95% CI, 0.72–0.82]; *P*<0.001, respectively). There was no difference in adjusted risk of any type of stroke in Black adults compared with White adults (HR, 0.97 [95% CI, 0.94–1.00]; *P*=0.080).

Ischemic Stroke

The overall age-adjusted ischemic stroke hospitalization rate was 1980 per 100 000 at 1 year and 4890 per 100 000 at 3 years (Table 2). Women had a higher 1- and 3-year incidence of age-adjusted ischemic stroke per 100 000 compared with men (2329 versus 1719, *P*<0.001, and 5746 versus 4225, *P*<0.001; Table 2, Figure 2B). The risk of age-adjusted ischemic stroke hospitalization at both 1 and 3 years was lowest during the period spanning 2014 to 2016 (1605 and 3983, respectively), compared with 1918.4 and 4729 between 2010 to 2013, and 2296 and 5692 per 100 000 from 2006 to 2009 (*P*<0.001; Table 3). This downtrend was observed in both men and women (Table 3).

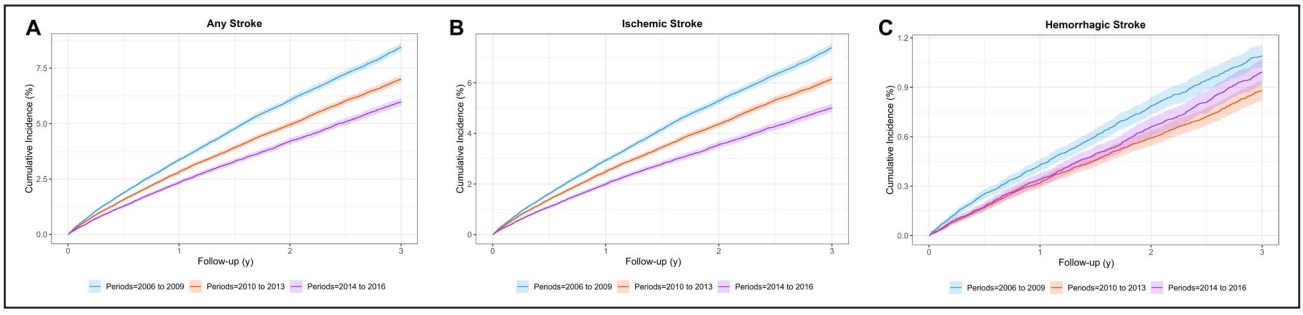

Figure 3. Comparison of cumulative incidence for stroke-related hospitalizations across 3 time periods (2006–2009, 2010–2013, and 2014–2016): (A) any stroke, (B) ischemic stroke, (C) hemorrhagic stroke.

Table 4. Age-Standardized Stroke Incidence by Race (per 100 000 Population)

Outcome	Entire cohort	White adults	Black adults	Hispanic adults	Other	*P* value
1-y stroke	2385	2466	2345	2376	2079	<0.001
3-y stroke	5988.4	6101	6078	5665	5062	<0.001
1-y ischemic stroke	1980	2076	1975	1764	1621	<0.001
3-y ischemic stroke	4890	5161	4895	4289	3919	<0.001
1-y hemorrhagic stroke	409	300	370	615	460	<0.001
3-y hemorrhagic stroke	1125	912	1204	1395	1169	<0.001

White adults exhibited a higher risk of 1- and 3-year ischemic stroke hospitalization per 100 000 compared with other racial groups (White adults, 2076, 5161; Black adults, 1975, 4895; Hispanic adults, 1764, 4289; Other, 1621, 3919; *P*<0.001; Table 4, Figure 4B). A decreasing trend in the risk of ischemic stroke hospitalization was observed at both 1 and 3 years across all racial groups, except for the Other category (Table 5).

The crude ischemic stroke rates demonstrated similar trends to the age-adjusted rates, as shown in Tables S3 through S5.

Several baseline characteristics were found to be associated with an increased risk of ischemic stroke (Table 6) including increasing age, atrial fibrillation, diabetes, CAD, and peripheral artery disease. A previous history of CVA was strongly associated with ischemic stroke (HR, 1.64 [95% CI, 1.58–1.71]; *P*<0.001) followed by female sex (HR, 1.35 [95% CI, 1.30–1.39]; *P*<0.001). Hypertension was not associated with higher risk of ischemic stroke (*P*=0.12). Compared with White adults, other racial groups exhibited lower adjusted risk of ischemic stroke hospitalization: Black adults (HR, 0.93 [95% CI, 0.90–0.97]; *P*=0.0007), Hispanic adults (HR, 0.87 [95% CI, 0.83–0.92]; *P*<0.001), and Other (HR, 0.66 [95% CI, 0.61–0.72]; *P*<0.001).

Hemorrhagic Stroke

The overall incidence of age-adjusted hemorrhagic stroke per 100 000 was relatively low at both 1 and 3 years after the initiation of hemodialysis (409 and 1125, respectively). There was no significant difference in 1-year hemorrhagic stroke hospitalizations per 100 000 between men and women (390 versus 432; *P*=0.12), but women had a significantly higher 3-year incidence per 100 000 (1217 versus 1048.8, *P*=0.005; Table 2 and Figure 2C). Temporal trends stratified by sex showed a small but statistically significant difference in 1-year hemorrhagic stroke among women (515 in 2006–2009 to 383 in 2014–2016; *P*=0.001, Table 3) but not the 3-year rate.

Compared with White adults (912.3 per 100 000), other racial groups (Black adults, 1204 per 100 000; Hispanic adults, 1395 per 100 000; Others, 1169 per 100 000) had significantly higher 3-year hemorrhagic stroke hospitalization rates (*P*<0.001; Table 4, Figure 4C). When stratified by race, the 1- and 3-year risk of hemorrhagic stroke did not decrease for White adults and Others but small decreases in the 1-year risk of hemorrhagic stroke were seen among Black adults (480–282; *P*=0.007) and Hispanic adults (639–444; *P*=0.004; Table 5).

The crude hemorrhagic stroke rates demonstrated similar trends to the age-adjusted rates, as shown in Tables S3 through S5.

Table 6 shows the baseline characteristics associated with hemorrhagic stroke risk. Female sex, atrial fibrillation, smoking history, previous CVA, and initiation of hemodialysis in the first year of the study period were associated with a higher risk. Age had slightly lower HR for hemorrhagic stroke (HR, 0.99 [95% CI, 0.98–0.99]; *P*<0.001). Compared with White adults, Black adults (HR, 1.22 [95% CI, 1.12–1.34]), Hispanic adults (HR, 1.45 [95% CI, 1.29–1.64]), and those categorized as Other (HR, 1.63 [95% CI, 1.40–1.90]) were

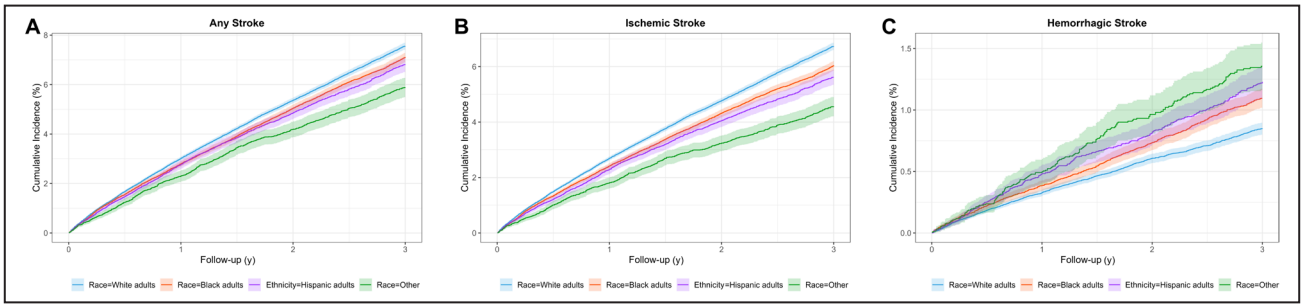

Figure 4. Racial disparities in cumulative stroke incidence: (A) any stroke, (B) ischemic stroke, (C) hemorrhagic stroke.

Table 5. Age-Standardized Stroke Incidence Trends by Race (per 10 000 Population)

Outcome	Race	Entire cohort	2006–2009	2010–2013	2014–2016	*P* value
1-y stroke	White adults (n=233 122)	2466	2880	2470	1929	<0.001
	Black adults (n=99 706)	2345	2731	2109	2097	<0.001
	Hispanic adults (n=39 124)	2376	2597	2459	1917	<0.001
	Other (n=19 243)	2079	1976	2274	1973	0.08
3-y stroke	White adults	6101	6920	6059	5145	<0.001
	Black adults	6078	7056	5501	5488	<0.001
	Hispanic adults	5665	6179	5620	4967	<0.001
	Other	5062	5075	5737	4123	0.02
1-y ischemic stroke	White adults	2076	2487	2111	1504	<0.001
	Black adults	1975	2256	1802	1815	<0.001
	Hispanic	1764	1961	1774	1473	<0.001
	Other	1621	1628	1752	1422	0.031
3-y ischemic stroke	White adults	5161	6087	5119	4078	<0.001
	Black adults	4895	5725	4549	4181	<0.001
	Hispanic adults	4289	4805	4122	3803	<0.001
	Other	3919	3894	4570	3039	0.02
1-y hemorrhagic stroke	White adults	392	395	360	430	0.14
	Black adults	370	480	314	282	0.007
	Hispanic	615	639	688	444	0.004
	Other	460	350	524	550	0.71
3-y hemorrhagic stroke	White adults	912	856	958	1081	0.55
	Black adults	1204	1366	967	1321	0.11
	Hispanic	1395	1401	1514	1178	0.03
	Other	1169	1204	1187	1094	0.46

associated with higher risk of hemorrhagic stroke (*P*<0.001).

DISCUSSION

To our knowledge, this is the first nationwide study to assess the incidence of both ischemic and hemorrhagic stroke in patients initiated on hemodialysis and the first to study sex and race reacted trends in these patients.

The main findings of the study are that (1) there has been a consistent and significant decline in the 1- and 3-year incidence of any stroke in patients starting hemodialysis; (2) this decrease in stroke risk is driven mainly by a reduction in ischemic stroke, which comprises 87% of strokes; (3) any stroke and ischemic stroke risk is higher in women, but both men and women showed a similar decrease in stroke incidence over the study period; (4) rates of hemorrhagic stroke are relatively low in both men and women, with the later having a higher 3-year stroke hospitalization; and (5) White adults had a higher risk of ischemic stroke compared with all other races studied, though for hemorrhagic stroke White adults had a lower risk. However, the observed downtrend in overall stroke was similar across White adults, Black adults, and Hispanic adults.

Previous literature has documented declining trends in stroke incidence rates in the general population. A study by Ramirez et al showed that age-adjusted acute ischemic stroke hospitalization rates in the United States decreased by 18.4% from 2000 to 2010 among the general population.[22] Our study observed a more pronounced decline in 3-year risk of acute ischemic stroke hospitalization rates in patients undergoing dialysis, from 5692 in 2006 to 2009 to 3983 in 2014 to 2016. Similarly, Madsen et al demonstrated a decline in stroke incidence from 1993 to 2015, with rates decreasing from 229 to 174 per 100 000 in women and from 282 to 211 per 100 000 in men.[23] In patents undergoing dialysis, Alqahtani et al found an 8-fold higher incidence of ischemic stroke hospitalization compared with patients not on dialysis.[12] Further, they showed a significant decrease in the incidence of ischemic stroke hospitalization in the dialysis population over the period studied from 1390 per 100 000 in 2003 to 783 per 100 000 in 2014.[12] However, due to the database used, they included patients with all duration of dialysis and not incident dialysis, and thus stroke rate after initiation of dialysis could not be ascertained. Our

Table 6. Multivariate Analysis (Cox Proportional Hazard Model)

Variable	Any stroke, HR (95% CI)	*P* value	Ischemic stroke, HR (95% CI)	*P* value	Hemorrhagic stroke, HR (95% CI)	*P* value
Age	1.01 (1.01–1.01)	<0.001	1.02 (1.01–1.02)	<0.001	0.99 (0.98–0.99)	<0.001
Female sex	1.32 (1.28–1.36)	<0.001	1.35 (1.3–1.39)	<0.001	1.124 (1.04–1.22)	0.003
Race (ref: White adults)						
Black adults	0.97 (0.94–1.00)	0.086	0.93 (0.91–0.974)	<0.001	1.22 (1.11–1.34)	<0.001
Hispanic adults	0.94 (0.89–0.98)	0.009	0.87 (0.83–0.92)	<0.001	1.45 (1.29–1.64)	<0.001
Other*	0.77 (0.72–0.8)	<0.001	0.66 (0.61–0.72)	<0.001	1.63 (1.40–1.90)	<0.001
Smoker	1.2 (1.13–1.27)	<0.001	1.17 (1.10–1.25)	<0.001	1.39 (1.2–1.61)	<0.001
Hypertension	1.0 (1.0–1.1).	0.15	1.0 (1.0–1.1)	0.12	1.0 (0.9–1.1)	0.99
Diabetes	1.09 (1.05–1.13)	<0.001	1.11 (1.06–1.15)	<0.001	0.98 (0.88–1.09)	0.68
CAD	1.0 (1.06–1.135)	<0.001	1.11 (1.07–1.149)	<0.001	1.02 (0.92–1.123)	0.75
Peripheral artery disease	1.17 (1.12–1.21)	<0.001	1.20 (1.16–1.25)	<0.001	0.93 (0.84–1.04)	0.23
CVA	1.62 (1.56–1.68)	<0.001	1.64 (1.58–1.71)	<0.001	1.48 (1.33–1.65)	<0.001
Atrial fibrillation	1.25 (1.21–1.30)	<0.001	1.23 (1.19–1.28)	<0.001	1.36 (1.23–1.50)	<0.001
CHF	1.05 (1.02–1.08)	0.002	1.06 (1.03–1.1)	<0.001	0.97 (0.89–1.05)	0.45
Primary reasons for ESKD (ref: diabetes)						
Hypertension	0.95 (0.92–1.0)	0.02	0.94 (0.90–1.0	0.05	1.02 (0.92–1.14)	0.72
Glomerulonephritis	0.73 (0.68–0.79)	<0.001	0.69 (0.64–0.75)	<0.001	0.99 (0.81–1.18)	0.9
Other	0.73 (0.69–0.77)	<0.001	0.70 (0.66–0.75)	<0.001	0.88 (0.76–1.02)	0.09

CAD indicates coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; and HR, hazard ratio.

*The Other category encompassed Native American participants and those whose racial and ethnic identification did not align with the classifications.

study extends these findings by showing significant downtrend in the incidence of stroke hospitalization over the 10-year period from 2006 to 2016 including the 1- and 3-year risk after initiation of dialysis. This decrease could be attributed to several factors, including better secondary prevention of atherosclerotic disease, blood pressure management, and advancement in dialysis techniques.

Our study found a significant hemorrhagic stroke risk in patients undergoing hemodialysis, with 1- and 3-year risks of 409 and 1125 per 100 000, respectively. These rates are markedly higher than in the general population. Previous research reported a relative risk of 5.1 for hemorrhagic stroke hospitalization in patients undergoing hemodialysis compared with the general population.[8] A study using the National Inpatient Sample showed annual intracranial hemorrhage rates in the general population of 23.5 per 100 000, with 3-year rates increasing from 62.79 to 78.86 per 100 000 from 2004 to 2018, which has been attributed to increase in hypertension and use of anticoagulant use.[24] Our study also showed that the risk of hemorrhagic stroke was largely unchanged except for a slight decrease in the 1-year risk among women, Black adults, and Hispanic adults. However, the 3-year rate was unchanged, and thus this finding is of uncertain clinical significance. There could be several reasons for this higher risk and flat trends. There was an increase in the prevalence of atrial fibrillation during the study period from 2006 to 2009 (18.7%) to 2014 to 2016 (27.1%) that was likely due to enhanced surveillance and earlier detection of atrial fibrillation.[25] One possible explanation for a lack of reduction in hemorrhagic stroke could be that while ischemic and hemorrhagic strokes share similar risk factors, such as hypertension, previous CVA, and diabetes, the increased prevalence of atrial fibrillation may have led to more cases of hemorrhagic stroke due to earlier initiation of anticoagulation, thus offsetting any benefit of better secondary prevention measures that may have helped reduce ischemic stroke risk. A recent meta-analysis showed that oral anticoagulant use (warfarin, rivaroxaban, and dabigatran but not apixaban) in patients with atrial fibrillation on maintenance dialysis did not decrease the risk of thromboembolism but was associated with an increased risk of hemorrhage.[15] Another reason for the higher rate of hemorrhagic stroke in patients undergoing hemodialysis could be platelet dysfunction.[26]

Interestingly, our study did not find any association between ischemic or hemorrhagic stroke hospitalization and hypertension. This could be attributed to the fact that 88% of our patient population had a history of hypertension, and our data set lacked information on the degree of blood pressure control.

Our study demonstrated a higher risk of stroke hospitalization for women compared with men, which held true for any type of stroke, ischemic stroke, and hemorrhagic stroke over the 3-year follow-up period.

These findings are consistent with the study by Seliger et al, which assessed first stroke rates in patients who started dialysis between 1993 and 1997 per the USRDS.[8] In this study, they identified older age and female sex as risks for any stroke. This study had only 100 hemorrhagic strokes occurring but did find female sex to be an independent predictor even after adjustments. Seliger et al did not study 1- or 3-year stroke risk, but overall, our analysis shows similar fundings even 2 decades later. In the ESKD population, several factors could contribute to the potential stroke-risk disparity between sexes. Women with ESKD may experience menopause earlier than the general population, which could partially explain the higher stroke risk observed due to the loss of protective effects of estrogen earlier in life. According to Kramer et al, the median age for menopause in women with ESKD was 48 years compared with 51 to 52 years in the general population.[27] In the non-ESKD population, prior studies have identified disparities in stroke prevention and management for women, such as lower likelihood of receiving appropriate medications and antiplatelet[28] or anticoagulation therapy.[29] While these findings may not be directly applicable to the ESKD population, they highlight the need for further research to investigate potential sex-specific disparities in stroke prevention and management among patients with ESKD. Although our study showed an increased risk of stroke hospitalization in women, the trend of overall decreased rate of stroke hospitalization from 2006 to 2016 was also present in women, similar to that seen in men.

The ischemic stroke group encompassed 87% of all strokes, and correspondingly, the findings for ischemic stroke were similar to those of the any-stroke group. Our study revealed that White adults were at relatively higher risk of any stroke compared with other races. This finding contrasts with observations in the general, non-ESKD population, where non-White adults have been associated with an elevated risk for ischemic stroke hospitalization.[22] One potential explanation for this discrepancy could be the differential access to health care. Black adult patients undergoing dialysis may have improved insurance coverage (Medicare) and health care access compared with the Black adult patients in the general population, potentially mitigating the disparities seen in broader studies. Our study findings are indeed supported by previous study from USRDS from over 2 decades ago. Seliger et al also reported that in patients with ESKD, the risk of first hospitalization was lower in Black adults as compared with White adults. This was statistically significant only for Black adults with underlying cardiovascular disease.[30] For Hispanic adults, we were unable to find prior studies in ESKD patients; thus, the findings of our study that show that Hispanic adults undergoing hemodialysis have lower 1- and 3-year ischemic stroke rates than White adults are novel and need to be confirmed in future studies. Analysis of stroke hospitalization trends showed declining rates for all racial groups, except the Other category, which remained stable and had lower hospitalization rates overall. Limited sample sizes in the Other category prevented analysis of specific racial subgroups, potentially obscuring important trend variations within this diverse group that could include individuals from various racial backgrounds.

For hemorrhagic stroke, our study findings align with previous studies in both ESKD and general populations regarding higher hemorrhagic stroke risk for races other than White adults.[31] Inadequate treatment of hypertension in these populations could be a contributing factor to this disparity.

Despite the strengths of our study, including a large sample size, there are a few limitations that should be acknowledged. First, since our study was observational, we were unable to adjust for unmeasured confounders that may have influenced our findings. The analysis adjusts for several covariates, but important potential confounders such as socioeconomic status, access to care, and medication adherence are not considered. Additionally, the possibility of coding errors cannot be entirely ruled out. It is also possible that not all comorbidities were consistently entered by the physician at the start of dialysis. Furthermore, the completeness of comorbidity data may vary. While we captured the presence of comorbidities at the initiation of dialysis, we may not have a complete picture of their severity or control. For example, we lacked information on how well hypertension or diabetes were managed, which could potentially influence stroke risk. We also did not have data on medication use, such as anticoagulants for conditions like atrial fibrillation or aspirin for prior history of CAD or CVA, which could also be relevant to stroke risk. Additionally, our exclusion of patients without Medicare A and B coverage may impact the generalizability of our findings, as this subset may differ in age, employment status, socioeconomic factors, or overall health status. Our study is limited using data only up to 2016, which may not fully capture current trends or developments in ESKD treatment and patient outcomes as of 2024. Our Cox model with censoring for death and transplantation partially addresses competing risks but may not fully capture their impact on stroke hospitalization risk. This could affect our rate estimates and analyses of trends and demographic differences. Future research using dedicated competing risks methods, like the Fine and Gray model, could offer more precise insights and help validate our findings. However, despite these limitations, our study provides valuable insights into recent trends in stroke hospitalization in patients undergoing hemodialysis and sex disparities.

In conclusion, this study highlights sex- and race-related differences in stroke risk in patients with ESKD undergoing hemodialysis with female sex and White adults being associated with a higher risk of all stroke hospitalization driven mostly by ischemic stroke. The study also demonstrates a consistent decrease in stroke hospitalization among both men and women and across all races for the period studied. This finding emphasizes the importance of considering sex and race in assessing stroke risk in this overall high-risk population. Further research is needed to explore the underlying mechanisms contributing to these sex and race disparities and to identify targeted interventions that can mitigate the risk of stroke among this vulnerable population.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5
Figures S1–S3

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