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ORIGINAL ARTICLE

Renal replacement modality and stroke risk in end-stage renal disease—a national registry study

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ABSTRACT

Background. The risk of stroke in end-stage renal disease (ESRD) on renal replacement therapy (RRT) is up to 10-fold greater than the general population. However, whether this increased risk differs by RRT modality is unclear.

Methods. We used data contained in the Scottish Renal Registry and the Scottish Stroke Care Audit to identify stroke in all adult patients who commenced RRT for ESRD from 2005 to 2013. Incidence rate was calculated and regression analyses were performed to identify variables associated with stroke. We explored the effect of RRT modality at initiation and cumulative dialysis exposure by time-dependent regression analysis, using transplant recipients as the reference group.

Results. A total of 4957 patients commenced RRT for ESRD. Median age was 64.5 years, 41.5% were female and 277 patients suffered a stroke (incidence rate was 18.6/1000 patient-years). Patients who had stroke were older, had higher blood pressure and were more likely to be female and have diabetes. On multivariable regression older age, female sex, diabetes and higher serum phosphate were associated with risk of stroke. RRT modality at initiation was not. On time-dependent analysis, haemodialysis (HD) exposure was independently associated with increased risk of stroke.

Conclusions. In patients with ESRD who initiate RRT, HD use independently increases risk of stroke compared with transplantation. Use of peritoneal dialysis did not increase risk on adjusted analysis.

Keywords: cardiovascular, dialysis, ESRD, kidney transplantation, stroke

INTRODUCTION

The incidence of stroke increases with declining kidney function and is highest rate in those with end-stage renal disease (ESRD) [1, 2]. The choice of renal replacement therapy (RRT) in ESRD is a joint decision between clinician and patient, taking comorbidity and patient preference into account. Haemodialysis (HD) is the most common modality, peritoneal dialysis (PD) may not be practical for some patients and renal transplantation may not be possible due to operative risk and availability of organs. Each of these RRT options causes physiological and pharmacological stresses that may differentially influence stroke risk. Previous reports have described stroke incidence rates in RRT: highest in HD [3–7], followed by PD [8, 9] and lowest in those with a functioning renal transplant [10–12]. While RRT is a life-saving treatment in ESRD, recent data have suggested that initiating dialysis may be associated with a rise in stroke incidence [9], putting forward the hypothesis that the process of HD may be associated with increased stroke risk.

To explore whether a particular dialysis modality is associated with differentially higher stroke risk, we performed analyses using data from the Scottish Renal Registry (SRR) and Scottish Stroke Care Audit (SSCA) to analyse the influence of treatment modality on stroke risk in all adult patients commencing RRT for ESRD between 2005 and 2013 in Scotland.

MATERIALS AND METHODS

Data sets

The SRR is a nation-wide data set, contributed to by all nine adult renal units in Scotland [13]. Data include baseline demographics, primary renal diagnosis, renal replacement modality history, laboratory data and an annual census of clinical variables. All patients receiving RRT for ESRD are included. The SRR Scottish Mortality Audit in Renal Replacement Therapy (SMARRT), which consistently achieves ≥95% completeness of data [14], ensured capture of enhanced data around primary cause of death for all ESRD patients.

The SSCA [15] was established in 2002 to monitor performance of stroke care against guideline-based clinical standards throughout Scotland. Data are collected on patient demographics, stroke subtype and outcomes. This data set has provided complete coverage of all hospitals managing acute stroke since 2005.

The Scottish Morbidity Records 01 (SMR01) collects data on hospital discharges since 1968 [16]. Since 1989 SMR01 has been used to plan financial management of hospitals in order to ensure high completion rates. Internal audit of these data supports overall 89% accuracy for Main Condition diagnosis—a result that has remained stable for over 25 years [17].

All three data sets were linked, over the period 1 January 2005 to 31 December 2013, to create a data set allowing determination of the following: (i) stroke incidence rates by modality; (ii) factors associated with stroke in ESRD; and (iii) the influence of exposure to each dialysis modality on stroke risk.

Definitions

End-stage renal disease. All patients commencing RRT for ESRD in Scotland are recorded within the SRR. We analysed adults (those ≥18 years at initiation) who began RRT for ESRD during our study period. Therefore, we excluded all patients commencing RRT outside of Scotland and all those who began RRT for acute kidney injury (AKI) recovering within 90 days, unless RRT was reinitiated for ESRD during the study period. The date of commencing RRT for ESRD was used as date of cohort entry in all cases.

Modality of RRT. The first RRT modality was extracted from the SRR (hospital or home HD, automated or continuous ambulatory PD and pre-emptive kidney transplant). Further, we calculated RRT modality use on a month-by-month basis to assess exposure over the study period in time-dependent analysis.

Stroke incidence rate. The stroke incidence rate is presented as events per 1000 patient-years, calculated using stroke events as the numerator and cumulative follow-up in years as the denominator. Patient follow-up continued until first episode of stroke, death or end of follow-up, whichever came first. We present the total incidence rate of all ESRD patients and incidence rates split by RRT modality using the first RRT modality. We calculated the stroke incidence rate over three time periods: during the entire follow-up, during the first 90 days of commencing RRT ('incident RRT population') and finally, after the first 90 days of RRT ('prevalent RRT population').

Stroke. All non-fatal and fatal strokes were included in our analyses. From the SSCA, we extracted the date and subtype of first stroke during the study period. To ensure complete capture of stroke, SMR01 was interrogated for presence and dates of International Classification of Diseases, Tenth Revision (ICD-10) codes pertaining to stroke episodes (I60, I61, I62.9, I63 and I64), excluding subdural and extradural haemorrhage. Using SMARRT data within the SRR all cases where 'cerebrovascular accident, ERA-EDTA mortality code 22' was listed as the primary cause of death were extracted.

Baseline characteristics

The SMR01 was interrogated from 1 January 1981 until 31 December 2013 for the presence of ICD-10 codes relating to atrial fibrillation/flutter (I48), ischaemic heart disease (I21, 24, 24.8, I24.9, I25, I25.1, I25.2, I25.5 and I25.8), diabetes mellitus (E10 and E11), hypercholesterolaemia (E78), obesity (E66), smoking (F17) and hypertension (I10 and I15). To prevent overlap of diagnoses, ICD codes for prior stroke (I60, I61, I62.9, I63 and I64) were pulled from 1981 until date of first stroke in those who suffered stroke, or until 31 December 2013 in those who do not.

Using patient postcode, the Scottish Government urban–rural classification [http://www.isdscotland.org/Products-and-Services/GPD-Support/Geography/Urban-Rural-Classification/ (Februray 2016, date last accessed)] and divisions of socioeconomic deprivation [Scottish Index of Multiple Deprivation (SIMD)] [http://www.gov.scot/Topics/Statistics/SIMD (Februray 2016, date last accessed)] were calculated. Using postcode at commencement of RRT, deprivation quintiles were categorized into most (quintiles 1–2) or least deprived (quintiles 3–5). The sixfold urban–rural classification was subdivided into urban (population >3000) and rural (population <3000).

Clinical and laboratory values

The annual census collects data on blood pressure, weight, use of erythropoietin-stimulating agents and blood results, namely blood haemoglobin, serum albumin, phosphate, adjusted calcium and quality of dialysis as assessed by urea reduction ratio (in those receiving HD). Data were collected and have been provided as a median [interquartile range (IQR)] of all results over the entire study period or until date of stroke, whichever comes first.

Statistical analyses

Data are presented as medians (IQR) for continuous data or total number (%) for categorical data. Demographics are compared using Mann–Whitney *U* or Chi-squared testing as appropriate. In keeping with previous studies we examined factors influencing time to stroke by applying a Cox proportional hazard model to all variables, including the initial RRT modality. A multivariable model using variables relevant to stroke was then constructed. A backward stepwise selection procedure was applied, removing variables with $P > 0.1$. With the knowledge that RRT modality can change over time, we expressed the dialysis modality as a time-dependent covariate allowing analysis of the cumulative exposure of each dialysis modality on the risk of stroke. Three adjusted multivariable models were constructed: Model 1, adjusting for age and sex; Model 2, Model 1 adjustments plus prior atrial fibrillation and stroke; and Model 3, Model 2 adjustments plus prior ischaemic heart disease, hypertension, diabetes and serum phosphate. All analyses were completed using SAS v9.4.

Ethical Approval

The data sets used in this manuscript work within the 'NHS Code of Practice on Protecting Patient Confidentiality', which incorporates the requirements of statute and common law including the Data Protection Act, the Human Rights Act and the Adults with Incapacity (Scotland) Act. Access and use of the data for the purpose of this study were approved following a NSS proportionate governance review by the Privacy Advisory Committee of ISD, NHS Scotland, Reference 55/14.

RESULTS

A total of 4957 adult patients commenced RRT for ESRD in Scotland during our study period. The median age (IQR) at commencing RRT was 64.5 (23.5) years, 2068 (41.5%) were female, 3913 (78.9%) began on HD (3908 in-centre, 5 at home) 843 (17%) PD (562 continuous ambulatory PD, 281 automated PD) and 201 (4.1%) received a pre-emptive kidney transplant. Median duration of follow-up was 856 (1354) days. Demographics are outlined in Tables 1 and 2.

There were 277 strokes during the follow-up period (5.6% of patients). Thirty-eight (13.75%) were haemorrhagic, and the remainder ischaemic or unspecified (including those listed as primary cause of death). Twenty-one (7.6%) strokes were fatal at diagnosis. Cumulative follow-up was 14 926.9 years. Unadjusted stroke incidence rate for all ESRD patients was 18.6 strokes per 1000 patient-years. Using first RRT modality the stroke incidence rate for each of HD, PD and renal transplant is 21.2, 13.2 and 5.4 per 1000 patient-years, respectively, $P < 0.0001$ (Figure 1). We recalculated incidence rate for each modality based on those who suffer stroke within the first 90 days of commencing RRT or who suffer stroke from 90 days onwards. The incidence rate of stroke in the incident population (≤90 days of RRT) was 35.0, 24.5 and 19.9 per 1000

Table 1. Baseline demographics of all ESRD patients, no stroke versus all stroke

	No stroke	Stroke	All	P-value
N	4680	277	4957	
Median age, years (IQR)	64 (24.1)	70.6 (15)	64.5 (23.5)	<0.0001
Female (%)	1922 (41.1)	136 (49.1)	2068 (41.5)	0.010
Primary renal diagnosis (%)				
Glomerulonephritis	690 (14.7)	26 (9.4)	716 (14.4)	0.014
Interstitial disease	1019 (21.8)	38 (13.7)	1057 (21.3)	0.001
Multisystem	1112 (23.8)	79 (28.5)	1191 (24.0)	0.082
Diabetes	1071 (22.9)	86 (31.1)	1157 (23.3)	0.003
Other	778 (16.6)	47 (17.0)	825 (16.6)	0.868
Missing	10 (0.2)	1 (0.4)	11 (0.2)	
Urban rurality status (%)				
Urban	3861 (82.5)	232 (83.8)	4093 (82.6)	
Rural	819 (17.5)	45 (16.3)	864 (17.4)	0.626
Deprivation status (%)				
Least (SIMD quintiles 3–5)	3464 (74.0)	213 (76.9)	3677 (74.2)	
Most (SIMD quintiles 1 and 2)	1216 (26)	64 (23.1)	1280 (28.8)	0.323
First RRT modality (%)				
HD	3685 (78.7)	228 (82.3)	3913 (78.9)	0.172
PD	798 (17.1)	45 (16.3)	843 (17.0)	0.805
Transplant	197 (4.2)	4 (1.4)	201 (4.1)	0.018
Past medical history (%)				
Atrial fibrillation	185 (4.0)	17 (6.1)	202 (4.1)	0.085
Ischaemic heart disease	1449 (31.0)	90 (32.5)	1539 (31.1)	0.641
Stroke	122 (2.6)	12 (4.3)	134 (2.7)	0.123
Diabetes	1677 (35.8)	128 (46.2)	1805 (36.4)	0.001
Hypercholesterolaemia	643 (13.7)	51 (18.4)	694 (14.0)	0.040
Obesity	316 (6.8)	19 (6.9)	335 (6.8)	0.903
Smoking	307 (6.6)	14 (5.1)	321 (6.5)	0.380
Hypertension	3249 (69.4)	197 (71.1)	3446 (69.5)	0.686
Clinical variables, median (IQR)				
SBP (mmHg)	139 (30.0)	144 (30.0)	139.5 (30.0)	0.001
DBP (mmHg)	71 (19.0)	70 (20.5)	71 (19.0)	0.902
Weight (kg)	73.9 (23.9)	72.5 (26.2)	73.8 (23.9)	0.007
Use of ESA	3272 (69.9)	188 (67.9)	3460 (69.8)	0.501
Laboratory variables, median (IQR)				
Haemoglobin (g/dL)	11.3 (1.9)	11.2 (1.8)	11.3 (1.8)	0.358
Serum albumin (g/L)	37 (7.0)	36 (7.5)	37 (7.0)	0.025
Serum phosphate (mmol/L)	1.46 (0.6)	1.55 (0.6)	1.46 (0.6)	0.002
Serum-adjusted calcium (mmol/L)	2.36 (0.2)	2.34 (0.2)	2.35 (0.2)	0.022
Urea reduction ratio (HD only)	70.5 (10.0)	70 (12.5)	70.5 (10)	0.896
Death at follow-up	2412 (51.5)	238 (85.9)	2650 (53.5)	<0.0001

SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent.

Table 2. Baseline demographics of patients split by initial RRT modality

	HD	P-value	PD	P-value	Transplant
N	3913		843		201
Median age, years (IQR)	66.7 (21.7)	<0.0001	57.3 (24.2)	<0.0001	44.3 (20.8)
Female (%)	1585 (40.5)	0.015	374 (44.4)	0.237	99 (49.3)
Primary renal diagnosis (%)					
Glomerulonephritis	509 (13.0)	0.003	165 (19.6)	0.694	42 (20.9)
Interstitial disease	732 (18.7)	<0.0001	235 (27.9)	<0.0001	90 (44.8)
Multisystem	1027 (26.3)	<0.0001	140 (16.6)	0.107	24 (11.9)
Diabetes	962 (24.6)	<0.0001	170 (20.2)	0.012	25 (12.4)
Other	673 (17.2)	0.007	132 (15.7)	0.045	20 (10.0)
Missing	10 (0.3)		1 (0.1)		0
Urban rurality status (%)					
Urban	3303 (84.4)		631 (74.9)		159 (79.1)
Rural	610 (15.6)	0.048	212 (25.2)	0.234	42 (20.9)
Deprivation status (%)					
Least (SIMD quintiles 3–5)	2838 (72.5)		674 (80.0)		165 (82.1)
Most (SIMD quintiles 1 and 2)	1075 (27.5)	0.003	169 (20.1)	0.554	36 (17.9)
Past medical history (%)					
Atrial fibrillation	182 (4.7)	0.003	19 (2.3)	0.151	1 (0.5)
Ischaemic heart disease	1309 (33.5)	<0.0001	223 (26.5)	<0.0001	7 (3.5)
Stroke	116 (3.0)	0.065	17 (2.0)	0.224	1 (0.5)
Diabetes	1515 (38.7)	<0.0001	252 (29.9)	0.01	38 (18.9)
Hypercholesterolaemia	552 (14.1)	0.022	127 (15.1)	0.011	15 (7.5)
Obesity	292 (7.5)	<0.001	41 (4.9)	0.013	2 (1.0)
Smoking	259 (6.6)	0.284	54 (6.4)	0.393	8 (4.0)
Hypertension	2706 (69.2)	<0.001	636 (75.4)	<0.0001	104 (51.7)
Clinical variables, median (IQR)					
SBP (mmHg)	139.5 (30.0)	0.420	139 (30.0)	0.389	153.3 (38.5)
DBP (mmHg)	70.5 (19.0)	0.078	75 (18.3)	0.113	90 (19.0)
Weight (kg)	73.8 (24.3)	0.787	73.9 (19.9)	0.854	77.8 (23.5)
Use of ESA	2865 (73.2)	<0.0001	591 (70.1)	<0.0001	4 (2.0)
Laboratory variables, median (IQR)					
Haemoglobin (g/dL)	11.2 (1.8)	<0.0001	11.7 (1.5)	<0.0001	12.3 (2.4)
Serum albumin (g/L)	36 (7.5)	<0.0001	38 (7.5)	<0.0001	40 (6.0)
Serum phosphate (mmol/L)	1.47 (0.6)	<0.0001	1.49 (0.5)	<0.0001	1.01 (0.4)
Serum-adjusted calcium (mmol/L)	2.35 (0.2)	<0.0001	2.38 (0.2)	0.179	2.39 (0.2)
Stroke cases	228 (5.8)	0.018	45 (5.3)	0.04	4 (2.0)
Death at follow-up	2314 (59.1)	<0.0001	328 (38.9)	<0.0001	8 (4.0)

Mann–Whitney *U* or Chi-square testing are applied, comparing HD with transplant, and PD with transplant. SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent.

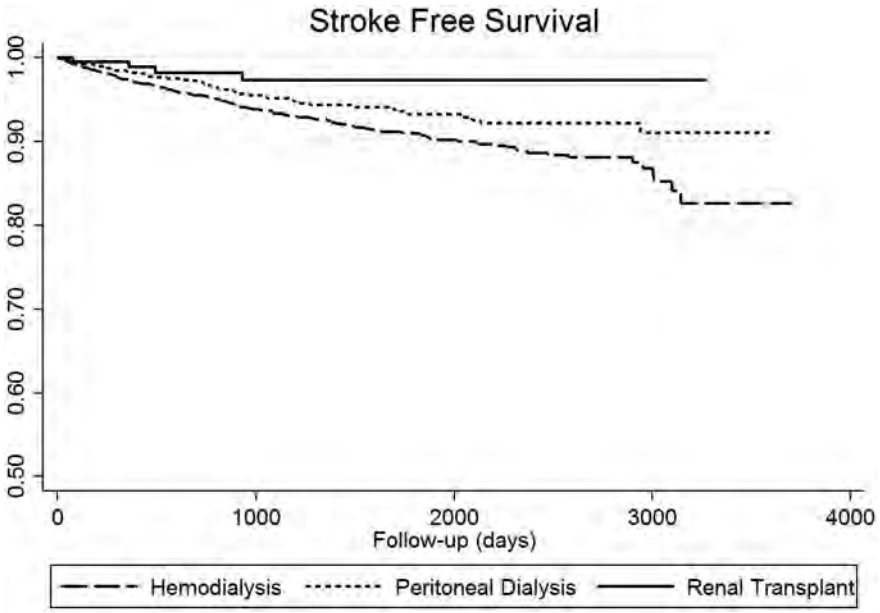

FIGURE 1: Stroke free survival of all stroke split by starting RRT modality, log-rank test $P < 0.0001$.

Table 3. Variables associated with time to all stroke in all end-stage patients, unadjusted and adjusted

	Univariable regression		Multivariable regression	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age per year	1.05 (1.04–1.06)	<0.0001	1.05 (1.04–1.06)	<0.0001
Female (%)	1.41 (1.11–1.78)	0.004	1.41 (1.10–1.82)	0.007
Primary renal diagnosis (%)				
Glomerulonephritis	0.55 (0.37–0.83)	0.004		
Interstitial disease	0.46 (0.33–0.65)	<0.0001		
Multisystem	1.53 (1.18–1.99)	0.001		
Diabetes	1.61 (1.25–2.08)	<0.001		
Other	1.07 (0.78–1.47)	0.664		
Urban rurality status (%)				
Rural	0.88 (0.64–1.21)	0.430		
Deprivation status (%)				
Least (SIMD quintiles 3–5)	1.11 (0.84–1.47)	0.457		
First RRT modality (%)[a]				
Haemodialysis	3.74 (1.39–10.05)	0.009	–	–
Peritoneal dialysis	2.46 (0.89–6.85)	0.084	–	–
Past medical history (%)				
Atrial fibrillation	2.21 (1.35–3.61)	0.002	–	–
Ischaemic heart disease	1.10 (0.86–1.42)	0.442	0.79 (0.60–1.04)	0.094
Stroke	1.80 (1.01–3.22)	0.046	–	–
Diabetes	1.67 (1.32–2.12)	<0.0001	1.81 (1.40–2.34)	<0.0001
Hypercholesterolaemia	1.34 (0.99–1.82)	0.057		
Obesity	1.01 (0.63–1.61)	0.968		
Smoking	0.78 (0.46–1.33)	0.362		
Hypertension	0.95 (0.73–1.23)	0.694	–	–
Clinical variables, median (IQR)				
SBP (mmHg)	1.01 (1.01–1.02)	0.001		
DBP (mmHg)	1.00 (0.99–1.01)	0.722		
Weight (kg)	0.98 (0.97–0.99)	<0.001		
Use of ESA	0.45 (0.35–0.57)	<0.0001		
Laboratory variables, median (IQR)				
Haemoglobin (g/dL)	0.79 (0.72–0.87)	<0.0001		
Serum albumin (g/L)	0.93 (0.90–0.95)	<0.0001		
Serum phosphate (mmol/L)	1.91 (1.48–2.46)	<0.0001	2.03 (1.58–2.60)	<0.0001
Serum-adjusted calcium (mmol/L)	0.16 (0.07–0.39)	<0.0001		

Variables were selected for the multivariable model on the basis of clinical relevance to stroke risk in ESRD and modelled using a backward stepwise selection procedure (removal $P > 0.1$). HR, hazard ratio; 95% CI, 95% confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent.
[a]Renal transplant patients were used as the reference.

patient-years for each of HD, PD and transplant, respectively ($P = 0.04$). In the prevalent population, rates were 19.9, 12.5 and 4.3 per 1000 patient-years, for HD, PD and transplant, respectively ($P < 0.01$).

Patients who suffered stroke were older (70.6 versus 64 years, $P < 0.0001$), more likely to be female (49.1% versus 41.1%, $P = 0.01$), and more likely to have diabetic nephropathy (31.1% versus 22.9%, $P < 0.01$), a past medical history of diabetes (46.2% versus 35.8%, $P < 0.001$) and hypercholesterolaemia (18.4% versus 13.7%, $P = 0.04$). Clinical variables revealed higher median systolic blood pressure (144 versus 139 mmHg, $P < 0.01$), lower body weight (72.5 versus 73.9 kg, $P < 0.01$), lower serum albumin (36 versus 37 g/L, $P = 0.03$) and higher serum phosphate (1.55 versus 1.46 mmol/L, $P < 0.01$) in those who suffer from stroke.

There were significant differences between patients who commenced HD, PD and renal transplant as their first modality (Table 2).

Risk of Stroke

Univariable regression revealed age, female sex, presence of atrial fibrillation, prior stroke and diabetes were significantly associated with stroke ($P < 0.01$). In addition, higher phosphate and systolic blood pressure were associated with greater risk, as was lower body weight, lower haemoglobin, lower serum calcium and use of HD as first RRT modality ($P \leq 0.01$). After multivariable adjustment age, female sex, diabetes and higher serum phosphate associated with stroke (Table 3). The initial RRT modality was not significant.

On time-dependent analysis, both HD and PD exposure were associated with greater unadjusted stroke risk than renal transplant. Models 1, 2 and 3 progressively adjust for demographics, covariates relevant to stroke and covariates relevant to cardiovascular disease. HD but not PD was associated with increased risk in the fully adjusted model (Table 4).

DISCUSSION

In this population-based national study, we report the high burden of stroke in patients with ESRD and the impact of both conventional and renal-specific factors associated with stroke occurrence. Of interest, we found that exposure to HD, but not PD as the modality of RRT increases the risk of stroke compared with renal transplantation, after correcting for

Table 4. Regression analyses of time to stroke with dialysis modality adjusted to a time-dependent covariate

	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Dialysis modality								
Haemodialysis	5.57 (3.07–10.10)	<0.0001	2.77 (1.49–5.18)	0.001	2.70 (1.45–5.04)	0.002	1.95 (1.03–3.71)	0.041
Peritoneal dialysis	4.46 (2.16–8.39)	<0.0001	2.57 (1.29–5.15)	0.008	2.52 (1.26–5.04)	0.009	1.71 (0.82–3.56)	0.151
Age (years)			1.04 (1.03–1.05)	<0.0001	1.04 (1.03–1.05)	<0.0001	1.05 (1.04–1.06)	<0.0001
Female			1.42 (1.12–1.81)	0.004	1.44 (1.13–1.83)	0.003	1.47 (1.13–1.90)	0.004
Past medical history								
Atrial fibrillation					1.40 (0.84–2.34)	0.198	1.43 (0.83–2.48)	0.202
Prior stroke					1.39 (0.76–2.55)	0.283	1.42 (0.77–2.62)	0.257
Ischaemic heart disease							0.75 (0.57–0.99)	0.044
Hypertension							0.88 (0.66–1.17)	0.386
Diabetes							1.81(1.40–2.34)	<0.0001
Laboratory value								
Serum phosphate							1.93 (1.48–2.52)	<0.0001

The following are presented: the unadjusted hazard ratio; Model 1—adjusted for age and sex; Model 2—adjusted for Model 1 + factors influential to stroke; and Model 3—Model 2 + additional cardiovascular risk factors. In all models time on HD is associated with greater risk of stroke, HR 1.95–5.57, $P < 0.05$. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence intervals.

demographics and risk factors. This suggests that treatment with HD may be an additional stroke risk factor. Stroke is up to 10 times more common in those with ESRD [7], making the findings of our study noteworthy for nephrologists discussing choice of dialysis modality at the low clearance clinic.

Prolonged exposure to PD is often limited to reduce the risk of devastating complications such as encapsulating peritoneal sclerosis [18]. With increasing data describing the vascular-driven end-organ damage associated with HD exposure [19] it may be time to consider a similar approach in HD.

Incidence of stroke

We report an incidence rate of 18.6/1000 patient-years in all incident ESRD patients over a 9-year period. Although high, this is in keeping with previous literature in ESRD [4, 20]. For context, the unadjusted stroke rate in Scotland's population over the study period is 2.4/1000 patient-years [21], demonstrating a 7.5-fold increase in incidence for those with ESRD. Split by modality the incidence rate is greatest in the order: HD, 21.2/1000 patient-years; PD, 13.2/1000 patient-years; and finally, transplant at 5.4/1000 patient-years. Those commencing RRT are classified as the 'incident' ESRD population until their first 90 days of RRT and 'prevalent' thereafter. For interest, we calculated the stroke incidence rate for the incident and prevalent groups and found a higher stroke incidence in the incident population receiving all forms of RRT, when compared with the prevalent (HD, 35.0 versus 19.9; PD, 24.5 versus 12.5; transplant, 20.7 versus 4.3 per 1000 patient-years). This finding is intriguing. The rise in stroke incidence in the first 90 days following dialysis initiation has been previously reported [9], but this is a new finding in the transplant population. At the time of transplant patients receive significant doses of immunosuppressive drugs, often large and rapid fluid and/or blood pressure shifts and a general anaesthetic with its associated cardiovascular stress. Any one of these stressors could act as a physiological 'stress-test' capable of inducing a vascular event in a vulnerable patient. However, understanding the mechanism behind this is outside the scope of this study.

'Static' risk factors for stroke

Cardiovascular disease is the leading cause of morbidity and mortality in ESRD and has been extensively studied. However, the impact from conventional risk factors on cerebrovascular disease in ESRD varies [4, 5, 22–25]. For instance, atrial fibrillation—a treatable risk factor of stroke in the general population—is inconsistently reported as a risk factor in ESRD [6, 24, 26–28] and while this was associated with stroke on univariable testing, this association was not present on multivariable analysis, presumably due to the close association of atrial fibrillation with other vascular comorbidity and age. Furthermore, the use of warfarin for stroke prevention has been brought into doubt. Studies have suggested harm without reduction in stroke risk from the use of warfarin [26] in ESRD. Unfortunately, no randomized control data exist to guide anticoagulation use. Therefore, risk factors unique to ERSD are often explored. We describe, as others have [4, 23, 29], an increased stroke risk with lower weight, lower haemoglobin and higher serum phosphate. Although use of HD as the initial RRT modality is associated with stroke on univariable analysis, this is lost in the adjusted model. In this model, age, female sex, diabetes and higher serum phosphate are predictive of stroke.

Impact of modality exposure on stroke risk

Choice of RRT modality is a decision made between the patient and clinician taking into consideration physical fitness to undergo treatments, and the likelihood of sustainability [30]. For example, those with extensive cardiac disease are rarely considered for transplantation, and those with significant functional disabilities rarely opt for a home-based treatment. Therefore, patients receiving each dialysis modality are inherently different.

Data suggest that the initiation of dialysis increases the risk of stroke, ranging from a two-fold increase in those who commence PD to a seven-fold increase in those who undergo in-hospital initiation of HD [9]. While the increased stroke rate at HD initiation may be a consequence of cumulative insults

peaking at HD, further data suggest that the association of HD with stroke continues beyond this. Specifically, stroke events are temporally associated with HD session [31], HD is believed to alter cerebral blood flow [32–34] and intradialytic hypotension is associated with small vessel disease and frontal atrophy [35]. In fact, even short-term HD exposure has been associated with an increased stroke risk. A retrospective registry-based study from Taiwan reported an increase in the risk of incident stroke in those who had suffered an episode of AKI requiring temporary HD—a finding that persisted despite correction for residual chronic kidney disease. The impact of transient HD was comparable to being diabetic [36]. These data suggest that exposure to HD may exert an unwanted cerebrovascular effect; an effect less well reported in those on PD.

A recent prospective study from China [8] examined the effect of dialysis modality on stroke risk, describing an approximate doubling in adjusted risk for stroke in those on HD compared with PD (hazard ratio 2.03, $P = 0.005$). While interesting, their results are not directly comparable to ours due to differences in methodology; specifically, they examined their prevalent dialysis population only, omitted transplant recipients and—most importantly—used the first dialysis modality throughout their analyses, without adjusting for modality switching.

HD is a life-prolonging therapy, essential to over 25 000 patients in the UK alone. Data supporting a cerebrovascular 'side-effect' must lead to intervention in order to mitigate this effect. Recently, the effect of cooled versus normothermic dialysis on white matter microstructure [37] has been observed. A pattern of ischaemic injury was observed at 12 months in those with normothermic, but not in those who underwent cooled HD, concluding that the haemodynamic stress of HD was responsible. Patients can find cooled HD uncomfortable, limiting its use. Another option therefore would be the use of PD, or switching to PD in cases of cerebral injury. PD is effective at reducing serum glutamate [38], with the ability to reduce infarct size in animal models [39]. The relative ease of PD catheter insertion, haemodynamic stability, absence of anticoagulation and portability of this treatment would make initiating, or transiently switching to, PD on arrival to the stroke unit an attractive treatment strategy for stroke in ESRD. Data confirming its efficacy in humans are lacking, and trials are desperately needed.

Limitations

We acknowledge that this study has limitations. Firstly, our data are retrospective, therefore we cannot prove causation but only describe association. Further, after multivariable adjustment, we saw no increase in stroke risk in those on PD compared with transplantation. However, confidence intervals were wide so a small increase cannot be completely excluded. We lack data on the reason for modality switching, which may affect our results. For example, deterioration in health could result in switching to hospital HD, thus overestimating an effect of HD. However, adjustment in our regression analyses for cardiovascular comorbidity should limit this effect. In addition, we do not have access to prescription records to examine the effect of warfarin, or anti-platelet therapy on stroke risk. However, as international normalized ratio data are not held in any data set the use of prescription data would be limited. Unfortunately, we did not have access to multiple blood pressure measurements to sufficiently analyse the effect of blood pressure magnitude on stroke risk. Rather, we used the coded diagnosis of hypertension in our analyses. Despite this limitation, we believe this method is superior as it allows consideration for prior exposure to hypertension, which could be missed from isolated readings. Further, we have used coded diagnoses to define stroke. However, both the SSCA—which is internally validated by stroke physicians—and the SMR01, which is regularly audited confirming an approximately 90% accuracy rate, are validated sources. Finally, while the rise in stroke incidence within the first 90 days following transplant is an interesting and novel finding in our study, we acknowledge the small absolute numbers of stroke in our transplant group, which under-power any formal assessment of this difference.

CONCLUSIONS

Our study confirms the high incidence rate of stroke in our UK-based study of patients commencing RRT for ESRD. Further, it has re-affirmed that the rate of stroke is higher in those on HD followed by PD, with transplant having the lowest rate of all ESRD treatment modalities. Conventional, in addition to renal-specific factors are associated with stroke. Our novel finding, that exposure to HD increases risk for stroke, despite adjustment for age, sex and cardiovascular comorbidity in the incident ESRD population, is alarming. There is an urgent need for further study of the effects of HD on the cerebral circulation and trials of interventions to reduce this risk.

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AUTHORS' CONTRIBUTIONS

M.F., P.B.M. and J.D. had the original idea. W.M., J.P.T. and M.J.M. are responsible for data management of renal and stroke registries, respectively. M.F. and R.M. performed the analyses. M.F. wrote the first draft and all authors contributed to the final draft.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part.

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