Inflammatory Markers and Risk of Cerebrovascular Events in Patients Initiating Dialysis


Summary

Background and objectives Stroke remains a leading cause of morbidity and mortality for patients on dialysis; however, its risk factors in this population and measures to prevent it are not well understood.

Design, setting, participants, & measurements We investigated whether inflammation was associated with cerebrovascular events in a national US cohort of 1041 incident dialysis patients enrolled from October 1995 to June 1998 and followed until January 31, 2004. Incident cerebrovascular events were defined as nonfatal (hospitalized stroke, carotid endarterectomy) and fatal (stroke death) events after dialysis initiation. With Cox proportional hazards regression analysis accounting for the competing risk of nonstroke death, we assessed the independent event risk associated with baseline levels of multiple inflammatory markers (high-sensitivity C-reactive protein [hsCRP], interleukin-6 (IL-6), matrix metalloproteinase-3 [MMP-3], and P-selectin) and hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) use, which may have pleiotropic inflammatory effects.

Results 165 patients experienced a cerebrovascular event during 3548 person-years of follow-up; overall incidence rate was 4.9/100 person-years. None of the inflammatory markers were associated with cerebrovascular event risk (adjusted hazard ratios [HRs] per log unit [95% confidence interval]: hsCRP, 0.97 [0.85 to 1.11]; IL-6, 1.04 [0.85 to 1.26]; MMP-3, 1.02 [0.70 to 1.48]; P-selectin, 0.98 [0.57 to 1.68]). Statin use was also not associated with significant risk of events in unadjusted (HR 1.07 [0.69 to 1.68]) or propensity-score adjusted analyses (HR 0.98 [0.61 to 1.56]).

Conclusions In conclusion, neither inflammatory markers nor statin use was associated with risk of cerebrovascular events. Further studies are needed to understand the pathophysiology and prevention of stroke in patients on dialysis.


Introduction

In the dialysis population, there are few studies of cerebrovascular disease despite incident dialysis patients being at three to nine times greater risk for strokes than patients without renal failure (1). Even though traditional risk factors for cerebrovascular disease are common, there are also risk factors unique to the uremic process (2–6) that may predispose individuals on dialysis to cerebrovascular events. Inflammation is thought to be an important nontraditional mediator of coronary atherosclerosis in patients with ESRD (7), but the effects on cerebrovascular disease are unknown.

The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial found that patients with inflammation who were treated with rosuvastatin had a 48% lower risk of stroke (8). Via its possible pleiotropic effects on reducing inflammation (9) or effects in reducing cholesterol, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) have been shown to reduce incident (10) and recurrent (11) risk of stroke in those without chronic kidney disease (CKD). However, prevalent diabetic hemodialysis patients in the Die Deutsche Diabetes Dialyse (4D) trial had an unexpected higher (although statistically nonsignificant) rate of stroke when treated with statins than placebo (12). It is unclear whether statins initiated earlier in the process of ESRD would have similar effects. The aims of our study were to determine whether markers of inflammation are associated with increased risk of cerebrovascular events in patients initiating dialysis and whether use of statins is associated with decreased risk of cerebrovascular disease.

Materials and Methods

Study Design

The study participants were from the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study (13). This national prospective cohort study of incident dialysis patients was initiated to investigate...
treatment choices and clinical outcomes in dialysis care. The Johns Hopkins University School of Medicine Institutional Review Board and the clinical centers’ review boards approved the study, and all participants provided informed consent. A total of 1041 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 kidney transplantation or December 31, 2004. A main outcome in CHOICE was any cardiovascular event; all cerebrovascular events underwent evaluation in CHOICE. The primary outcome of this ancillary investigation was the first cerebrovascular event after dialysis initiation, including ischemic stroke, hemorrhagic stroke, or carotid endarterectomy. Assignment of cerebrovascular events in CHOICE has been described previously (14), and was based primarily upon review of adjudicated records by a Cardiovascular Disease Endpoints committee.

Data on patient demographics and medical history were collected from a self-report questionnaire. Baseline individual comorbidities were abstracted from dialysis unit records, hospital discharge summaries, medication lists, consultation notes, diagnostic imaging, and cardiac imaging reports. Statin use at baseline was determined by review of dialysis clinic notes, hospital discharge summaries, and computerized order entry records (15).

Baseline nonfasting venous blood specimens were routinely collected at the DCI facilities just before a dialysis session. Laboratory values were obtained from monthly dialysis laboratory tests or sent to Quest Diagnostics (Baltimore, MD). A 0–80°C specimen bank was established to store blood samples from the DCI enrollees, with specimens obtained for 895 (97%) of the DCI participants. High-sensitivity C-reactive protein (hsCRP) (high sensitivity ELISA, coefficient of variation (CV) 8.9%), IL-6 (ultrasensitive ELISA, CV 7%), matrix metalloproteinase 3 (MMP-3) (ultrasensitivity ELISA, CV 10.7%), and P-selectin (ultrasensitive ELISA, CV 8.9%) were measured at the Laboratory for Clinical Biochemistry Research at University of Vermont (Colchester, VT). Longitudinal hsCRP were also measured on specimen bank samples approximately 6 months apart, with 5079 total (baseline and repeated) measures.

Statistical Methods
Baseline characteristics between those individuals who suffered a cerebrovascular event after dialysis initiation were compared with those individuals who did not using Cox proportional hazards regression analysis. Follow-up time was defined as the period from initiation of dialysis to cerebrovascular event occurrence, with death and transplantation in these analyses treated as censored events. The unadjusted incidence rate of cerebrovascular events was calculated using Poisson regression.

Cox proportional hazards regression analysis was also used to assess the risk of cerebrovascular events associated with markers of inflammation, with staggered entry to allow for the times at which inflammatory markers were measured. Patients were censored for kidney transplantation (n = 253) or last follow-up on December 31, 2004 (n = 112). Because the occurrence of death from causes other than stroke (n = 511) 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 (16). Cause-specific hazard ratios (HRs) of cerebrovascular events were calculated from these competing risk models (17).

To assess for linear and nonlinear effects, the inflammatory markers were analyzed both as log-transformed continuous variables and by quartiles of each marker. In multivariate models, we adjusted for potential confounders, which were identified by assessing the relation between each variable and log-transformed hsCRP, as well as risk of cerebrovascular events (P ≤ 0.2 for both associations). Clinically relevant variables that did not meet these statistical criteria (such as race) were still included. Missing covariates occurred with frequency ≤ 20% (mean 2%); multivariate imputation by chained equations was used for these missing covariates to give the least biased estimates (18,19). Imputation was not performed on the inflammatory markers.

We conducted a number of sensitivity analyses to account for potential biases and interaction. For individuals with repeated hsCRP measures, we used time-dependent Cox models, updating the most recent laboratory value in a staggered re-entry fashion. We repeated the main analyses excluding individuals with missing data. We stratified by baseline dialysis modality, prior atherosclerotic cardiovascular disease (ASCVD), and prior stroke. We also examined the risk of stroke alone, excluding carotid endarterectomy, and examined the risk of ischemic stroke alone. We examined the risk of fatal and nonfatal events separately. Finally, we included all inflammatory covariates in the final model and performed a Wald nonlinear test across the markers with the P value estimated by the delta method.

Cox proportional hazards regression analysis was also used to determine the association of statin use with risk of cerebrovascular events. To adjust for the multiple factors related to statin use, a propensity-score–based approach was undertaken as described previously (20).

In the final analysis, we accounted for the interaction of inflammation and statins by calculating the hazard of cerebrovascular events associated with each inflammatory marker stratifying by baseline statin use. Because the propensity score also accounts for many risk factors related to cerebrovascular disease, the adjusted model included only demographic factors, statin use, and propensity score.

A two-sided P value < 0.05 was used as the level of statistical significance for all of the tests. Analyses were performed using Stata SE 9.2 (StataCorp, College Station, TX).

Results
Patient Characteristics
Baseline characteristics are presented in Table 1. Age, gender, race, and dialysis modality distributions were similar to that of the 1997 United States dialysis population (21). Fifty-seven percent of patients had ASCVD at study
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 1041)</th>
<th>Patients without Cerebrovascular Event (n = 876)</th>
<th>Patients with Cerebrovascular Event (n = 165)</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 15</td>
<td>57 ± 15</td>
<td>62 ± 13</td>
<td>1.31 (1.17 to 1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>564 (54)</td>
<td>490 (56)</td>
<td>74 (45)</td>
<td>0.73 (0.54 to 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>695 (67)</td>
<td>585 (67)</td>
<td>110 (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>black</td>
<td>295 (28)</td>
<td>249 (28)</td>
<td>46 (28)</td>
<td>0.66 (0.47 to 0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>other</td>
<td>51 (5)</td>
<td>42 (5)</td>
<td>9 (5)</td>
<td>0.75 (0.38 to 1.48)</td>
<td>0.4</td>
</tr>
<tr>
<td>Systolic BP (mmHg) (n = 944)</td>
<td>149 ± 19</td>
<td>148 ± 19</td>
<td>150 ± 18</td>
<td>0.99 (0.94 to 1.06)</td>
<td>0.9</td>
</tr>
<tr>
<td>Diastolic BP (mmHg) (n = 944)</td>
<td>79 ± 10</td>
<td>79 ± 11</td>
<td>76 ± 9</td>
<td>0.73 (0.66 to 0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure (mmHg) (n = 944)</td>
<td>70 ± 15</td>
<td>69 ± 15</td>
<td>74 ± 16</td>
<td>1.13 (1.06 to 1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modality: hemodialysis</td>
<td>767 (74)</td>
<td>637 (73)</td>
<td>130 (79)</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Tobacco use: current/former (n = 977)</td>
<td>592 (61)</td>
<td>498 (60)</td>
<td>94 (62)</td>
<td>1.23 (0.88 to 1.70)</td>
<td>0.2</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>561 (54)</td>
<td>447 (51)</td>
<td>114 (69)</td>
<td>2.04 (1.47 to 2.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>any ASCVD</td>
<td>593 (57)</td>
<td>482 (55)</td>
<td>111 (67)</td>
<td>1.85 (1.34 to 2.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cerebrovascular disease</td>
<td>176 (17)</td>
<td>132 (15)</td>
<td>44 (27)</td>
<td>2.18 (1.54 to 3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>coronary heart disease</td>
<td>457 (44)</td>
<td>382 (44)</td>
<td>75 (45)</td>
<td>1.29 (0.95 to 1.75)</td>
<td>0.1</td>
</tr>
<tr>
<td>peripheral vascular disease</td>
<td>270 (26)</td>
<td>216 (25)</td>
<td>54 (33)</td>
<td>1.63 (1.18 to 2.26)</td>
<td>0.003</td>
</tr>
<tr>
<td>left ventricular hypertrophy</td>
<td>259 (24)</td>
<td>213 (24)</td>
<td>46 (28)</td>
<td>1.13 (0.81 to 1.59)</td>
<td>0.5</td>
</tr>
<tr>
<td>arrhythmia</td>
<td>308 (30)</td>
<td>258 (30)</td>
<td>50 (30)</td>
<td>1.20 (0.86 to 1.68)</td>
<td>0.3</td>
</tr>
<tr>
<td>valvular disorder</td>
<td>189 (18)</td>
<td>153 (18)</td>
<td>36 (22)</td>
<td>1.46 (1.01 to 2.11)</td>
<td>0.05</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>466 (46)</td>
<td>383 (45)</td>
<td>83 (51)</td>
<td>1.50 (1.10 to 2.04)</td>
<td>0.009</td>
</tr>
<tr>
<td>Index of coexistent disease score</td>
<td>1.94 ± 0.81</td>
<td>1.92 ± 0.82</td>
<td>2.04 ± 0.77</td>
<td>1.33 (1.16 to 1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl) (n = 999)</td>
<td>189 ± 48</td>
<td>188 ± 49</td>
<td>193 ± 45</td>
<td>1.00 (0.98 to 1.03)</td>
<td>0.7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl) (n = 872)</td>
<td>104 ± 40</td>
<td>104 ± 40</td>
<td>107 ± 41</td>
<td>1.00 (0.97 to 1.03)</td>
<td>0.9</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl) (n = 867)</td>
<td>44 ± 17</td>
<td>43 ± 17</td>
<td>45 ± 16</td>
<td>1.04 (0.97 to 1.11)</td>
<td>0.3</td>
</tr>
<tr>
<td>Triglycerides (mg/dl) (n = 916)</td>
<td>206 ± 129</td>
<td>203 ± 129</td>
<td>217 ± 131</td>
<td>1.00 (0.99 to 1.01)</td>
<td>0.3</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.62 ± 0.37</td>
<td>3.63 ± 0.38</td>
<td>3.59 ± 0.36</td>
<td>0.65 (0.44 to 0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Corrected calcium phosphate product (mg²/dl²)</td>
<td>48.9 ± 12.6</td>
<td>49.0 ± 12.8</td>
<td>48.3 ± 12.0</td>
<td>1.00 (0.96 to 1.04)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32.5 ± 4.1</td>
<td>32.5 ± 4.1</td>
<td>32.3 ± 3.8</td>
<td>1.00 (0.97 to 1.03)</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>statins</td>
<td>143 (14)</td>
<td>120 (14)</td>
<td>23 (14)</td>
<td>1.07 (0.69 to 1.67)</td>
<td>0.8</td>
</tr>
<tr>
<td>antihypertensives</td>
<td>843 (81)</td>
<td>709 (81)</td>
<td>134 (81)</td>
<td>0.94 (0.64 to 1.39)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

To convert total, LDL, and HDL cholesterol in mg/dl to mmol/L, multiply by 0.02586; to convert triglycerides in mg/dl to mmol/L, multiply by 0.01129; to convert albumin in g/dl to g/L, multiply by 10; to convert calcium-phosphate product in mg²/dl² to mmol²/L², multiply by 0.0805355. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval.

- Hazard ratio of cerebrovascular event censoring for death. For age, blood pressure, cholesterol, and calcium-phosphate product, the HR reflects per 10-unit change.
- For all variables, the HR reflects per 10-unit change.
- \( p \) values by Cox proportional hazards model.

The table includes variables such as age, gender, race, systolic and diastolic blood pressure, pulse pressure, modality, tobacco use, comorbidities including diabetes mellitus, any ASCVD, cerebrovascular disease, coronary heart disease, peripheral vascular disease, left ventricular hypertrophy, arrhythmia, valvular disorder, congestive heart failure, and index of coexistent disease score. Additionally, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, albumin, corrected calcium phosphate product, and hematocrit are also presented. Baseline medication use includes statins and antihypertensives. The table compares characteristics between patients without and with cerebrovascular events, along with unadjusted hazard ratios and \( p \) values.
entry, with 17% having a history of cerebrovascular disease. During a total of 3548 person-years and a median follow-up of 2.7 years (range, 0.1 to 9.5 years), a total of 165 patients experienced a cerebrovascular event after dialysis initiation yielding an incidence rate of 4.9 per 100 person-years (95% confidence interval [CI], 4.2 to 5.7). Of these first events, 121 were ischemic strokes, 23 were hemorrhagic strokes, and 21 were carotid endarterectomies. Those with cerebrovascular events during the study were more likely to be older and female, have a higher pulse pressure, and have a history of diabetes mellitus, prior cerebrovascular disease, or prior peripheral vascular disease at baseline than those without subsequent cerebrovascular events. Statins were prescribed in 143 (14%) of the patients at baseline.

Figure 1 shows the baseline distributions of hsCRP, IL-6, MMP-3, and P-selectin. Although normal values have not been established, 56% of patients with measured hsCRP and 78% of patients with measured IL-6 had a level considered “abnormal,” defined by the 75th percentile of hsCRP (0.47 mg/dl) in the National Health And Nutrition Examination Survey (NHANES III) (22) and the 75th percentile of IL-6 (3.09 pg/ml) in the Health, Aging, and Body Composition study (23).

Risk of Cerebrovascular Events with Inflammation

Table 2 shows the hazard ratios associated with cerebrovascular events for each of the inflammatory markers. There was no statistically significant increased risk associated with a logarithmic difference in any of the inflammatory markers, either at baseline (all markers) or time-varying (hsCRP only). Analyzing nonlinear effects, those at the highest quartile of IL-6 were at a moderately increased risk of cerebrovascular events in unadjusted analysis (HR, 1.70; 95% CI, 1.06 to 2.74) compared with the lowest quartile, but this association was no longer statistically significant after adjustment for demographic factors, and there was no linear trend noted. For the remainder of the inflammatory markers, there was no statistically-significant association between any of the quartiles of inflammatory markers and risk of cerebrovascular events. Those at the highest quartile of each inflammatory marker had similar risk to those in the lowest quartile, with or without adjustment for basic demographics and clinical factors.

There were also no significant interactions for risk of cerebrovascular events between the inflammatory markers and dialysis modality ($P_{interaction}$, 0.22 to 0.38), between the inflammatory markers and prior ASCVD ($P_{interaction}$, 0.57 to 0.98), or between the inflammatory markers and prior stroke ($P_{interaction}$, 0.71 to 0.96). When analyzing for stroke without carotid endarterectomy, the results were similar and remained statistically nonsignificant (see Supplemental Table 1). Among those with ischemic stroke only, the results were again similar in magnitude and remained nonstatistically significant. Analyzing by vital status (fatal or nonfatal stroke) and those individuals only with complete data (excluding imputed data) also yielded similar results in direction and magnitude (data not

Figure 1. | Distribution of baseline inflammatory markers in incident dialysis patients. Markers measured a median of 1.22 to 1.35 months after study enrollment. For hsCRP, $n = 866$. For IL-6, $n = 865$. For MMP-3, $n = 818$. For P-selectin, $n = 819$. *Above the linear range of the assay. IQR, interquartile range.
shown). Finally, when including all of the inflammatory markers together in the final model, our model $P$ value was 0.91 for a Wald nonlinear test across the markers.

**Risk of Cerebrovascular Events with Statin Use**

Figure 2 shows the unadjusted cumulative incidence curves for the first cerebrovascular event after dialysis initiation stratified by baseline statin use, after accounting for the competing risk of nonstroke death. A cumulative incidence of 21.8% of patients on statins experienced a cerebrovascular event after dialysis initiation, whereas 20.6% of patients not on statins experienced a cerebrovascular event. In unadjusted analysis, statin use was not associated with a risk of cerebrovascular events, with a HR of 1.07 (95% CI, 0.69 to 1.68). Adjustment for demographics and quintiles of propensity to use statins score, although slightly attenuating the risk, continued to show no significant association (HR, 0.98; 95% CI, 0.61 to 1.56). Analyzing by type of cerebrovascular event (carotid endarterectomy, or ischemic or hemorrhagic stroke) and vital status (fatal or nonfatal stroke) yielded similar results in direction and magnitude (data not shown).

Table 3 shows the joint effect of inflammation and statin use on the risk of cerebrovascular events. There were no statistically significant associations of any of the markers of inflammation with cerebrovascular events, either in those taking statins or in those not taking statins. In addition, statin use did not appear to modify the relationship between inflammation and cerebrovascular events.

**Discussion**

In this national prospective cohort study of patients initiating dialysis, baseline markers of inflammation and use of statins did not appear to be associated with increased or decreased risk of cerebrovascular events. No statistically significant associations emerged, despite examination of multiple inflammatory markers, including both early and late markers of inflammation; having an overall cerebrovascular event incidence rate of 4.9 per 100 person years, which is 10 times higher than that in the
general population (24,25); and following participants for up to 9.5 years. In the elderly nondialysis population, inflammatory markers have been associated with an increased risk of clinical stroke and subclinical stroke (26,27). Markers of the inflammatory cascade may reflect very early endothelial disease, such as the MMP-3 and P-selectin, or may capture the burden of inflammation and the combined late downstream effect of inflammation, such as IL-6 and hsCRP (28). Among dialysis patients, hsCRP and IL-6 have been associated with twice the risk of sudden cardiac death (29) and 1.43-fold higher risk of cardiovascular mortality (30). There have been few studies of the effects of inflammation exclusively on cerebrovascular disease in the dialysis population. Using administrative data with single measurements, Seliger et al. (6) noted that higher mean BP and malnutrition were associated with risk of incident stroke. However, they were unable to test the hypothesis of inflammation as a risk of stroke per se but instead demonstrated that low albumin was associated with poor outcomes. In our study, we were able to specifically capture multiple markers of the inflammatory cascade and analyze the risk associated with stroke, and observed no associations for hsCRP, IL-6, MMP-3, or P-selectin.

Despite the cardiovascular benefit of statins seen in those with inflammation in the general population, we demonstrate no attributable benefit of statins with respect to cerebrovascular events, even after taking into account indications for prescription differences in statins, several different definitions of cerebrovascular events (both broad and narrow), and the joint effect of statins with inflammation. In the most recent Study of Heart and Renal Protection trial, there was an overall major atherosclerotic event reduction for statins among those with CKD but not among the subgroup on dialysis and no benefit seen for fatal stroke in either CKD or dialysis patients (31). The 4D clinical trial demonstrated no benefit for overall cardiovascular disease and a potentially two-fold higher rate of fatal stroke among diabetic hemodialysis patients treated with a statin (12). In addition, the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) found no overall cardiovascular benefit of rosuvastatin in prevalent hemodialysis patients, with a 17% nonsignificant increased risk of nonfatal strokes (32). We did not observe a similar increased risk of stroke in those taking statins. We also observed no significant interaction between statin use and any of the inflammatory markers, arguing against pleotropic cerebrovascular benefits of statins in dialysis patients.

Without inflammation as a proven cerebrovascular risk factor for patients on dialysis, the greater risk of stroke in dialysis patients compared with the general population still needs to be explained. We previously reported that age, race, and comorbidity were some of the strongest risk factors for stroke in the dialysis population (14), and a study by Tripepi et al. (5) reports that traditional stroke risk factors account for the majority of the risk. For patients on dialysis, clinical factors such as change in volume status,
Although our point estimates for the ability to fully evaluate specific risk factors for stroke and cerebrovascular events was also relatively small, limiting our ability to comprehensively capture changes (38), and subclinical strokes (39), as well as imaging techniques with magnetic resonance imaging to earlier identification of cerebrovascular disease, with similar results across all definitions. Because of the lengthy follow-up, we also observed more cerebrovascular events than seen in the 4D (12), JUPITER (8), or AURORA studies (32). Another limitation of this study is that most exposure factors, such as inflammation and statin use, were measured at baseline, which may not reflect later levels. We did use multiple inflammatory markers and added time-varying models for hsCRP yielding similar results, but most of the analytes were only measured once. Although the stability and low coefficient of variation of several of the inflammatory markers have been previously described (36), a concern does exist that these markers were measured in frozen samples. Misclassification of statin use can also result in bias of these results; the bias would likely be even further to the null if patients prescribed statins discontinued their medications or if subjects originally not taking statins subsequently began them. The best answer to the question of whether statins offer protection from stroke in incident dialysis patients, with or without inflammation, would only come from additional randomized controlled trials.

The lengthy follow-up and well-described characteristics and events are unique strengths of this study. As a national prospective cohort study, the results of this study likely are generalizable to the population of patients initiating dialysis. The extensive follow-up in this study also allowed for evaluation of stroke over a long period of time. Because nonstroke death was a much more common event than stroke, we also accounted for this competing risk of death from other causes.

**Conclusions**

Statin use and inflammation among incident dialysis patients do not appear to be associated with either increased or decreased risk of cerebrovascular events. Further studies are needed to understand the pathophysiology, prevention, and treatment of cerebrovascular disease in ESRD, with additional focus on subclinical disease, including cognitive function (37), cerebral white matter changes (38), and subclinical strokes (39), as well as imaging techniques with magnetic resonance imaging to earlier identify cerebrovascular disease.

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BP, and cardiac function (5) have the potential to account for some of the additional increased stroke risk in this population. Hypertension is highly prevalent in dialysis patients, but only 30% are adequately controlled (33). Hypertension is also one of the strongest and most studied risk factors for stroke in the general population (34). In our study, 81% of patients were on antihypertensive medications, and study patients had a mean BP of 149/79 mmHg. The optimal BP goals pre- and postdialysis to reduce the risk of stroke are still unknown.

Another potential risk factor altering cerebral flow is increasing vascular calcification, which involves a dynamic process for patients with kidney disease (35) and may lead to increased arterial stiffness. The effects of decreased compliance caused by calcification may be exacerbated by perfusion changes that occur on dialysis. In fact, hemodialysis therapy itself may result in a 13% to 32% reduction in cerebral blood flow velocity (4). Thus, preventing vascular calcification and arterial stiffness may be another focus of long-term stroke prevention in dialysis patients.

This study has some limitations that deserve mention. Several of our measures, such as left ventricular hypertrophy, required trained nurse abstraction of available records and thus could have resulted in misclassification in the case of incomplete records. The total number of cerebrovascular events was also relatively small, limiting our ability to fully evaluate specific risk factors for stroke and each of its subtypes. Although our point estimates for associations were near the null, the CIs caused by this smaller sample size could hide clinically relevant associations, especially when accounting for individual subtypes of stroke. However, we used both broad and narrow definitions of cerebrovascular disease, with similar results across all definitions. Because of the lengthy follow-up, we also observed more cerebrovascular events than seen in the 4D (12), JUPITER (8), or AURORA studies (32). Another limitation of this study is that most exposure factors, such as inflammation and statin use, were measured at baseline, which may not reflect later levels. We did use multiple inflammatory markers and added time-varying models for hsCRP yielding similar results, but most of the analytes were only measured once. Although the stability and low coefficient of variation of several of the inflammatory markers have been previously described (36), a concern does exist that these markers were measured in frozen samples. Misclassification of statin use can also result in bias of these results; the bias would likely be even further to the null if patients prescribed statins discontinued their medications or if subjects originally not taking statins subsequently began them. The best answer to the question of whether statins offer protection from stroke in incident dialysis patients, with or without inflammation, would only come from additional randomized controlled trials.

The lengthy follow-up and well-described characteristics and events are unique strengths of this study. As a national prospective cohort study, the results of this study likely are generalizable to the population of patients initiating dialysis. The extensive follow-up in this study also allowed for evaluation of stroke over a long period of time. Because nonstroke death was a much more common event than stroke, we also accounted for this competing risk of death from other causes.
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Disclosures
None.

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