## Dialysis

# Cerebrovascular Disease Incidence, Characteristics, and Outcomes in Patients Initiating Dialysis: The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study

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**Background:** Stroke is the third most common cause of cardiovascular disease death in patients on dialysis therapy; however, characteristics of cerebrovascular disease, including clinical subtypes and subsequent consequences, have not been well described.

**Study Design:** Prospective national cohort study, the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study.

**Settings & Participants:** 1,041 incident dialysis patients treated in 81 clinics enrolled from October 1995 to July 1998, followed up until December 31, 2004.

**Predictor:** Time from dialysis therapy initiation.

**Outcomes & Measurements:** Cerebrovascular disease events were defined as nonfatal (hospitalized stroke and carotid endarterectomy) and fatal (stroke death) events after dialysis therapy initiation. Stroke subtypes were classified by using standardized criteria from the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) system. The incidence of cerebrovascular event subtypes was analyzed by using time-to-event analyses accounting for competing risk of death. Clinical outcomes after stroke were abstracted from medical records.

**Results:** 165 participants experienced a cerebrovascular event with an overall incidence of 4.9 events/100 person-years. Ischemic stroke was the most common (76% of all 200 events), with cardioembolism subtype accounting for 28% of the 95 abstracted ischemic events. Median time from onset of symptoms to first stroke evaluation was 8.5 hours (25th and 75th percentiles, 1 and 42), with only 56% of patients successfully escaping death, nursing home, or skilled nursing facility.

**Limitations:** Relatively small sample size limits power to determine risk factors.

**Conclusions:** Cerebrovascular disease is common in dialysis patients, is identified late, and carries a significant risk of morbidity and mortality. Stroke etiologic subtypes on dialysis therapy are multifactorial, suggesting risk factors may change the longer one has end-stage renal disease. Additional studies are needed to address the poor prognosis through prevention, early identification, and treatment.

*Am J Kidney Dis* 54:468-477. © 2009 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Cerebrovascular disease; stroke; dialysis; prognosis; epidemiology.

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Cardiovascular disease is the leading cause of death for patients on dialysis therapy, with stroke as the third leading cause of cardiovascular disease death.[1] In the dialysis population, there have been only a few studies of cerebrovascular disease, including such outcomes as clinical or subclinical stroke or carotid endarterectomy (CEA).[2,3] Although traditional atherosclerotic risk factors for cerebrovascular disease, such as age, hypertension, diabetes mellitus, and dyslipidemia, are common in dialysis

patients, there also are risk factors unique to the uremic process[2,4,5] and the dialysis process itself[6] that may predispose individuals on dialysis therapy to either ischemic or hemorrhagic stroke. Given this dynamic accumulation of traditional and nontraditional risk factors on dialysis therapy, type of stroke, whether hemorrhagic or ischemic and particular ischemic subtypes, may change the longer one has end-stage renal disease.

Directed therapy, prognosis, and prevention of recurrence require identification of specific stroke subtypes to appropriately prescribe care.[7] In the general population, stroke is a significant cause of morbidity and mortality despite these measures aimed at early treatment.[8] For patients on dialysis therapy, the timing of presentation after stroke and immediate clinical outcomes have not been systematically studied. As such, optimal management of patients on dialysis therapy with stroke lacks an evidence base.

The aims of our study were to determine the incidence of cerebrovascular events and stroke subtypes, clinical characteristics of cerebrovascular events, and postevent outcomes in patients initiating dialysis therapy.

## METHODS

### Study Design

Study participants were from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study.[9] This national prospective cohort study of incident dialysis patients was initiated in 1995 to investigate treatment choices and clinical outcomes in dialysis care. Eligibility criteria for enrollment in CHOICE included new onset of long-term dialysis therapy in the preceding 3 months, ability to provide informed consent, age 18 years or older, and ability to speak English or Spanish. The Johns Hopkins University School of Medicine Institutional Review Board (Baltimore, MD) and the clinical centers' review boards approved the study. A total of 1,041 participants from 19 states were enrolled from October 1995 to June 1998 at 81 dialysis clinics associated with the nonprofit Dialysis Clinic Inc (DCI; Nashville, TN; n = 923), New Haven CAPD (New Haven, CT; n = 86), or Saint Raphael's Hospital (New Haven, CT; n = 32).

### Data Collection

The observation period for each patient began on the date of enrollment and continued through transplantation (n = 267) or December 31, 2004, the last follow-up date at CHOICE Study completion. A main outcome in CHOICE was any cardiovascular event; all possible cerebrovascular events underwent evaluation in CHOICE. The primary outcome of this ancillary investigation was the first cerebrovascular event after dialysis therapy initiation, including ischemic or hemorrhagic stroke, CEA, or stroke death.

Assignment of a nonfatal cerebrovascular event in CHOICE was based on information from the 4 data sources by using the following process. (1) Adjudicated records were considered the primary source of information for a nonfatal event. A Cardiovascular Disease Endpoints Committee of trained physicians reviewed hospital records to determine cause of hospitalization by using uniformly applied criteria modified from the Cardiovascular Health Study[10] and the Hemodialysis (HEMO) Study.[11] Each chart was independently reviewed by 2 members of the committee, and the cause of hospitalization was defined as either a definite or probable cerebrovascular event, then verified by an independent adjudicator. If the 2 initial reviews differed in assigned cause of hospitalization, a third independent reviewer resolved the disagreement. (2) In the absence of an adjudicated record, any US Renal Data System (USRDS) or Health Care Financing Administration (HCFA) billing data code for CEA (38.10, 38.11, and 38.12) or report from DCI confirmed a procedure event. (3) For nonprocedure events without an adjudicated record, the algorithm for assigning stroke, based on the strength of the data source, was as follows: (A) any USRDS or HCFA billing data code for cerebrovascular disease (430 to 436, 437.0, 437.1, 437.8, and 437.9); (B) a clinic (DCI) record when supported by the corresponding comorbidity record; and (C) subsequent stroke events in the same broad category within 30 days of discharge from a prior hospitalization for an assigned stroke event were not assigned as separate events. Administrative data containing *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnostic and procedural codes were available through December 31, 2004. Stroke death was assigned by using information from adjudicated death records and National Death Index records.

Medical charts from all available strokes were reviewed further by 2 independent abstractors for this ancillary investigation. Stroke was classified as ischemic or hemorrhagic based primarily on medical chart review. When charts were unavailable, *ICD-9* codes 430 (subarachnoid hemorrhage), 431 (intracerebral hemorrhage), and 432 (other and unspecified intracranial hemorrhage) were classified as hemorrhagic stroke, whereas the other cerebrovascular disease *ICD-9* codes mentioned were classified as ischemic stroke, similar to classification performed in other studies of stroke in dialysis patients.[2]

Ischemic stroke was subclassified further by using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into 5 etiologic subtypes.[12] These subtypes were large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined cause, and stroke of undetermined cause. Stroke from rare causes (such as nonatherosclerotic vasculopathy, hypercoagulable states, or hematologic disorders) were grouped with unknown causes because of the low frequency. Diagnosis of each subtype required clinical, radiographical, imaging, and laboratory findings. If the 2 initial reviewers disagreed on the etiologic subtype, a third reviewer reviewed and resolved these discrepancies.

Data for patient demographics and medical history were collected from a baseline self-report questionnaire. Race/

ethnicity was self-reported by patients. Dialysis modality at baseline was defined as the modality at 4 weeks after study enrollment.

Baseline individual comorbid conditions were abstracted from dialysis unit records, hospital discharge summaries, medication lists, consultation notes, diagnostic imaging, and cardiac imaging reports. A comorbidity score, the Index of Coexistent Disease (ICED), was calculated based on the presence and severity of comorbid conditions; scores range from 0 to 3, with 3 as the highest severity level.[13] The reliability of data abstraction and ICED severity scoring was assessed with a masked recoding of 45 medical records with high interrater reliability ($\kappa = 0.93$).

Baseline nonfasting venous blood specimens were routinely collected at DCI facilities just before a dialysis session. Laboratory values were obtained from monthly dialysis laboratory tests or sent to Quest Diagnostics (Baltimore, MD).

Information abstracted from hospitalized records for this ancillary investigation included items related to presentation and outcomes after CEA and stroke. These included time from symptom onset to presentation at the hospital emergency department, length of hospital stay, and discharge location. Discharge locations were predefined as home, death, acute rehabilitation center, nursing home, or skilled nursing facility. Successful recovery from the hospital was defined as discharge to home or acute rehabilitation center, as opposed to death, nursing home, or skilled nursing facility. Stroke death and case fatality were defined as those occurring within 30 days of the stroke and related to the stroke itself, defined as either a primary or underlying cause of death obtained from review of adjudicated death records or National Death Index records.

### Statistical Methods

Baseline characteristics in individuals who experienced a subsequent cerebrovascular event were compared with individuals who were free of cerebrovascular event at last follow-up by using Fisher exact test and Mann-Whitney rank sum test. The crude incidence rate of cerebrovascular events was calculated by dividing the number of patients with an event by the cumulative time at risk from study enrollment to first cerebrovascular event, with 95% confidence intervals constructed by using a Poisson model. In addition, incidence rates were calculated for several periods after dialysis therapy initiation (0 to 2, 2 to 4, 4 to 6, and >6 years).

Because the occurrence of death from causes other than stroke precludes the occurrence of cerebrovascular events, cumulative incidence curves accounting for the competing risk of nonstroke death were generated for each type of cerebrovascular event by using methods described by Coviello and Boggess.[14] Cumulative incidences at 2, 4, and 6 years and end of study period were obtained from these curves. Multivariate Cox cause-specific hazard ratios of cerebrovascular events associated with age, sex, race, ICED score, presence of diabetes, and presence of cerebrovascular disease were calculated from these competing risk models by using methods of Lunn and McNeil[15] in separate models excluding and including CEA as a cerebrovascular event.

Descriptive statistics for each clinical outcome were reported by etiologic stroke subtype.

A 2-sided *P* less than 0.05 was used as the level of statistical significance for all tests. Statistical analyses were performed using Stata SE software, version 9.2 (StataCorp, College Station, TX).

## RESULTS

Approximately two-thirds of eligible patients were enrolled in CHOICE from participating dialysis units. Eligible patients enrolled were similar to eligible, but unenrolled, patients with regard to age, sex, dialysis modality, albumin level, and blood pressure. Baseline characteristics of the 1,041 CHOICE participants are listed in Table 1. Age, sex, race, and dialysis modality distributions were similar to those of the 1997 US dialysis population, as described previously.[16] During a median follow-up of 2.7 years (range, 0.1 to 9.5 years), 165 patients experienced an incident cerebrovascular event after dialysis therapy initiation; 27% of these patients had cerebrovascular disease before dialysis therapy initiation (19% prior stroke). Those with cerebrovascular events during the study were more likely to be older, be men, have lower diastolic blood pressure, and have a history of diabetes mellitus, prior cerebrovascular disease, or prior peripheral vascular disease at baseline than those without subsequent cerebrovascular events. Other common risk factors, such as systolic blood pressure, presence of arrhythmias, presence of left ventricular hypertrophy, and cholesterol level, were not statistically significantly different between the 2 groups. In multivariate Cox proportional hazards regression analysis accounting for the competing risk of death, age, race, ICED score, previous diabetes mellitus, and previous cerebrovascular disease were significantly associated with increased risk of cerebrovascular disease events (Table 2). Results were similar between models that included or excluded CEA as a cerebrovascular event.

Figure 1 shows the characterization of cerebrovascular events. From the 165 patients who experienced an incident event during the study, there were 35 additional repeated events in 29 patients because patients could experience multiple separate events during the course of the study. One hundred sixteen (58%) of these 200 events were ascertained by means of chart adjudication (95 ischemic strokes, 10 hemorrhagic strokes, and 11

**Table 1. Baseline Characteristics of 1,041 Incident Dialysis Patients**

| Characteristic | All Patients (N = 1,041) | Patients Without Cerebrovascular Event (n = 876) | Patients With Cerebrovascular Event (n = 165) | P |
|---|---|---|---|---|
| Age (y) | 58 ± 15 | 57 ± 15 | 62 ± 13 | <0.001 |
| Men | 564 (54) | 490 (56) | 74 (45) | 0.006 |
| Race | | | | 0.9 |
| White | 695 (67) | 585 (67) | 110 (67) | |
| Black | 295 (28) | 249 (28) | 46 (28) | |
| Other | 51 (5) | 42 (5) | 9 (5) | |
| Systolic blood pressure (mm Hg) (n = 944) | 149 ± 19 | 148 ± 19 | 150 ± 18 | 0.3 |
| Diastolic blood pressure (mm Hg) (n = 944) | 79 ± 10 | 79 ± 11 | 76 ± 9 | <0.001 |
| Modality: hemodialysis | 767 (74) | 637 (73) | 130 (79) | 0.1 |
| Tobacco use: current or former (n = 977) | 592 (61) | 498 (60) | 94 (62) | 0.8 |
| Comorbid conditions | | | | |
| Diabetes mellitus | 561 (54) | 447 (51) | 114 (69) | <0.001 |
| Cerebrovascular disease | 176 (17) | 132 (15) | 44 (27) | 0.001 |
| Coronary heart disease | 457 (44) | 382 (44) | 75 (45) | 0.7 |
| Peripheral vascular disease | 270 (26) | 216 (25) | 54 (33) | 0.03 |
| Left ventricular hypertrophy | 259 (24) | 213 (24) | 46 (28) | 0.4 |
| Arrhythmia | 308 (30) | 258 (30) | 50 (30) | 0.9 |
| Valvular disorder | 189 (18) | 153 (18) | 36 (22) | 0.2 |
| Congestive heart failure | 466 (46) | 383 (45) | 83 (51) | 0.2 |
| Index of Coexistent Disease score | 1.94 ± 0.81 | 1.92 ± 0.82 | 2.04 ± 0.77 | 0.08 |
| Total cholesterol (mg/dL) (n = 999) | 189 ± 48 | 188 ± 49 | 193 ± 45 | 0.1 |
| Low-density lipoprotein cholesterol (mg/dL) (n = 872) | 104 ± 40 | 104 ± 40 | 107 ± 41 | 0.3 |
| High-density lipoprotein cholesterol (mg/dL) (n = 867) | 44 ± 17 | 43 ± 17 | 45 ± 16 | 0.4 |
| Triglycerides (mg/dL) (n = 916) | 206 ± 129 | 203 ± 129 | 217 ± 131 | 0.2 |
| Albumin (mg/dL) | 3.62 ± 0.37 | 3.63 ± 0.38 | 3.59 ± 0.36 | 0.2 |
| Corrected calcium-phosphate product (mg²/dL²) | 48.9 ± 12.6 | 49.0 ± 12.8 | 48.3 ± 12.0 | 0.7 |
| Hematocrit (%) | 32.5 ± 4.1 | 32.5 ± 4.1 | 32.3 ± 3.8 | 0.6 |

*Note:* Values expressed as mean ± SD or number (percent). Less than 5% missing unless otherwise noted. *P* values by using Fisher exact test or Mann-Whitney rank sum test. Conversion factors for units: total, low-, and high-density lipoprotein cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129; albumin in g/dL to g/L, ×10; calcium-phosphorus product in mg²/dL² to mmol²/L², ×0.08056355.

CEAs) with 68% agreement from USRDS or HCFA records and 13% from the combination of DCI and comorbidity records. Seventy-seven (39%) events were assigned by using USRDS or HCFA records (8% agreement with the combination of DCI and comorbidity records), and 7 (4%) events were assigned solely by using the combination of DCI and comorbidity records. Fourteen of 105 abstracted stroke events were recurrent strokes.

The majority of the 200 total cerebrovascular events were ischemic strokes. Of the 95 (62%) ischemic strokes available for chart abstraction, the largest proportion of events was cardioembolic in origin at 28%, although other ischemic stroke subtypes also were common. Of 11 CEAs available for chart abstraction, 55% were preceded by symptoms of stroke or transient ischemic attack, whereas the rest were performed for

intraluminal stenosis that was greater than 60%, but asymptomatic. Median stenosis measured by using ultrasonography or angiography was 90% (range, 70% to 99%). The subset of patients with available medical charts for chart abstraction did not differ significantly by demographics, clinical characteristics, or comorbid conditions compared with patients without available medical records (data not shown).

Figure 2 shows the cumulative incidence of first cerebrovascular event type accounting for the competing risk of nonstroke death. Twenty-one percent of patients experienced a cerebrovascular event by the end of the study, with 15% of patients experiencing an ischemic stroke; 3%, a hemorrhagic stroke; and 3%, a CEA. The overall incidence rate of cerebrovascular events was 4.9 events/100 person-years (95% confidence interval, 4.2 to 5.7 events/100 person-years). Al-

**Table 2. Association of Risk Factors With Cerebrovascular Disease Events Among CHOICE Participants**

| Risk Factor | HR (95% CI) of Stroke Without CEA (n = 147) | HR (95% CI) of Stroke or CEA (n = 165) |
|---|---|---|
| Age (/10 y) | 1.26 (1.19-1.34)* | 1.26 (1.19-1.34)* |
| Sex | | |
|   Men | Reference | Reference |
|   Women | 1.04 (0.90-1.21) | 1.04 (0.90-1.21) |
| Race | | |
|   White | Reference | Reference |
|   Black | 0.64 (0.54-0.77)* | 0.64 (0.53-0.76)* |
|   Other | 0.68 (0.50-0.91)† | 0.69 (0.51-0.94)† |
| Modality | | |
|   Hemodialysis | Reference | Reference |
|   Peritoneal dialysis | 1.12 (0.93-1.35) | 1.14 (0.95-1.36) |
| Comorbid conditions | | |
|   Diabetes mellitus | 1.32 (1.13-1.54)* | 1.35 (1.16-1.57)* |
|   Cerebrovascular disease | 1.20 (0.99-1.46) | 1.23 (1.02-1.49)† |
| Index of Coexistent Disease score | | |
|   0 or 1 | Reference | Reference |
|   2 | 1.40 (1.18-1.65)† | 1.35 (1.14-1.59)† |
|   3 | 1.68 (1.39-2.03)* | 1.64 (1.36-1.98)* |

*Note:* Multivariate adjustment accounting for the competing risk of death from causes other than stroke.

Abbreviations: CEA, carotid endarterectomy; CHOICE, Choices for Healthy Outcomes in Caring for End-Stage Renal Disease; CI, confidence interval; HR, hazard ratio.

*$P < 0.001$.

†$P < 0.05$.

though the incidence rate for cerebrovascular events was greatest in the first 2 years after dialysis therapy initiation at 21.0 events/100 person-years, the majority of incident cerebrovascular events occurred after being on dialysis therapy for more than 2 years. Ischemic stroke accounted for the majority of events at all times. The incidence across time was similar for CEA and hemorrhagic stroke.

Nineteen of 176 strokes (10%) occurred in the setting of hospitalization for acute myocardial infarction (8) and/or a cardiovascular disease
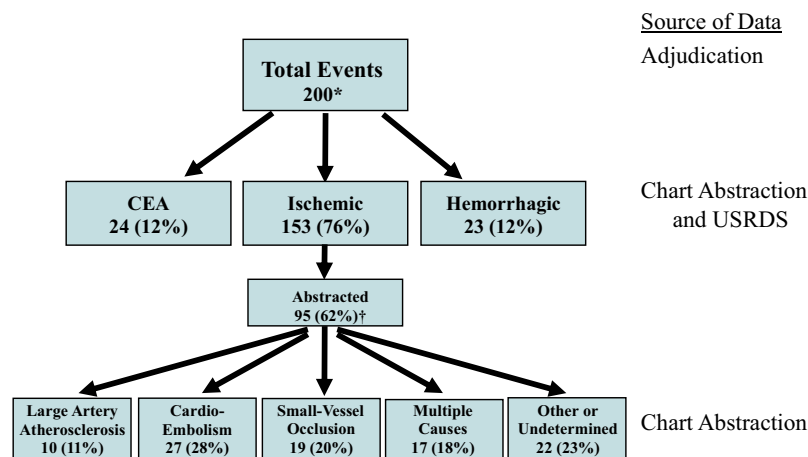


**Figure 1.** Cerebrovascular event classification in 1,041 incident dialysis patients. The number of each cerebrovascular event, including recurrent events, is shown. Event types were determined from *International Classification of Diseases, Ninth Revision* codes and chart abstraction. Ischemic stroke subtypes were defined using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system by 2 abstractors. *Of 165 patients, 35 had repeated events. †No statistically significant differences from nonabstracted patients with regard to demographics, comorbid conditions, or baseline laboratory results. Abbreviations: CEA, carotid endarterectomy; USRDS, US Renal Data System.
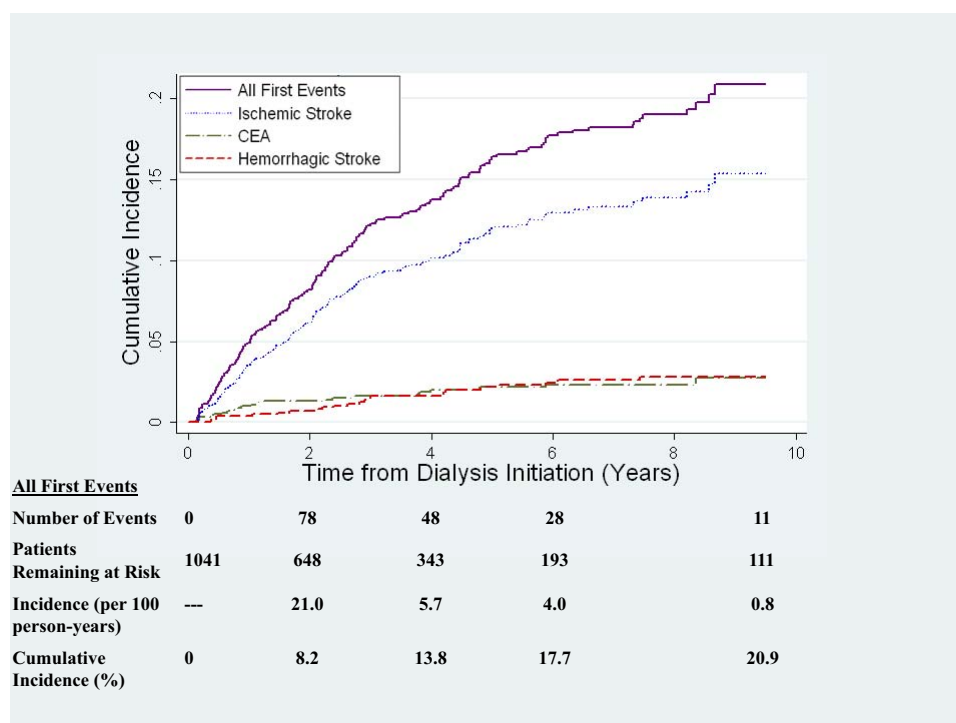
| All First Events | | | | | |
|---|---|---|---|---|---|
| Number of Events | 0 | 78 | 48 | 28 | 11 |
| Patients Remaining at Risk | 1041 | 648 | 343 | 193 | 111 |
| Incidence (per 100 person-years) | --- | 21.0 | 5.7 | 4.0 | 0.8 |
| Cumulative Incidence (%) | 0 | 8.2 | 13.8 | 17.7 | 20.9 |

**Figure 2.** Cumulative incidence of cerebrovascular events in incident dialysis patients accounts for the competing risk of death from causes other than stroke. Abbreviation: CEA, carotid endarterectomy.

procedure (3 coronary artery bypass surgeries, 1 percutaneous transluminal coronary angioplasty, 4 nontraumatic amputations, 2 peripheral bypass surgeries, and 2 CEAs). For the 90 abstracted strokes that occurred in hemodialysis patients, 10 occurred during the dialysis session, 17 occurred on the same day as the dialysis procedure, 35 occurred on a nondialysis day, and 28 occurred at a remote indeterminate time from the last dialysis.

Table 3 lists presentation and follow-up characteristics of strokes in CHOICE. Overall, the time from stroke symptom onset to presentation was long (median, 8.5 hours; 25th and 75th percentiles, 1 and 42), but shortest for cardioembolic and hemorrhagic causes of stroke (median times, 2.5 hours). Stroke from multiple causes and small-vessel occlusion had the longest times to presentation (median, 13 and 18 hours, respectively). Median hospital stay for all events was 6 days. Stroke from small-vessel occlusion and hemorrhagic stroke had the shortest lengths of stay at a median of 3.5 days, whereas strokes

**Table 3.  Stroke Presentation and Follow-up Characteristics in Incident Dialysis Patients**

| | Median Time From Symptoms to Presentation (h) | Median Hospital Stay (d) | Case-Fatality (%) | Successful Recovery (% discharged to home or acute rehabilitation) |
|---|---|---|---|---|
| Stroke overall (n = 105) | 8.5 (1, 42) | 6 (3, 13) | 35 | 56 |
| Ischemic stroke (n = 95) | 11 (1, 48) | 7 (4, 13) | 28 | 54 |
| Large artery | 7.5 (3, 13) | 10.5 (5, 14) | 29 | 56 |
| Cardioembolism | 2.5 (1, 16) | 9 (6, 17) | 36 | 54 |
| Small-vessel occlusion | 18 (6, 48) | 3.5 (3, 7) | 17 | 78 |
| Multiple causes | 13 (1, 72) | 7 (4, 15) | 41 | 41 |
| Other/undetermined | 4 (1, 48) | 6 (3, 13) | 19 | 70 |
| Hemorrhagic stroke (n = 10) | 2.5 (1, 19) | 3.5 (1, 9) | 90 | 10 |

*Note:* Values in parentheses are 25th, 75th percentiles. Data from strokes that were chart abstracted.

from cardioembolism and large-artery atherosclerosis had the longest lengths of stay at 9 and 10.5 days, respectively. Thirty-five percent of all events were fatal, 28% of ischemic strokes were fatal, and 90% of hemorrhagic strokes were fatal. Overall, 56% of patients who experienced a stroke were able to be discharged to home or acute rehabilitation, with the best recovery seen in those with small-vessel occlusion (78% discharge rate). However, only 10% of patients with hemorrhagic stroke were able to be discharged to home or acute rehabilitation. Baseline dialysis modality was not associated with significant differences in stroke etiologic subtype ($P = 0.6$), time from symptom onset to presentation ($P = 0.09$), length of hospital stay ($P = 0.2$), or discharge location ($P = 0.5$).

## DISCUSSION

In this national prospective cohort study of patients initiating dialysis therapy for end-stage renal disease, cerebrovascular events, including fatal and nonfatal clinical stroke and CEA, occurred 10 times more frequently than in the general population,[8,17] with an incidence rate of 4.9 events/100 person-years. The majority of events were related to ischemic stroke, with cardioembolic stroke the most common form of ischemic stroke in dialysis patients. To our knowledge, this is 1 of the first studies to classify ischemic stroke in dialysis patients into etiologic subtypes based on TOAST criteria.[12] This allows us to potentially alter our stroke prevention strategies from those used in the general population. We found that dialysis patients with stroke present late after symptom onset, leaving little room for early interventions. Dialysis patients also have high fatality and low recovery rates. Dialysis patients and their families may need better education about stroke warning signs and symptoms and encouragement to bring these symptoms to their providers' attention quickly.

We found that ischemic stroke was more common than hemorrhagic stroke in our national US dialysis cohort. This is consistent with a prior study relying on national administrative data.[2] Few other studies have characterized stroke types, except for a Japanese cohort of 151 patients, in whom hemorrhagic stroke was the most common type of stroke.[18] Causes of hemorrhagic stroke may differ from ischemic stroke in patients on

long-term dialysis therapy and thus acquired risk factors could account for this later hemorrhagic stroke risk. Reasons could include excess vascular calcification and stiffness,[19,20] leading to worsening hypertension. This, combined with use of anticoagulation on dialysis therapy, could increase hemorrhagic stroke.

For ischemic stroke, cardioembolism was the most common subtype, although all ischemic stroke subtypes were well represented. In addition to preventing vascular calcification and arterial stiffness, treatment of underlying cardiac disease at dialysis therapy initiation may mitigate future stroke risk in this high-risk population. The use of aspirin in dialysis patients has been associated with a reduced risk of stroke, but the overall strength of this association was modest, as noted in the international Dialysis Outcomes and Practice Patterns Study (DOPPS).[21] Baseline cardioembolism risk factors in our study, such as arrhythmias, left ventricular hypertrophy, valvular disease, and congestive heart failure, were not significantly different between individuals who experienced a cerebrovascular event versus those who did not in our cohort, suggesting that these aspects may not be correctly identified in dialysis patients. Measurement of cardiac function by means of echocardiography has been suggested[22] for all patients initiating dialysis therapy because of its more accurate assessment than physical examination and chest radiography in identifying cardiac dysfunction and valvular disease. Furthermore, arrhythmias are common in dialysis patients, and early recognition and treatment of these arrhythmias may also reduce the risk of stroke. Use of other prevention measures, such as statins, was not associated with decreased risk of stroke in prevalent diabetic hemodialysis patients in the Die Deutsche Diabetes Dialyse (4D) study.[23] Whether similar findings hold for incident dialysis patients is unclear.

Median time to presentation was more than 8 hours, much longer than that observed in a systematic review of the literature on all strokes,[24] signifying symptoms of stroke may be missed by providers and/or patients. This is especially problematic because patients on hemodialysis therapy have regular access to the health care system. With this delay in presentation, any benefit from earlier interventions in this population, such as

thrombolytic use,[25] may not be practiced, thus worsening mortality and morbidity after stroke. Improved education about symptoms of transient ischemic attack or stroke, such as numbness, weakness, confusion, or difficulty speaking, should be given to dialysis patients and their families. One might suspect that stroke is more common during or immediately after a dialysis session because of changes in cerebral blood flow.[6] In a study by Toyoda et al,[18] 34% of ischemic brain infarcts occurred within 30 minutes of the dialysis procedure. Thirty percent of abstracted strokes in this study occurred either during the dialysis session or several hours later, although this timing was not statistically different from events that occurred on a nondialysis day. A larger study may need to be undertaken to observe any temporal trends.[26]

Outcomes after stroke, especially hemorrhagic stroke, were poor, with a high case-fatality and low successful recovery rate. Based on this study, for every 100 dialysis patients who have a stroke, 35 will die within 30 days and only 56 of the 100 patients will be able to go home or to an acute rehabilitation facility. Although this low successful recovery rate is similar to that found in an earlier single-center cohort of prevalent hemodialysis patients followed up in New York,[27] it is inferior to the 10% adjusted stroke case-fatality rate seen in the Atherosclerosis Risk in Communities (ARIC) cohort[28] and the 20% of patients requiring institutional care in the general population.[28] This likely reflects the comorbid conditions that our patients on dialysis therapy accumulated before they experienced a stroke. The overall length of hospital stay surprisingly was similar to that observed in the general population by using the National Hospital Discharge Survey.[29] This implies that practice patterns of poststroke care, including evaluation, management, and disposition, may be similar across populations.

As a national prospective cohort study with characteristics similar to the 1997 US dialysis population, results of this study may be generalizable to the population of patients initiating dialysis therapy. The follow-up of up to 9.5 years in this study also allowed for evaluation of changing stroke causes over time on dialysis therapy. Our ability to have such lengthy follow-up with well-described characteristics and events is a unique aspect of this study.

This study has some limitations that deserve mention. We had a relatively small number of cerebrovascular events, which limited our ability to evaluate specific risk factors for stroke subtypes. We also did not have medical records for all stroke events to classify stroke; however, the subset of the population with medical records of the stroke event did not differ from those with no medical record. In cases in which a chart was not available, use of administrative data might not necessarily reflect an admission for an acute cerebrovascular event. In addition, CEA potentially could involve referral bias and thus may not represent an acute event; however, CEA events that we were able to abstract involved symptomatic disease or significant intraluminal stenosis, suggesting that these events were indicative of clinically meaningful cerebrovascular disease.

We conclude that cerebrovascular events are common in patients initiating dialysis therapy. Dialysis-related risk factors for all types of cerebrovascular events may differ by the type of event and timing of event after dialysis therapy initiation. This classification of cerebrovascular event types may help focus our efforts to better treat and prevent recurrence of stroke, thereby improving the prognosis of dialysis patients. Additional studies to understand the pathophysiological characteristics, prevention, and treatment of cerebrovascular disease in patients with end-stage renal disease need to focus on subclinical disease, including cognitive function,[30] cerebral white matter changes,[31] and subclinical strokes,[3] as well as imaging techniques with magnetic resonance imaging to earlier identify cerebrovascular disease.

The manuscript's contents are solely the responsibility of the authors and do not necessarily represent the official view of National Center for Research Resources (NCRR) or National Institutes of Health (NIH). Some of the data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

*Support:* Dr Sozio was supported by KL2RR025006 from the NCRR, a component of the NIH, and the NIH Roadmap for Medical Research. Dr Coresh was supported by Grants R21DK067651 and U01DK067651, Dr Powe was supported by Grant K24DK002643, and Dr Parekh was supported by Grants U01DK057304 and R01DK072367 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). CHOICE was supported by Grant RO1HL62985 from the National Heart, Lung, and Blood Institute, NIDDK Grant RO1DK059616, and Grant R01HS008365 from the Agency for Health Care Research and Quality.

*Financial Disclosure:* None.

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