Risk factors and outcome of Stroke in renal transplant recipients

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(4) Abstract

Stroke incidence is high in end-stage renal disease and risk factors differ between the dialysis and general populations. However, risk factors and outcomes following renal transplantation remain unclear.

We analysed all adult patients with a functioning renal transplant from 01/01/2007 to 31/12/2012. Data were extracted from the electronic patient record. Variables associated with stroke were identified by survival analyses; demographic, clinical, imaging and laboratory variables were assessed and case-fatality determined. Follow-up was until 05/12/2013.

956 patients were identified (median age 40.1 years, 59.9% male). Atrial fibrillation prevalence was 9.2% and 38.2% received a transplant during follow-up. 26 (2.7%) experienced a stroke during 4409 patient-years of follow-up (84.6% ischemic). Stroke incidence was 5.96/1000 patient-years. Factors associated with stroke on regression analysis were prior stroke, diabetes, age, systolic hypertension and hemoglobin. Atrial fibrillation was associated with time to stroke ($p<0.001$).Warfarin did not associate with ischemic stroke risk in those with AF. Fatality was 19.2% at 7, 23.1% at 28 and 42.3% 365 days after stroke.

Patients with a functioning renal transplant have a high stroke incidence and case-fatality. Unlike those on hemodialysis, risk factors are similar to the general population. We did not demonstrate benefit from warfarin use in those with AF.

(5) Keywords: Stroke, Cerebrovascular disease, atrial fibrillation, renal transplant

Introduction

End-stage renal disease (ESRD) is associated with increased cardiovascular morbidity and mortality[1] - an effect which is reduced but not obliterated by renal transplantation. In the last two decades, much attention has turned toward cerebrovascular disease and its complications in those with ESRD. A recent report has provided insight into the relevance of stroke affecting those with ESRD in the 21st century. Compared to the general population stroke incidence was found to be 6-fold greater and - of concern - younger patients were more likely to be affected[2]. It is recognised that effective preventive strategies are urgently needed.

Patients undergoing renal replacement therapy (RRT) experience a unique physiological environment where the conventional, general population-based, stroke risk factors are not consistently found to be associated with stroke[3]. For instance, although atrial fibrillation (AF) is a common finding in patients on hemodialysis the effect of AF on stroke risk remains unclear[4] and is further complicated by the absence of clear benefit from warfarin use[5,6]. Furthermore, vitamin K antagonists (warfarin) are associated with significant side effects, beyond that of bleeding in patients on hemodialysis, including accelerated vascular calcification[7]. Fortunately, the risk of stroke in those on the transplant waiting list can be reduced by receiving a renal transplant with sustained transplant function[8]. However, the assumption that return of “normal” renal function will produce stroke risk factors similar to those of the general population and provide benefit from their preventive strategies is unproven.

The goal of our study was to; 1) describe the incidence of stroke in those with a functioning renal transplant; 2) examine risk factors associated with stroke with particular interest in the effect of AF and warfarin use; and 3) describe outcomes following stroke.

Methods

All adult patients attending Glasgow Renal and Transplant Unit with a functioning renal transplant for ESRD between 1st January 2007 and 31st December 2012 were identified using the electronic patient record (EPR), (Strathclyde Electronic Renal Patient Record, Vitalpulse, UK). All laboratory and imaging results within the west of Scotland are imported to this database improving capture of investigations and follow-up. Cohort entry was recorded as 1st January 2007 in those patients with a functioning transplant at study inception, or from date of transplantation. Clinical and demographic details at cohort entry were recorded including primary renal diagnosis, presence of diabetes, cardiovascular disease, cerebrovascular disease, AF and history of antithrombotic drug use. We also extracted blood hemoglobin, serum albumin, phosphate, adjusted calcium, creatinine and urinary protein to creatinine ratio from 90 to 180 days following cohort entry. Patient postcode was used to assign a deprivation category using the Scottish Index of Multiple Deprivation (SIMD). The SIMD is a relative ranking of all areas of Scotland produced by the Scottish Government[9] which uses a multidimensional model to assess deprivation using 38 indicators across seven domains; employment, income, health, education, crime, housing and geographic access to services. Deprivation quintiles were calculated and cases were subdivided into most deprived (quintiles 1 and 2) and least deprived (quintiles 3-5).

Outcomes and definition of stroke

The time to first stroke in those with a functioning renal transplant after cohort entry was recorded. Date of death was recorded and fatality expressed at 7, 28 and 365 days following stroke. Stroke was defined from the EPR as either 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., P.B.M.) with cases adjudicated by a third observer (P.T.) where disagreement arose. Subdural and extradural hemorrhages were excluded.

Statistical analysis

Follow up data were available to December 5th 2013. Patient follow up was censored at transplant failure (death or return to dialysis). Baseline demographics were compared using Mann-Whitney U test or Chi-square test as appropriate. Kaplan-Meier survival analysis was performed for time to first ischemic stroke. Cox regression analyses were performed to identify significant independent risk factors for stroke and a backward stepwise regression was performed to identify significantly influential variables (defined as $p<0.1$) for use in the final multivariable model. To assess risk factors for first ever stroke, we removed all cases with a prior history of cerebrovascular disease and repeated the analyses. The effect of stroke on mortality was assessed using a multivariable Cox regression, adjusted for age, sex, RRT vintage, systolic blood pressure, serum creatinine and prior cardiovascular disease. Data were analysed using SPSS version 21 (IBM, Armonk, New York).

Ethical approval

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. Caldicott Guardian approval was granted by the information governance manager of NHS Greater Glasgow and Clyde.

Results

A total of 956 patients with a renal transplant were included; 591(61.8%) had a functioning transplant at the time of study inception and 365(38.2%) received a transplant during the study period. The mean age at commencing RRT for ESRD was 40.1 years, 383 (40.1%) were female and 88 (9.2%) had a history of AF. The median dialysis vintage was 8.77 years [IQR 3.20,16.35] 128 (13.4%) patients returned to dialysis during follow up. Censoring for death or return to dialysis, median follow-up for the cohort was 5.4 (IQR 2. 3, 6.9) years.

Incidence and outcomes

26 patients (2.7% [95% CI 1.7-3.7%]) experienced a new stroke event over 4409 patient-years of follow up. 24 patients (92.3%) had brain imaging performed as part of diagnostic assessment, with the remainder considered to have a diagnosis of stroke based on the death certification. The majority (84.6%) of events were ischemic. Stroke incidence was 5.96/1000 patient-years. There were 186 deaths during follow-up and 157 deaths in those with a functioning transplant. Analyzing only cases of death with a functioning transplant the cause of death was

cardiovascular in 29.3% (46) of cases, infection in 28% (44), malignancy in 21.7% (34) and other causes in 35% (55). There were no cases of SAH in patients with autosomal dominant polycystic kidney disease (ADPKD). Baseline differences between patients who suffered stroke and patients who did not are described in table 1.

Survival analyses of variables associated with risk of stroke

Uni-variable regression analyses of all patients revealed significance ($p<0.05$) for age, presence of prior cerebrovascular disease, diabetes, AF and higher systolic blood pressure. Multivariable analysis was performed using variables identified as significant following backward stepwise regression ($p<0.1$). This revealed significant independent associations for stroke as age, presence of diabetes and prior cerebrovascular disease (table 2). We removed cases with prior stroke from the analysis to assess factors associated with first ever stroke and refit a backwards stepwise regression model. This revealed that prior diabetes (Hazard ratio (HR) 3.64, 95% CI 1.21 – 10.91. p=0.021) and higher hemoglobin (HR 1.04, 95% CI 1.00 – 1.07. p=0.026) were independently associated with stroke. Kaplan-Meier survival analysis of time to ischemic stroke in those with and without AF demonstrated a significant association between presence of AF and stroke, $p<0.001$ (figure 1). In patients with AF, warfarin use had no significant effect on time to stroke, p 0.573 (figure 2).

Outcome in patients following stroke

15 of 26 (57.7%) died during follow-up. Cardiovascular causes accounted for 75% of deaths (53.3% directly attributed to cerebrovascular disease). All-cause mortality was significantly higher following stroke (57.7% vs 18.4%, adjusted HR 2.08 [95% CI 1.17, 3.69], p=0.013). Fatality was 19.2% at 7 days, 23.1% at 28 days and 42.3% at 1 year. Assessing only those with first ever stroke, 60% (9) died on follow-up with 7, 28 and 365 day fatality of 26.7%, 33.3% and 40% respectively. Comparison of groups dead vs. alive at the end of follow-up is shown in supplementary table s1.

Discussion

Renal transplantation is the gold standard treatment for patients with ESRD[10]. Whilst it is recognised that reducing cardiovascular risk factors at all stages of CKD is important[11], the benefit of targeted therapies requires clarification in ESRD. We have described the incidence, associations of and outcomes following stroke in those with a functioning renal transplant in the west of Scotland over a 6-year period. Our large single centre study describes a high stroke incidence, presence of conventional cardiovascular risk factors and, most striking, fatality outcomes worse than that expected in the general population. Further to this, although AF was associated with time to ischemic stroke, the key prevention strategy – warfarin – was not associated with benefit in our cohort.

Incidence

The incidence of cerebrovascular disease increases with worsening renal function and peaks at ESRD[12]. Of concern, previous reports have suggested that the initiation of dialysis itself may cause stroke[3]. Renal transplantation improves

patient outcomes by reducing risk of cardiovascular related death[13,14] however, the effect of transplantation on stroke risk has only recently been described[8]. In this retrospective USRDS review the authors describe that renal transplantation predicts a 34% reduction in risk of subsequent cerebrovascular events compared to remaining on the transplant waiting list. They describe an incidence of 24.6 cerebrovascular events/1000 patient-years in those who receive a renal transplant compared to 45.6 events/1000 patient years in those remaining on the waiting list. In another USRDS review a more recent study[15] presented an event incidence of 7.4 ischemic strokes/1000 patient years. This apparent difference in rates can be explained by different selection criteria but more so by the definition of cerebrovascular events between the two studies. The report with the higher incidence included all of ischemic stroke, hemorrhagic stroke and TIA rather than strictly ischemic stroke. With focus on the UK population, we have recently reported the stroke incidence of those receiving maintenance hemodialysis for ESRD as 41.5/1000 patient years[6] – a result significantly higher than the observed rate in the transplant population. Our present study has described the incidence within a well-defined population, observing an incidence rate of 5.96 cerebrovascular events/1000 patient-years – greater than twice the underlying incidence of stroke in the general population for Scotland[16]. Although high, we note this is lower than the only other UK published study describing incidence at 12.4/1000 patient years[17]. Whereas we report incidence of stroke in all patients attending our unit, the other study retrospectively assessed only those who were selected for a steroid-sparing immunosuppressant regime. The two studies' populations are therefore affected by this bias; for example pre-existing ischemic heart disease and diabetes were greater

in their population compared to ours (14.8% and 25.4% v 7% and 17.2% respectively).

Stroke risk factors

Previous retrospective studies have attempted to clarify the risk factors underpinning stroke[18,19] in the ESRD population. Surprisingly, conventional risk factors such as hypertension, hyperlipidemia and AF are not consistently associated with stroke risk in those receiving dialysis. Conversely in the transplant population, described risk factors mimic those seen in the general population. Older age, diabetes, hypertension and AF are consistent findings on multivariable analyses[15,17,20,21]. Assessing our cohort as a whole we discovered age, prior stroke, diabetes, higher systolic blood pressure and AF were associated with stroke on univariable regression. Multivariable analysis found diabetes, systolic BP, age and prior stroke were significantly associated with stroke. Excluding cases with prior stroke we found that higher hemoglobin and presence of diabetes were independently associated with stroke. Serum creatinine was not associated with stroke. Using Kaplan-Meir survival analyses, we demonstrated a significant association between presence of AF and stroke, although we could not demonstrate a significant influence of warfarin on stroke in those with AF (figures 1 and 2).

Outcomes

All-cause mortality was significantly higher following stroke. An adjusted multivariable Cox regression analysis demonstrated a significant association between stroke and time to death. Further, case fatality (death within first 7 days) following stroke was high and early outcomes were worse in those with first ever

stroke. Our findings reveal that fatality rates are higher than the background population and more in keeping with those reported in the dialysis population[22]. Whilst it is inevitable that suffering a stroke will negatively impact survival, the similarity of reported outcomes to those who remain on dialysis is notable and suggest an effect of ESRD which is not reduced by transplantation.

Study limitations

We describe the incidence, associations and outcomes of stroke in a large single centre renal transplant unit encompassing 956 patients over 4409 years of patient follow-up. Despite our large sample size and completeness of follow-up we do recognize the following limitations. As a retrospective study we can only describe association and not causation. The small number of strokes in the group of those receiving a transplant following a period on dialysis limits our ability to detect associations on multivariable regression – specifically, we acknowledge that the relatively low number of stroke events may lead to type 2 errors in our analyses, which may explain the absence of effect from atrial fibrillation on multivariable analysis. We have not included data on immunosuppressive medication, although we acknowledge recent evidence suggesting steroid use independently increases the risk of CVA[17]. Finally, important data were not available which may offer an explanation for the lack of effect from warfarin. For example, we are unable to comment on cases where warfarin was discontinued and the lack of INR reporting limits comment about time in the therapeutic range.

Conclusion

The incidence of stroke in those with a functioning renal transplant is higher than the background population, but markedly lower than those on hemodialysis. Stroke in transplant recipients is associated with similar conventional risk factors observed in the general population, but it remains unclear if reversal of modifiable factors can reduce stroke risk. Of primary interest, although AF is associated with time to stroke, prior warfarin use did not confer protection in this study. Further, the outcomes following stroke are dismal – resembling those who remain on dialysis. Dedicated trials for stroke therapies are needed in the transplant population to determine the reversibility of the increased stroke risk and the effects on outcomes.

Author Contributions

MDF, JD and PBM had the original idea and designed this study. MDF, PT and RF analysed and interpreted the data. MDF wrote the first draft and all authors contributed to the final draft.

Conflicts of Interest: None

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	No Stroke n=930	Ischemic Stroke n=22	Hemorrhagic Stroke n =4	P value (IS vs No Stroke)
Median age at starting RRT [IQR]	39.7 [29.2,50.5]	44.1 [35.6,51.7]	45.9.0 [41.0,61.0]	0.22
Female (%)	373 (40.1%)	10 (45.5%)	0	0.613
PRD n (%)				0.079
Diabetic Nephropathy	73 (7.8)	1 (4.5)	1 (25)	
Interstitial disease	129(13.9)	0	-	
SLE/HUS	14(1.5)	1 (4.5)	-	
PCKD	87 (9.4)	3 (13.6)	-	
Reno-vascular disease	24(2.6)	0	1 (25)	
GN	182(19.6)	2 (9.1)	1 (25)	
Other	36 (3.9)	3 (13.6)	1 (25)	
Missing	385 (41.4)	12 (54.5)	-	
RRT vintage, years; Median [IQR]	8.57 [3.16,16.19]	12.06 [8.80,19.91]	7.13 [2.68,16.80]	0.017
Prior CeVD (%)	30 (3.2)	9 (40.9)	3 (75)	<0.001
Prior CVD (%)	64 (6.9)	3(13.6)	0	0.221
Prior DM (%)	153 (16.5)	9 (40.9)	2 (50)	0.003
Prior AF (%)	81 (8.7)	6 (27.3)	1 (25)	0.003
Warfarin (%)	131 (14.1)	5 (22.7)	1 (25)	0.252
Antiplatelet (%)	636 (68.4)	16 (72.7)	4 (100)	0.665
Hb, g/L; Median [IQR]	12.4 [11.2,13.6]	12.7 [11.2,14.6]	13.1 [12.1.13.7]	0.227
Albumin, g/L; Median [IQR]	38.0 [36.0,40.0]	37.0 [35.0,39.0]	38.0 [37.5.41.0]	0.126
SCr, µmol/L; Median [IQR]	135.0 [107.0,173.0]	134.0 [121.0,161.0]	136.5 [115.151.5]	0.652
AdCal, mmol/L; Median [IQR]	2.4 [2.4,2.6]	2.5 [2.3,2.5]	2.5 [2.4.2.7]	0.429
PO4, mmol/L; Median [IQR]	0.9 [0.7,1.1]	0.9 [0.9,1.1]	1.0 [0.8.1.2]	0.106
SBP, mmHg; Median [IQR]	140.0 [128.0,153.0]	149.0 [140.0,155.0]	159.5 [145.5.163.0]	0.152
DBP, mmHg; Median [IQR]	79.0 [72.0,86.0]	81.0 [74.0,89.0]	82.0 [79.0.89.0]	0.670
uPCR, mg/mmol; Median [IQR]	19.8 [8.9,47.1]	27.0 [9.7,80.0]	8.8 [4.4.47.1]	0.350
Death (%)	142 (15.3)	12 (54.5)	3 (75)	<0.001
SIMD most deprived (%)	448 (48.6)	14 (63.6)	2 (50)	0.163

Table 1.Characteristics of all transplant recipients, Stroke vs no stroke, split by stroke subtype. Abbreviations used in the table; IS = Ischemic stroke, RRT = Renal Replacement Therapy, PRD = Primary Renal Diagnosis, SLE = Systemic Lupus Erythematosis, HUS = Hemolytic uraemic syndrome, PCKD =

Polycystic Kidney Disease, GN = Glomerulonephritis, CeVD = Cerebrovascular disease, CVD = Cardiovascular disease, DM = Diabetes Mellitus, AF = Atrial Fibrillation, Hb = Hemoglobin, SCr = serum creatinine, AdCal = Adjusted serum calcium, PO4 = serum phosphate, SBP = systolic blood pressure, DBP = diastolic blood pressure, uPCR = urinary protein:creatinine ratio, SIMD = Scottish Index of Multiple Deprivation.

Univariable				Multivariable			
Variable	HR	p	95% CI	Variable	HR	p value	95% CI
Age	1.04	0.010	1.01 – 1.07	Age	1.04	0.034	1.00 – 1.08
Female	0.89	0.766	0.40 – 1.96				
DM	3.68	0.001	1.69 – 8.00	DM	2.29	0.041	1.04 – 5.05
CeVD	23.73	<0.001	10. 91 – 51.63	CeVD	19.81	<0.001	8.98 – 43.72
CVD	1.37	0.607	0.41 – 4.57				
SBP (mmHg)	1.02	0.044	1.00 – 1.04				
DBP (mmHg)	1.02	0.229	0.99 – 1.07				
AF	4.59	0.001	1.92 – 10.94				
Warfarin	2.06	0.122	0.83 – 5.12				
Antiplatelet	1.72	0.242	0.69 – 4.3				
Hb (g/L)	1.01	0.332	0.99 – 1.03				
Albumin (g/L)	0.94	0.134	0.86 – 1.02				
SCr (µmol/L)	0.996	0.380	0.99 – 1.00				
AdCal (mmol/L)	0.57	0.641	0.05 – 6.2				
PO4 (mmol/L)	2.80	0.151	0.69 – 11.4				
uPCR (mg/mmol)	1.00	0.336	0.998 – 1.00				
RRT Vintage	1.0	0.157	1.0-1.0				
Deprivation	1.82	0.136	0.83 – 4.0				

Table 2 All transplant recipients. Variables entered into the multivariable analysis were selected following backward stepwise regression, using variables with p<0.1. Abbreviation used in the table; DM = Diabetes Mellitus, CeVD = Cerebrovascular disease, CVD = Cardiovascular disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, AF = atrial fibrillation, Hb = hemoglobin, SCr = serum creatinine, AdCal = adjusted serum calcium, PO4 = serum phosphate, uPCR = urinary protein:creatinine ratio.

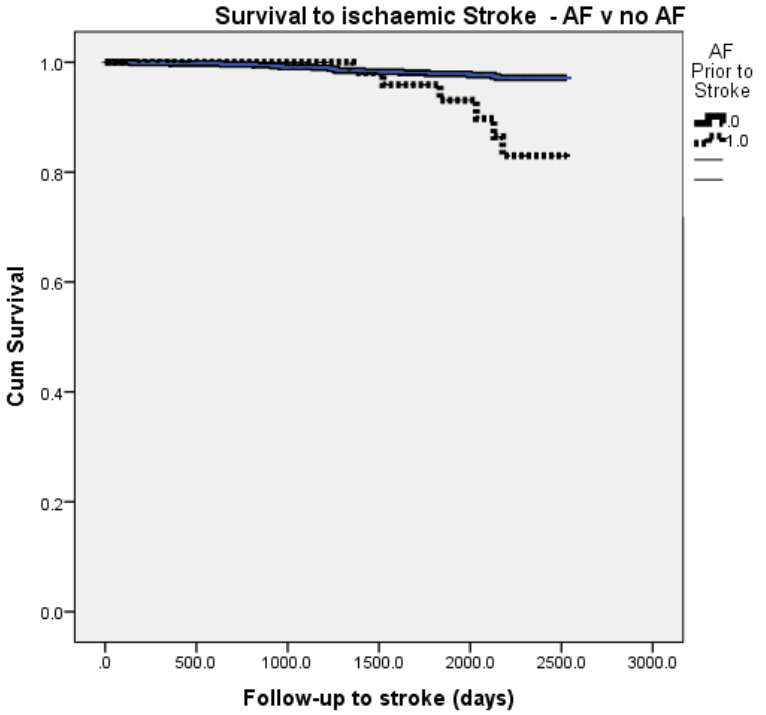

Figure 1 Time to ischemic stroke – AF v no AF in all transplant recipients, p <0.001

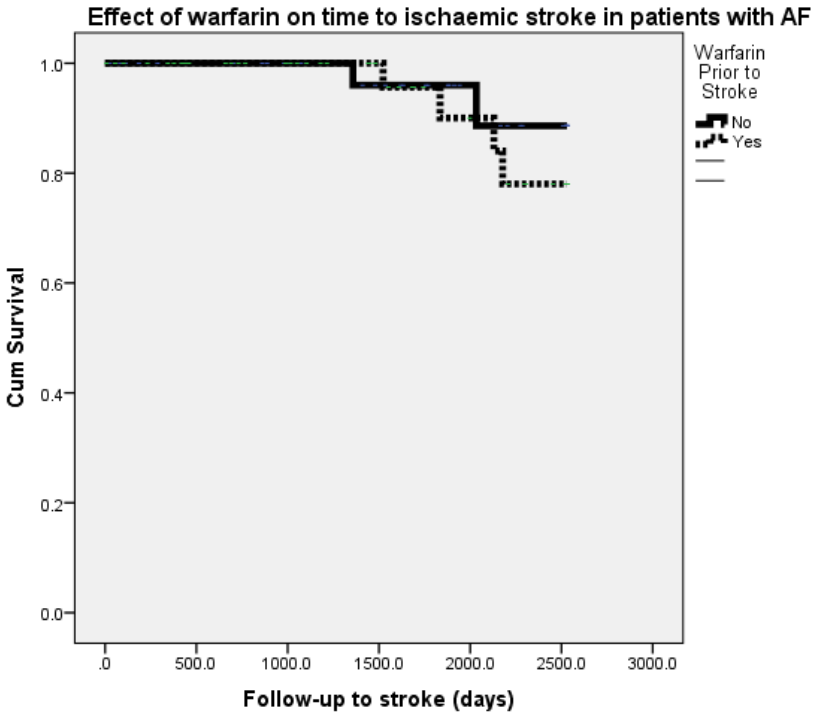

Figure 2 Time to ischemic stroke in patients with AF, warfarin v no warfarin, p=0.573

SUPPLEMENTARY TABLES

	Alive n=799	Dead n=157	P value
Median Age at Starting RRT [IQR]	39.0 [28.0,48.6]	45.4 [32.9,55.2]	<0.001
Female (%)	322 (40.3)	61 (38.9)	0.735
PRD Diagnosis, n (%)			
Diabetic Nephropathy	62 (7.8)	13 (8.3)	
Interstitial disease	115 (14.4)	14 (8.9)	
SLE/HUS	13(1.6)	2 (1.3)	
PCKD	75 (9.4)	15 (9.6)	
RVD	15(1.9)	10 (6.4)	
GN	170(21.3)	15 (9.6)	
Other	32 (4)	7 (4.5)	
Missing	317 (39.7)	81 (51.6)	<0.001
Median RRT Vintage; years [IQR]	7.45 [2.79,15.14]	14.18 [8.15,20.89]	<0.001
Prior CeVD (%)	28 (3.5)	14 (8.9)	0.002
Prior CVD (%)	46 (5.8)	21 (13.4)	0.001
Prior DM (%)	134 (16.8)	30 (19.1)	0.478
Prior AF (%)	55 (6.9)	33 (21)	<0.001
Warfarin (%)	106 (13.3)	31 (19.7)	0.034
Antiplatelet (%)	529 (66.2)	127 (80.9)	<0.001
Hb, g/dL [IQR]	124 [112,136]	124.0[111,137]	0.729
Albumin, g/L [IQR]	39.0 [36,41]	37.0 [33,39]	<0.001
SCr, µmol/L [IQR]	133.0 [107,165]	152.0 [152,113]	0.003
AdCal, mmol/L [IQR]	2.5 [2.4,2.6]	2.5 [2.4,2.5]	0.047
PO4, mmol/L [IQR]	0.9 [0.7,1.1]	1.0 [0.9,1.2]	<0.001
SBP, mmHg [IQR]	140 [127,152]	142.5 [130,157]	0.037
DBP, mmHg [IQR]	79.0 [72,86]	80.0 [70,84]	0.230
uPCR, mg/mmol [IQR]	18.9 [8.4,41.3]	35.1 [12.99,83.3]	<0.001
SIMD most deprived	383 [48.3]	81 [52.3]	0.367

Table s1 All transplant recipients, Dead v alive during follow-up. Abbreviations used in the table; RRT = Renal Replacement Therapy, PRD = Primary Renal Diagnosis, SLE = Systemic Lupus Erythematosis, HUS = Hemolytic uraemic syndrome, PCKD = Polycystic Kidney Disease, GN = Glomerulonephritis, CeVD = Cerebrovascular disease, CVD = Cardiovascular disease, DM = Diabetes Mellitus, AF = Atrial Fibrillation, Hb = Hemoglobin, SCr = serum creatinine, AdCal = Adjusted serum calcium, PO4 = serum phosphate, SBP = systolic blood pressure, DBP = diastolic blood pressure, uPCR = urinary protein:creatinine ratio, SIMD = Scottish Index of Multiple Deprivation.