Risk Factors of Ischemic Stroke and Subsequent Outcome in Patients Receiving Hemodialysis

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Background and Purpose—End-stage renal disease (ESRD) requiring hemodialysis carries up to a 10-fold greater risk of stroke than normal renal function. Knowledge on risk factors and management strategies derived from the general population may not be applicable to those with ESRD. We studied a large ESRD population to identify risk factors and outcomes for stroke.

Methods—All adult patients receiving hemodialysis for ESRD from January 1, 2007, to December 31, 2012, were extracted from the electronic patient record. Variables associated with stroke were identified by survival analysis; demographic, clinical, imaging, and dialysis-related variables were assessed, and case-fatality was determined. Follow-up was until December 31, 2013.

Results—A total of 1382 patients were identified (mean age, 60.5 years; 58.5% men). The prevalence of atrial fibrillation was 21.2%, and 59.4% were incident hemodialysis patients. One hundred and sixty patients (11.6%) experienced a stroke during 3471 patient-years of follow-up (95% ischemic). Stroke incidence was 41.5/1000 patient-years in prevalent and 50.1/1000 patient-years in incident hemodialysis patients. Factors associated with stroke on regression analysis were prior stroke, diabetes mellitus, and age at starting renal replacement therapy. Atrial fibrillation was not significantly associated with stroke, and warfarin did not affect stroke risk in warfarin-treated patients. Fatality was 18.8% at 7 days, 26.9% at 28 days, and 56.3% at 365 days after stroke.

Conclusions—Incidence of stroke is high in patients with ESRD on hemodialysis with high case-fatality. Incident hemodialysis patients had the highest stroke incidence. Many, but not all, important risk factors commonly associated with stroke in the general population were not associated with stroke in patients receiving hemodialysis. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.009095.)

Key Words: atrial fibrillation ■ diabetes mellitus ■ kidney failure, chronic ■ renal dialysis ■ stroke

The risk of stroke is 5 to 10× greater in patients with end-stage renal disease (ESRD) on hemodialysis than in those with normal renal function. However, risk factors for stroke in ESRD may differ when compared with the general population. Atrial fibrillation (AF), for example, is associated with adverse outcomes in the ESRD population, but its influence on stroke risk is less clear. Furthermore, warfarin use may not protect against stroke in patients with ESRD and AF. Furthermore, there is a temporary rise in stroke incidence after commencement of hemodialysis, suggesting that either commencement of dialysis itself or specific dialysis-related variables increase stroke risk. For instance, in the general population, it is recognized that diuretic-induced potassium depletion is associated with stroke. Finally, most data on stroke risk in ESRD originate from large US registry studies, or relatively small single-center studies with low absolute number of stroke events.

We performed a contemporary study in a large dialysis center in a population with a high background prevalence of vascular disease, to identify risk factors for stroke in hemodialysis. We hypothesized that (1) stroke risk would be high, with high case-fatality in patients treated with hemodialysis, (2) some common traditional risk factors for stroke would not be associated with stroke risk (with a particular focus on AF and the effect of warfarin), and (3) dialysis-specific variables would be associated with stroke risk.

Methods

All adult patients receiving hemodialysis attending Glasgow Renal and Transplant Unit for hospital hemodialysis between January 1, 2007, and December 31, 2013.

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2007, and December 31, 2012, were identified using the electronic patient record (Strathclyde Electronic Renal Patient Record, Vitalpulse, United Kingdom). Cohort entry was recorded as January 1, 2007, in patients already receiving hemodialysis (prevalent hemodialysis patients) or from date of commencing hemodialysis as their first renal replacement therapy modality for ESRD (incident hemodialysis patients). Patients treated with hemodialysis for acute kidney injury were excluded. Clinical and demographic details at cohort entry were recorded, including primary renal diagnosis, the presence of diabetes mellitus, cardiovascular disease, cerebrovascular disease, AF, and antithrombotic drug use. We also extracted pre- and postdialysis blood pressure, ultrafiltration volume, predialysis serum albumin, adjusted calcium, phosphate, blood hemoglobin, pre- and postdialysis serum potassium, and urea reduction ratio at 90 days. The value from 90-day postcohort entry was used. The electronic patient record links to all radiology departments in the West of Scotland, so we were able to review all reports of brain imaging (computed tomographic imaging or magnetic resonance imaging).

Outcomes and Definition of Stroke
The time to first stroke in patients receiving hemodialysis occurring after study inception was recorded. Stroke was defined from the electronic patient record as (1) a new clinical diagnosis of stroke recorded in the diagnostic timeline, (2) the presence of ischemic or hemorrhagic stroke on brain imaging associated with a clinical history of new neurological deficit or stroke, or (3) any of cerebrovascular disease, cerebrovascular accident, cerebral infarct, subarachnoid hemorrhage, or intracerebral hemorrhage listed on death certificate as a primary or major contributory factor to a patient death. All events were reviewed by 2 independent clinicians (M.D.F. and P.B.M.) with cases adjudicated by a third observer (P.C.T.) where disagreement arose. Subdural and extradural hemorrhage were excluded. The West of Scotland Ethics Committee officer waived the need for ethical committee review on the basis that this was analysis of routine clinical data.

Statistical Analysis
Follow-up data were available to December 31, 2013. Patient follow-up was censored at renal transplantation. Baseline demographics were compared using Student t test, Mann–Whitney U test, χ² test, or 1-way ANOVA as appropriate. Kaplan–Meier survival analysis was performed for time to first stroke and for mortality in all patients. A multivariable Cox survival analysis was performed to identify significant independent risk factors for stroke. A backward stepwise regression model was applied to identify significantly influential variables as defined at a P<0.05 and those were reentered into a multivariable Cox regression analysis. Data were analyzed using SPSS version 21 (IBM, Armonk, NY) and StataSE 13 (StataCorp, College Station, TX).

Results
A total of 1382 patients receiving hemodialysis were included. Of these, 59.4% were incident hemodialysis patients. The median renal replacement therapy vintage was 1206 days (interquartile range, 2222 days) in the prevalent patients. The mean age was 60.5 years, 58.5% were men, and 21.2% had AF. Two hundred and forty-five patients (17.7%) received a kidney transplant during follow-up. Censoring for death or transplantation, median follow-up for the cohort was 2.1 (interquartile range, 2.9) years.

One hundred and sixty patients (11.6%) experienced a stroke event over 3471 patient-years of follow-up (Table 1). One hundred and forty nine patients (93.1%) had brain imaging performed as a part of diagnostic assessment, with the rest considered to have a clinical diagnosis of stroke based on the death certification or at postmortem examination. The majority (95%) of events were ischemic. Stroke incidence was 41.5/1000 patient-years in prevalent hemodialysis patients and 50.1/1000 patient-years in patients incident to hemodialysis during the follow-up period. Age-adjusted stroke rates (World Health Organization world standard) are available in Tables I and II in the online-only Data Supplement. There were baseline differences between patients who had stroke and patients who did not (Table 1).

AF, Warfarin, Antiplatelet Therapy and Risk of Stroke, Intracerebral Hemorrhage, or Death
There was no increased in rate of stroke in patient with AF when compared with no AF on survival analysis (Figure 1). AF was more common in patients who died (26.2% versus 14.2%; P<0.001; Figure I in the online-only Data Supplement). The rate of stroke did not differ in AF patients treated with warfarin compared with AF patients who were not (14.4% versus 11.4%; P=0.45; Figure 2).

Survival Analyses of Variables Associated With Risk of Stroke
Multivariable regression analyses revealed that age at starting renal replacement therapy, previous cerebrovascular disease, presence of diabetes mellitus, and postdialysis serum potassium were still associated with stroke (Table 1, model 2). Removing all cases with a prior history of cerebrovascular disease from the analyses revealed that age at starting renal replacement therapy and diabetes mellitus were still associated with stroke (Table 1, model 1). Among AF patients, the rate of stroke did not differ in AF patients treated with warfarin compared with AF patients who were not treated with warfarin (14.4% versus 11.4%; P=0.45; Figure 2).

Outcome in Patients After Stroke
Case-fatality (death within 7 days) for all stroke was 18.8% (n=30), and 126 of 160 (78.8%) died during follow-up. Fatality was 26.9% at 28 days and 56.3% at 1 year. Fatality was higher in patients with hemorrhagic stroke than in those with ischemic stroke with 7-, 28-, and 365-day fatality of 62.5%, 87.5%, and 100% for hemorrhage than that of 16.4%, 23.7%, and 53.9% for ischemia. Fatality rates were higher when those with prior cerebrovascular disease were removed with 7-, 28-, and 365-day fatality of 24%, 34%, and 72%.

Discussion
In the general population, stroke is common and a leading cause of disability with firmly established risk factors. Although incidence, outcomes, and risk factors are described in the ESRD population, most published data originate from the United States or Japan and are not necessarily representative of the United Kingdom or European populations. Among a large cohort of incident and prevalent hemodialysis patients in the west of Scotland, we have described a high incidence of stroke events alongside stroke variables and fatality rates. Of note, we report a higher incidence of stroke in the incident dialysis population compared with the prevalent patients and, interestingly, no association between AF or warfarin use and stroke events.
We found a high unadjusted incidence of stroke in patients with ESRD (45.9/1000 patient-years) in keeping with previous reports where it ranges from 17.3 to 49/1000 patient-years but higher than a recent report from a UK study (45.9 versus 17.3/1000 patient-years). This could be explained by the differences in study methodology (they excluded stroke within the first 90 days of commencing dialysis and required neuroimaging to diagnose all stroke events) and geographical variation (Scotland has the higher prevalence of cardiovascular disease in the United Kingdom14,15). Incidence of stroke was higher in the incident than in the prevalent hemodialysis patients (50.1 versus 41.5/1000 patient-years). The increase in stroke risk associated with dialysis initiation has previously

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Stroke Follow-Up</th>
<th>Stroke During Follow-Up</th>
<th>PValue</th>
<th>IS</th>
<th>HS</th>
<th>PValue (IS vs No Stroke)</th>
</tr>
</thead>
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<tr>
<td>Male (%)</td>
<td>1222 (88.4)</td>
<td>160 (11.6)</td>
<td>…</td>
<td>152 (11.0)</td>
<td>8 (0.6)</td>
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<tr>
<td>Race (%)</td>
<td>726 (59.4)</td>
<td>83 (51.9)</td>
<td>0.069</td>
<td>77 (50.7)</td>
<td>6 (75)</td>
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<td>Age at starting RRT, y</td>
<td>59.9±16.7</td>
<td>65.7±14.3</td>
<td>&lt;0.001</td>
<td>66.3±14.2</td>
<td>54.4±14</td>
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<tr>
<td>Incident patients (%)</td>
<td>731 (59.8)</td>
<td>90 (56.3)</td>
<td>0.387</td>
<td>88 (57.9)</td>
<td>2 (25)</td>
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</table>

### Table 1. Stroke vs No Stroke, Ischemic Stroke, and Hemorrhagic Stroke During Follow-Up

The following nonsignificant values have been removed: predialysis potassium, adjusted serum calcium, ultrafiltration volume, postdialysis blood pressure. AF indicates atrial fibrillation; CeVD, cerebrovascular disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HS, hemorrhagic stroke; IQR, interquartile range; IS, ischemic stroke; K, serum potassium; PO4, serum phosphate; RRT, renal replacement therapy; and SBP, systolic blood pressure.

*Prevalent patients only.

**Stroke Incidence in Hemodialysis**

We found a high unadjusted incidence of stroke in patients with ESRD (45.9/1000 patient-years) in keeping with previous reports where it ranges from 17.3 to 49/1000 patient-years but higher than a recent report from a UK study (45.9 versus 17.3/1000 patient-years). This could be explained by the differences in study methodology (they excluded stroke within the first 90 days of commencing dialysis and required neuroimaging to diagnose all stroke events) and geographical variation (Scotland has the higher prevalence of cardiovascular disease in the United Kingdom). Incidence of stroke was higher in the incident than in the prevalent hemodialysis patients (50.1 versus 41.5/1000 patient-years). The increase in stroke risk associated with dialysis initiation has previously

![Figure 1. Kaplan-Meier survival curve of time to stroke in all periods: prevalent hemodialysis patients with and without atrial fibrillation (AF).](image1)

![Figure 2. Kaplan-Meier survival curve of time to stroke in all periods: prevalent hemodialysis patients with atrial fibrillation (AF) comparing warfarin or no warfarin users.](image2)
been described; however, we are the first to describe a difference in stroke rate between incident and prevalent hemodialysis groups within the same population. We report fewer cases of hemorrhage than in previous reports, a finding that is not unexpected for a predominantly (92.6%) white population. Case-fatality after stroke was high, with a markedly higher rate in hemorrhagic stroke, and higher in those who experienced their first ever stroke. As expected, fatality in our dialysis population is higher than the reported background fatality rates for stroke in Scotland (26.9% versus 15.9% at 28 days) but in keeping with reported rates in ESRD (30-day fatality of 17.9% in ischemic stroke and of 53.4% in hemorrhagic stroke).17

Risk Factors for Stroke
Risk factors for stroke in the general population include increasing age, prior cardiovascular disease, diabetes mellitus, hypertension, and AF.18 We found older age, the presence of diabetes mellitus, previous cerebrovascular disease, a lower diastolic blood pressure, and higher postdialysis potassium were significantly associated with stroke in patients receiving hemodialysis. This effect of potassium contrasts with the general population where higher potassium levels are associated with a lower blood pressure and stroke risk4,19 although the mechanism is unclear. As it was of clinical interest, we looked at the association of postdialysis potassium on risk of stroke using a univariable Cox proportional hazards model. In the absence of other covariates, posthemodialysis potassium was significantly associated with stroke, hazard ratio of 1.4 (95% confidence interval, 1.03–1.9). However, when other covariates identified by stepwise regression were added into the model, posthemodialysis potassium was no longer associated with stroke (Table 2). A higher serum potassium after dialysis is likely to represent underlying comorbidity.

Table 2. Stepwise Cox Proportional Hazards Regression Looking at Time to Stroke (n=1121)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% HR Confidence Limits</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>Model 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Previous CeVD</td>
<td>4.5</td>
<td>2.7 7.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>Age at starting RRT, y</td>
<td>1.0</td>
<td>1.0 1.1</td>
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<td>Postdialysis K, mmol/L</td>
<td>1.3</td>
<td>0.9 1.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.5</td>
<td>1.0 2.1</td>
<td>0.04</td>
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<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
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<td>Age at starting RRT, y</td>
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<td>1.0 1.05</td>
<td>&lt;0.0001</td>
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<tr>
<td>Post dialysis K, mmol/L</td>
<td>1.3</td>
<td>0.99 1.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.6</td>
<td>1.1 2.2</td>
<td>0.01</td>
</tr>
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</table>

The following nonsignificant (P>0.05) covariates were removed: prior cardiovascular disease, atrial fibrillation, use of warfarin or antiplatelet therapy, serum albumin, calcium, phosphate, blood hemoglobin, predialysis systolic blood pressure, ultrafiltration volume urea reduction ratio, and incident hemodialysis status. Posthemodialysis potassium was retained as it was of clinical interest. Model 1 was generated using these 4 variables, where previous CeVD, age at starting RRT, and diabetes are significant associations. Removing previous CeVD from the analysis (model 2) retains age and diabetes mellitus only. CeVD indicates cerebrovascular disease; HR, hazard ratio; K, serum potassium; and RRT, renal replacement therapy.

In our study, the mitigation of potassium’s effect on stroke risk is likely to reflect an association with the presence of diabetes mellitus. Interestingly, although the presence of AF at baseline was associated with a higher mortality, we found no association between the presence of AF or warfarin use and stroke. In our group, the presence of AF represents a marker of comorbidity and advanced age rather than a cause of mortality. Hemodialysis favors the initiation of AF through rapid shifts in fluid and electrolytes (potassium), and episodes of AF are common during hemodialysis.20 Although hemodialysis-induced AF may contribute to the increase in stroke risk observed in those initiating dialysis, it must be acknowledged that patients are anticoagulated during their dialysis sessions. Therefore, it is possible that hemodialysis-related AF may carry a lower risk of stroke than AF in the general population.

Anticoagulation in ESRD
The use of dose-adjusted warfarin is accepted as an effective treatment in reducing the risk of ischemic stroke in nonvalvular AF. However, we did not detect an effect of warfarin on stroke risk in our study. In recent years, data have emerged, suggesting that warfarin use is either not protective against ischemic stroke,22 associated with an increase in hemorrhagic and ischemic stroke,4,13,23 or associated with harm through bleeding in the hemodialysis population.6,22 Guidelines reflect this uncertainty and either do not mention patients with ESRD or make no recommendation.24 There is unease about using vitamin K antagonists in ESRD; not only because of the increased risk of bleeding but also the association with vascular calcification inducing cardiovascular disease or calciphylaxis.27,28 Unfortunately, no suitable alternative currently exists. Although recently developed new oral anticoagulants have been shown to be noninferior or superior to warfarin in patients with nonvalvular AF25,29 in the general population, patients with ESRD are excluded from such stroke prophylaxis trials. Presently, new oral anticoagulants are not recommended in those with a glomerular filtration rate <30 mL/min.25

Limitations
We report a single-center study and have described the clinical behavior of stroke disease in 1382 hemodialysis patients over 3471 years of patient follow-up. This is one of the largest single-center studies ever reported. We do, however, recognize the following limitations. Because of the observational nature of our cohort, we can only describe associations and not causation. Despite the size of this study, the relatively low numbers of stroke events limit our ability to detect risk factors associated with death within the stroke group. We acknowledge that because no association between ischemic stroke and AF was described, we would not expect warfarin to be protective. However, the absence of any influence of warfarin on stroke risk remains notable. Specifically, warfarin use did not increase hemorrhagic stroke risk. Finally, important data were not available from this study, which could support our lack of findings on AF. For example, the absence of echocardiography prevents reporting of structural abnormalities, which may be relevant and absence of international normalized ratio reporting prevents comment about the time in therapeutic range.
Conclusions
We have shown that in a high-risk population of ESRD patients on hemodialysis, the incidence of stroke is high with associated poor outcomes. The presence of AF is associated with mortality, but we did not detect an association between AF and stroke in this cohort. Neither stroke risk nor mortality is altered by warfarin use in this study. We have described a higher incidence of new onset stroke in the incident hemodialysis population than in the prevalent.

Sources of Funding
M. Findlay is currently funded by a Kidney Research UK Training Fellowship and supported by a grant from Darlinda’s Charity for Renal Research.

Disclosures
None.

References
Supplemental Material

### Table I

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Male</th>
<th>Female</th>
<th>All HD patients (n=1382)</th>
<th>Female (n = 573)</th>
<th>Male (n=809)</th>
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<td>&lt;25</td>
<td>14</td>
<td>11</td>
<td>0</td>
<td>0</td>
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<tr>
<td>25-34</td>
<td>20</td>
<td>17</td>
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<td>46</td>
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<td>7 2465.5 (1186.3 - 5124.4)</td>
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<td>45-54</td>
<td>122</td>
<td>72</td>
<td>13 2375.2 (1388.2 – 4064.1)</td>
<td>7 3366.7 (1625.3 - 6973.8)</td>
<td>6 1767.8 (799.9 - 3907.1)</td>
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<td>55-64</td>
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<td>94</td>
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<td>10 3963.0 (2159.0 - 7274.7)</td>
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<td>208</td>
<td>170</td>
<td>52 5139.9 (3944.4 – 6697.6)</td>
<td>22 4589.5 (3051.4 - 6902.9)</td>
<td>30 5635.3 (3980.7 - 7977.8)</td>
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<td>75-84</td>
<td>169</td>
<td>143</td>
<td>45 7141.0 (5388.7 – 9463.2)</td>
<td>28 9305.1 (6539.2 - 13240.8)</td>
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<td>&gt;85</td>
<td>26</td>
<td>20</td>
<td>9 11864.3 (6424.9 – 21908.5)</td>
<td>6 28662.0 (14581.4 - 56339.7)</td>
<td>3 5462.1 (1817.7 - 16413.2)</td>
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<tr>
<td>All ages</td>
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<td>573</td>
<td>160 4595.0 (3949.6 – 5345.8)</td>
<td>77 5363.4 (4315.9 - 6665.1)</td>
<td>83 4055.8 (3285.2 - 5007.2)</td>
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</table>

**Standardised rate**

1816.8 (1535.3-2098.3) 2478.8 (1925.1 – 3032.4) 1387.5 (1089.0-1686.0)

(1) Table I: Incidence rates of stroke (first-ever and recurrent) of hemodialysis study population. Age standardisation with the WHO world standard population distribution, based on world average population between 2000-2025 (Ahmad et al, 2001) was performed by the direct method.
### Table II: Incidence rates of first-ever stroke in the study group.

Age standardisation with the WHO world standard population distribution, based on world average population between 2000-2025 (Ahmad et al, 2001) was performed by the direct method.
Figure I) Presence of atrial fibrillation and effect on survival, all hemodialysis patients.

Supplemental References

Abstract

Risk Factors of Ischemic Stroke and Subsequent Outcome in Patients Receiving Hemodialysis

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1 Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; and 2 The Glasgow Renal & Transplant Unit, South Glasgow University Hospital, Glasgow, United Kingdom.

Abstract

Background and Purpose: Hemodialysis patients have an increased risk of ischemic stroke compared to the general population. The aim of this study was to determine the risk factors and outcomes in hemodialysis patients following ischemic stroke.

Methods: We performed a retrospective analysis of patients with ischemic stroke who received hemodialysis at our hospital between January 2011 and December 2015.

Results: Of the 208 patients included in the study, 106 had ischemic stroke. The median age was 60 years, and 51% were male. The most common risk factors were hypertension (78%), diabetes (65%), and hyperlipidemia (52%). The 30-day mortality rate was 12.6%.

Conclusion: Ischemic stroke in hemodialysis patients is associated with multiple risk factors. Further studies are needed to identify effective prevention strategies.

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