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 performed to identify variables associated with stroke. We explored 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 4,957 patients commenced RRT for ESRD. Median age was 64.5years, 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 exposure was independently associated with increased risk of stroke.

Conclusions

In patients with ESRD who initiate renal replacement therapy, haemodialysis use independently increases risk of stroke compared to transplantation. Use of peritoneal dialysis did not increase risk on adjusted analysis.

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 which 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). Whilst 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

Datasets

The Scottish Renal Registry (SRR) is a nation-wide dataset, 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 Scottish Stroke Care Audit(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 dataset 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 rate. Internal audit of these data supports overall 89% accuracy for Main Condition diagnosis - a result which has remained stable for over 25 years(17).

All three datasets were linked, over the period 1st January 2005 to 31st December 2013, to create a dataset allowing determination of the following: (1) stroke incidence rates by modality; (2) factors associated with stroke in ESRD and (3) 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 out-with Scotland

and all those who began RRT for acute kidney injury (AKI) recovering within 90days, 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 renal replacement therapy

The first RRT modality was extracted from the SRR (hospital or home HD, automated or continuous ambulatory peritoneal dialysis 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 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 01 January 1981 until 31 December 2013 for 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 31.12.2013 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/) and divisions of socioeconomic deprivation (Scottish Index of Multiple Deprivation (SIMD)) (http://www.gov.scot/Topics/Statistics/SIMD) were calculated. Using postcode at commencement of RRT, deprivation quintiles were categorized into most (quintiles 1–2) or least deprived (quintiles 3–5). The 6-fold urban-rural classification was subdivided into urban (population >3000) and rural (population <3000).

Clinical and Lab 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

(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 value >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. Four 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 datasets 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 was approved following a NSS proportionate governance review by the Privacy Advisory Committee of ISD, NHS Scotland, Reference 55/14.

Results

4,957 adult patients commenced renal replacement therapy for end-stage renal disease 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%) peritoneal dialysis (562 continuous ambulatory peritoneal dialysis, 281 automated peritoneal dialysis) 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). 38(13.75%) were haemorrhagic, and the remainder ischaemic or unspecified (including those listed as primary cause of death). 21 (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, peritoneal dialysis 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 90days onwards. The incidence rate of stroke in the incident population (≤90days of RRT) was 35.0, 24.5 and 19.9 per 1000 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 vs 64 years, $p<0.0001$), more likely to be female (49.1% vs 41.1%, $p=0.01$), have diabetic nephropathy (31.1% vs 22.9%, $p<0.01$), a past medical history of diabetes (46.2% vs 35.8%, $p<0.001$) and

hypercholesterolaemia (18.4% vs 13.7%, p=0.04). Clinical variables revealed higher median systolic blood pressure (144 vs 139mmHg, p<0.01), lower body weight (72.5 vs 73.9 kg, p<0.01), lower serum albumin (36 vs 37g/L, p=0.03) and higher serum phosphate (1.55 vs 1.46mmol/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 & diabetes were significantly associated with stroke (p<0.01). In addition, higher phosphate and systolic blood pressure was associated with greater risk, as was lower body weight, lower haemoglobin, lower serum calcium and use of HD as first RRT modality, p≤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 peritoneal

dialysis as the modality of renal replacement therapy increases the risk of stroke compared to renal transplantation, after correcting for 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 nephrologist 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 to the prevalent (HD, 35.0 vs 19.9; PD, 24.5 vs 12.5; transplant 20.7 vs 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 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 out with 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 whilst 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 use of warfarin(26) in ESRD. Unfortunately, no randomised 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 the initiation of dialysis increases the risk of stroke with a 2 to 7 fold increase, ranging from those who commence PD to those who undergo in-hospital initiation of HD(9). Whilst the increased stroke rate at HD initiation may be a consequence of cumulative insults peaking at HD, further data suggest 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 CKD. The impact of transient HD was comparable to being diabetic(36). These data suggest 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 to PD (HR 2.03, p=0.005). Whilst 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 to mitigate this effect. Recently, the effect of cooled vs 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 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, peritoneal dialysis 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 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 to 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 INR is not held in any dataset the use of prescription data would be limited. Unfortunately, we did not have access to multiple BP measurements to sufficiently analyse the effect of BP 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, whilst 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 the rate of stroke is higher in those on HD followed by PD and 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.

Conflict of Interest Statement

All authors confirm no conflicts. I can also declare that the results presented in this paper have not been published previously in whole or part

Authors Contributions

MDF, PBM and JD had the original idea. WM, JPT and MJM are responsible for data management of renal and stroke registries, respectively. MDF and RM performed the analyses. MDF wrote the first draft and all authors contributed to the final draft.

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	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&2)	1216 (26)	64 (23.1)	1280 (28.8)	0.323
First RRT Modality (%)				
Haemodialysis	3685 (78.7)	228 (82.3)	3913 (78.9)	0.172
Peritoneal Dialysis	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 fup	2412 (51.5)	238 (85.9)	2650 (53.5)	<0.0001

Table 1 Baseline demographics of all end-stage renal disease patients, no stoke vs all stroke. IQR, Interquartile Range; SIMD, Scottish Index of Multiple Deprivation; RRT, Renal Replacement Therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent.

	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&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 fup	2314 (59.1)	<0.0001	328 (38.9)	<0.0001	8 (4.0)

Table 2 Baseline demographics of patients split by initial RRT modality. Mann-Whitney U or Chi-square testing are applied, comparing HD to transplant, and PD to transplant. IQR, Interquartile Range; SIMD, Scottish Index of Multiple Deprivation; RRT, Renal Replacement Therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent.

	Univariate Regression		Multivariate 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		

Table 3 Variables associated with time to all stroke in all end-stage patients, unadjusted and adjusted. Variables were selected for the MV model on 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; SIMD, Scottish Index of Multiple Deprivation; RRT, Renal Replacement Therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESA, erythropoietin-stimulating agent. [a] Renal transplant patients were used as the reference.

	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

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

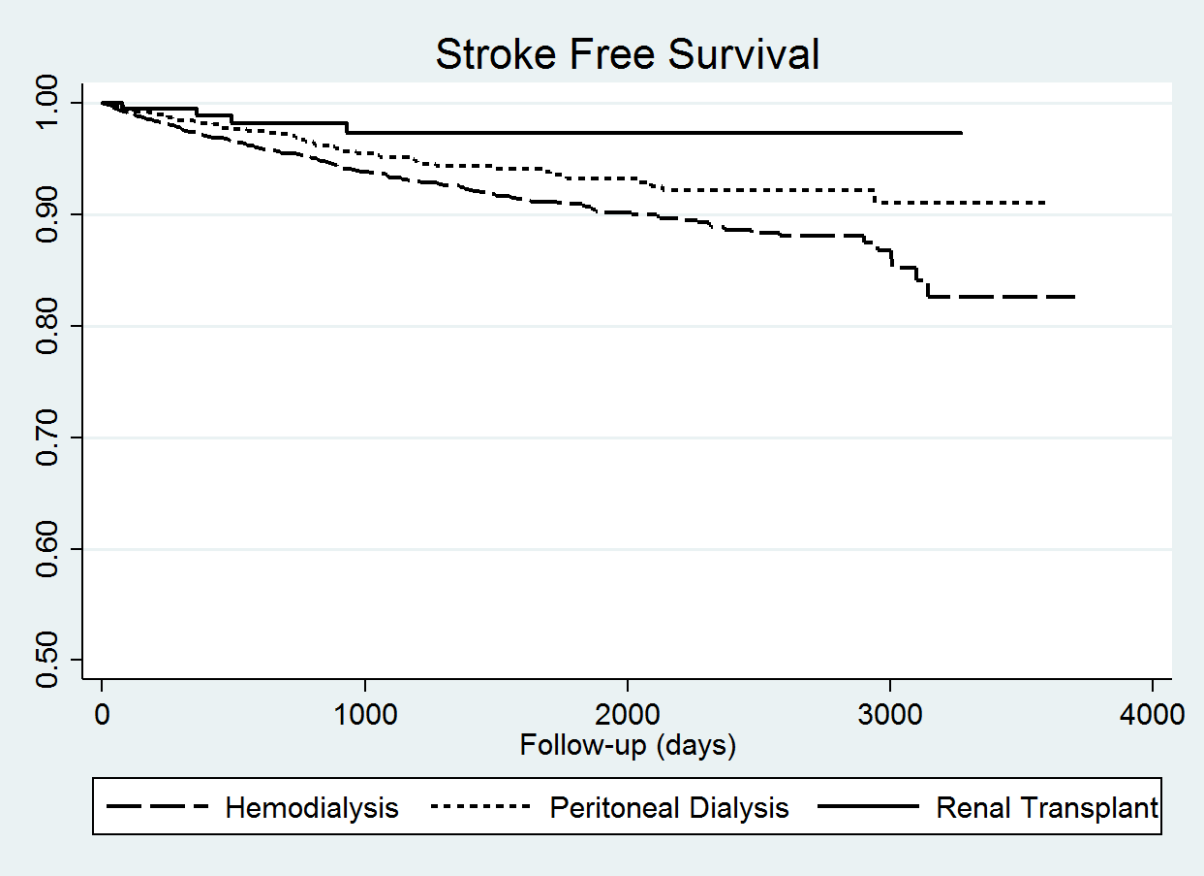

Figure 1 Incidence rate of all stroke, split by starting RRT modality, Log-Rank test p<0.0001.