

Characteristics and Prognosis of Stroke in Living Donor Renal Transplant Recipients

Takafumi Mizuno, Takao Hoshino, Kentaro Ishizuka, Sono Toi, Ayako Nishimura, Shuntaro Takahashi, Sho Wako and Kazuo Kitagawa

Department of Neurology, Tokyo Women's Medical University Hospital

Aims: We aimed to determine the characteristics and vascular outcomes of stroke in renal transplant (RT) recipients and compare them with those in patients on hemodialysis (HD) and those with no renal replacement therapy (RRT).

Methods: In this prospective observational study, 717 patients (mean age, 70.8 years; male, 60.5%) with acute ischemic stroke within one week of onset were consecutively enrolled and followed for one year. The patients were classified into three groups: (1) living donor RT recipients ($n=27$); (2) patients on maintenance HD before the index stroke ($n=39$); and (3) those with no history of RRT ($n=651$). The primary outcome was a composite of major adverse cardiovascular events (MACE).

Results: Diabetic nephropathy was the most common reason for RRT in both RT and HD patients. RT patients were more likely to have embolic stroke of undetermined source (33.3%) than others, whereas HD patients more often had cardioembolism (51.3%). No difference was observed in the MACE risk between the patients in RT and non-RRT groups (annual rate, 11.3% vs. 13.1%; log-rank $P=0.82$; hazard ratio [95% confidence interval], 0.92 [0.29-2.98]). In contrast, HD patients had a greater risk of MACE than those with no RRT (annual rate, 28.2% vs. 13.1%; log-rank $P=0.019$; hazard ratio [95% confidence interval], 2.24 [1.16-4.3]).

Conclusions: The underlying etiologies of stroke differed in RT and HD patients. The one-year risk of MACE for stroke patients who had received an RT was lower than that for patients undergoing HD and comparable with that of patients with no RRT.

Key words: Embolic stroke of undetermined source, End stage kidney disease, Hemodialysis, Renal transplantation, Stroke

Introduction

Renal replacement therapy (RRT), including renal transplant (RT) and hemodialysis (HD), remarkably increases the life expectancy of patients with end-stage kidney disease^{1, 2}. However, RRT patients have a substantial risk of cerebro- and cardiovascular events, which should be a major consideration for life-long managements after RRT. According to data from the United States Renal Data Systems³, the prevalence of stroke and coronary artery disease were 26% and 9%, respectively, in patients with a functioning RT. For patients undergoing HD,

the prevalence was even higher; 44% and 17% had experienced stroke and coronary events, respectively. Furthermore, the leading cause of death is vascular accidents for both RT and HD patients³. Hence, there is the need to develop a better approach to prevent and treat vascular diseases in patients undergoing RRT.

To date, stroke in HD patients have been well studied in terms of clinical aspects and prognosis⁴⁻⁸. On the other hand, limited data are available on stroke in RT recipients. Given the recent increase in the number of patients with renal failure receiving RT³, a better understanding of stroke after RT is of

Address for correspondence: Takao Hoshino, Department of Neurology, Tokyo Women's Medical University Hospital 8-1, Kawada-cho, Shinjuku-ku, 162-8666 Tokyo, Japan. E-mail: hoshino.takao@twmu.ac.jp

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utmost importance. Living donor RT is much more common than cadaveric RT in Japan, and it accounts for approximately 85.9 % of all RT cases, whereas cadaveric RT is more common in the majority of countries³). In the present study, we aimed to characterize stroke in living donor RT recipients based on robust clinical, laboratory, and imaging data and determine their one-year prognosis compared with those receiving HD as well as those with no history of RRT.

Methods

Study Design and Patients

The Tokyo Women's Medical University (TWMU) Stroke Registry is a single-center prospective observational study, in which patients with acute ischemic stroke or transient ischemic attack hospitalized at our center within one week of onset were consecutively enrolled. The study adhered to the ethical principles of the 1975 Declaration of Helsinki, as well as the Ethical Guidelines for Epidemiological Research by the Japanese government and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study protocol was approved by the ethics committee of Tokyo Women's Medical University Hospital (approval no. 2955-R2). Written informed consent was obtained from all the patients. The TWMU Stroke Registry is registered at UMIN000031913 (<https://upload.umin.ac.jp>). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Between December 2013 and September 2019, 806 patients were enrolled in the study. After excluding 7 patients who met the exclusion criteria (e.g., stroke mimics as final diagnosis or more than one week after stroke onset) and 82 patients with transient ischemic attack, the data of 717 patients with acute ischemic stroke were included for the present analysis (**Supplementary Fig. 1**).

All the cases of stroke were diagnosed by board-certified stroke neurologists based on neurological and radiological findings. Upon admission, the neurological symptoms were assessed using the National Institutes of Health Stroke Scale (NIHSS) score. The patient data collected included demographic data, clinical symptoms during the qualifying event, medical history, medications, investigations (including blood tests, brain and cerebral artery imaging, 24-hour Holter electrocardiogram, and ultrasonic echocardiography), management (medical treatment, revascularization procedure, and surgery), and the occurrence of clinical

events after the qualifying event using a structured case report form.

Renal Disease

We identified patients who had a history of living donor RT or were undergoing maintenance HD before the index stroke (RT and HD groups, respectively). Information on primary kidney diseases that necessitated RRT was obtained from previous medical records. None of the patients in our cohort received cadaveric RT. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula with the Japanese coefficient; chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m².

Evaluation of Atherosclerotic Disease

The intracranial arteries were examined using time-of-flight magnetic resonance angiography ($n=686$) and/or computed tomography angiography ($n=146$). The narrowest diameter of each stenosed vessel was measured and divided by the diameter of the normal vessel proximal to the lesion or distal to the lesion if the proximal artery was diseased. Significant intracranial artery stenosis was defined as $>50\%$ stenosis or occlusion.

Extracranial carotid atherosclerosis was evaluated using ultrasonography ($n=675$) and/or computed tomography angiography ($n=81$) and/or time-of-flight magnetic resonance angiography ($n=66$). We defined significant extracranial artery stenosis as the presence of atherosclerotic stenosis of $>50\%$ or occlusion according to the European Carotid Surgery Trial criteria⁹.

Aortic atherosclerosis was evaluated using transesophageal echocardiography ($n=226$). Mobile plaques were diagnosed as mobile components that swung on their peduncles. An ulcerative plaque was diagnosed as a discrete indentation of the luminal surface of the plaque with a base width, as well as a maximum depth, of at least 2 mm. Complex aortic atheroma was defined as any plaque with a thickness of ≥ 4 mm or ulceration or mobile components¹⁰.

Ischemic Stroke Subtype

The etiologies of ischemic stroke were classified into atherothrombosis, cardioembolism, small-vessel disease, other determined causes, and undetermined causes, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification¹¹. Strokes of undetermined causes were further divided into embolic stroke of undetermined source (ESUS), stroke with coexisting etiologies, and incomplete

Table 1. Primary renal diagnosis

| | Renal transplant (<i>n</i> =27) | Hemodialysis (<i>n</i> =39) |
|----------------------------|--|---|
| Diabetic nephropathy | 9 | 16 |
| IgA nephropathy | 4 | 2 |
| Renal sclerosis | 2 | 6 |
| Chronic glomerulonephritis | 1 | 6 |
| Polycystic kidney | 1 | 1 |
| Undetermined | 6 | 6 |
| Others | Lupus nephritis (<i>n</i> =1) HUS (<i>n</i> =1) Gouty kidney (<i>n</i> =1) Nephrotic syndrome (<i>n</i> =1) | CIN (<i>n</i> =1) MPGN (<i>n</i> =1) |

Abbreviations: CIN=contrast induced nephropathy; HUS=hemolytic uremic syndrome; MPGN=membranoproliferative glomerulonephritis.

investigations. ESUS was diagnosed based on the proposed criteria by the cryptogenic stroke/ESUS international working group (i.e., stroke detected by computed tomography or magnetic resonance imaging that is not lacunar; absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischemia; no major-risk cardioembolic source of embolism or no other specific cause of stroke identified)¹²).

Follow-Up and Outcomes

Patients visited our center after 3 months and thereafter every 1 year for 3 years after enrollment. This study reports one-year outcomes. At follow-up visits, findings from physical examinations, treatments, any occurrence of clinical events, and the modified Rankin Scale (mRS) scores were recorded. If the patient could not be reached for follow-up, a relative or caregiver was interviewed via telephone. The primary outcome was a composite of major adverse cardiovascular events (MACE), including nonfatal stroke (ischemic or hemorrhagic), nonfatal acute coronary syndrome, major peripheral artery disease, and vascular death. Vascular death was defined as fatal acute coronary artery disease, fatal stroke, and other cardiovascular deaths. Secondary outcomes included stroke subtype and all-cause mortality. Stroke-related functional outcomes were assessed using the mRS score at one year. A poor functional outcome was defined as an mRS score of ≥ 3 .

Statistical Analysis

Quantitative variables were expressed as mean (standard deviation) for normally distributed data or median (interquartile range). The qualitative variables were presented as frequencies (percentages). The patients were classified into the RT, HD, and non-RRT groups. We further divided the non-RRT

patients into those with and without CKD. The comparisons of the groups were performed using the *t*-test, Mann-Whitney *U* test, one-way analysis of variance, or Kruskal-Wallis test for quantitative variables and χ^2 test for qualitative variables, as appropriate. The event rates were estimated using the Kaplan-Meier method, and the inter-group differences were assessed using the log-rank test. Cox proportional hazard regression models were used to calculate the age- and sex-adjusted hazard ratios and 95% confidence intervals for the patients with RT and HD, in comparison with those without RRT. The data for the patients with no information at one year were censored at the time of the last available follow-up. For a given outcome, the patients who died of causes other than the outcome were censored at the time of death. Events that occurred after one year of follow-up were not included in the current analysis. To identify the predictors of poor functional outcomes, we performed multiple logistic regression analysis with adjustments for age, sex, RRT modality, and admission NIHSS score. For all the analyses, statistical significance was set at $P < 0.05$.

Results

Of the 717 patients (mean age, 70.8 years; male, 60.5%), 27 patients (3.8 %) had received living donor RT and 39 patients (5.4 %) were undergoing maintenance HD; the remaining 651 patients (90.8 %) had no history of RRT. The median duration from RT surgery to stroke onset was 33 months (interquartile range, 7-150 months) in the RT group. The median duration from HD initiation to stroke onset was 124 months (interquartile range, 63-157 months) in the HD patients. Diabetic nephropathy was the most frequent reason for RRT in both the RT and HD groups (Table 1). The usage rates of

Table 2. Baseline characteristics

| | Renal transplant (<i>n</i> =27) | Hemodialysis (<i>n</i> =39) | <i>P</i> -value* | No RRT (<i>n</i> =651) | <i>P</i> -value† |
|---------------------------|----------------------------------|------------------------------|------------------|-------------------------|------------------|
| Age, y | 59 ± 12 | 67 ± 13 | 0.018 | 71 ± 13 | <0.001 |
| Male | 22 (81.5) | 23 (59.0) | 0.049 | 389 (59.8) | 0.058 |
| Medical history | | | | | |
| Hypertension | 20 (74.1) | 34 (87.2) | 0.18 | 483 (74.2) | 0.15 |
| Diabetes mellitus | 12 (44.4) | 19 (48.7) | 0.73 | 250 (38.4) | 0.38 |
| Dyslipidemia | 14 (51.9) | 18 (46.1) | 0.65 | 308 (47.3) | 0.89 |
| Current smoking | 3 (11.1) | 3 (7.7) | 0.64 | 120 (18.5) | 0.11 |
| Atrial fibrillation | 6 (22.2) | 15 (38.5) | 0.16 | 142 (21.8) | 0.075 |
| Chronic heart failure | 2 (7.4) | 12 (30.8) | 0.016 | 65 (10.0) | 0.002 |
| Stroke | 4 (14.8) | 10 (25.6) | 0.28 | 130 (20.0) | 0.55 |
| Coronary artery disease | 2 (7.4) | 8 (20.5) | 0.13 | 92 (14.1) | 0.31 |
| Peripheral artery disease | 2 (7.4) | 8 (20.5) | 0.13 | 30 (4.6) | 0.003 |
| Investigations | | | | | |
| Intracranial artery | | | | | |
| >50% stenosis | 5 (18.5) | 13 (33.3) | 0.18 | 184 (28.4) | 0.39 |
| Extracranial artery | | | | | |
| >50% stenosis | 2 (7.4) | 4 (10.3) | 0.69 | 96 (14.9) | 0.37 |
| Extracranial artery | | | | | |
| 30%-50% stenosis | 4 (14.8) | 6 (15.4) | 0.95 | 84 (13.0) | 0.89 |
| Complex aortic atheroma | 2 (20.0) | 4 (33.3) | 0.48 | 51 (27.7) | 0.78 |
| Laboratory data | | | | | |
| Creatinine mg/dL | 2.4 ± 2.5 | 7.6 ± 2.7 | <0.001 | 1.0 ± 0.6 | <0.001 |
| LDL-c, mg/dL | 111 ± 41 | 98 ± 38 | 0.18 | 117 ± 38 | 0.009 |
| HDL-c, mg/dL | 50 ± 22 | 51 ± 15 | 0.74 | 55 ± 17 | 0.12 |
| Triglycerides, mg/dL | 139 ± 64 | 117 ± 58 | 0.16 | 132 ± 96 | 0.60 |
| HbA1c, % | 6.0 ± 0.7 | 6.2 ± 1.7 | 0.55 | 6.8 ± 5.4 | 0.59 |
| BNP, pg/mL | 99 ± 168 | 728 ± 790 | <0.001 | 136 ± 231 | <0.001 |
| Homocysteine, nmol/mL | 15.2 (11.6-19.4) | 21.5 (14.5-26.9) | 0.064 | 9.4 (7.2-12.6) | <0.001 |
| hsCRP, mg/mL | 1.3 (0.2-2.3) | 5.2 (1.5-14.8) | 0.44 | 1.4 (0.4-5.4) | 0.80 |
| IL-6, pg/mL | 4.0 (1.5-11.3) | 9.3 (4.3-13.5) | 0.14 | 3.5 (1.9-8.2) | 0.52 |
| NIHSS | 2 (1-4) | 4 (2-6) | 0.13 | 3 (1-5) | 0.40 |

Figures are expressed as *n* (%), mean ± standard deviation, or median (interquartile range).

*Comparisons between patients with renal transplant and hemodialysis.

†Comparisons among patients with renal transplant, hemodialysis, and no RRT.

Abbreviations: BNP=brain natriuretic peptide; HDL-c=high density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; IL-6=interleukin-6; LDL-c=low density lipoprotein cholesterol; NIHSS=National Institute of Health Stroke Scale; RRT=renal replacement therapy.

immunosuppressive agents in patients with RT are shown in [Supplementary Table 1](#). Immunosuppressive regimens were not changed after the index stroke.

Table 2 shows the baseline characteristics of the patients. Patients in the RT group were younger, and those in the HD group more often had chronic heart failure and peripheral artery disease than the others. There were no differences in the prevalence of atherosclerotic diseases in the intra- and extracranial arteries and aortas among the 3 groups. The low-density lipoprotein concentrations were lower, and the homocysteine concentrations were higher, in the RT and HD groups than in the non-RRT group. The

brain natriuretic peptide level was highest in the HD group. The comparisons of the baseline characteristics of the patients with the RT, HD, no RRT with CKD, and no RRT without CKD groups are shown in [Supplementary Table 2](#). Regarding the etiologic subtype ([Fig. 1](#) and [Supplementary Fig. 2](#)), ESUS was more frequent in the RT patients than in the others. As shown in [Supplementary Table 3](#), there were no relationships between specific immunosuppressive agents with the development of ESUS. On the other hand, cardioembolism was more frequent in the HD patients. In the HD group, unfractionated heparin and low-molecular-weight heparin were used in 32

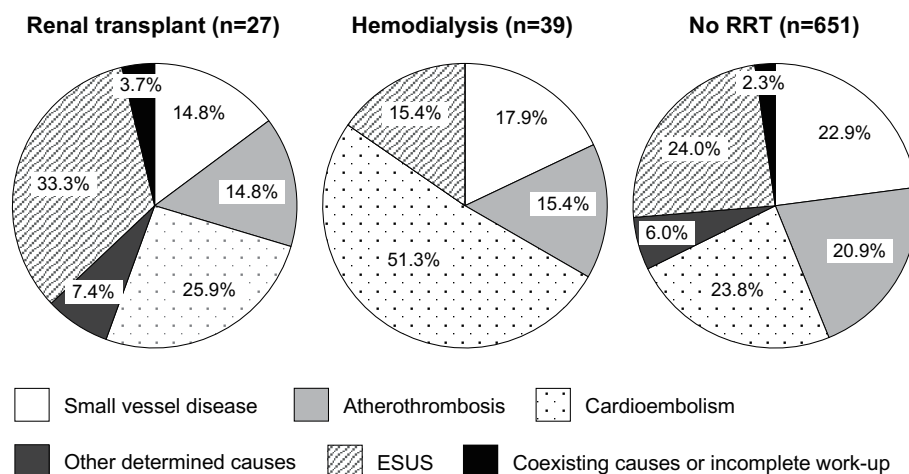


Fig. 1. Etiologic subtype of ischemic stroke

Distributions of etiologic subtype were significantly different between the groups ($P=0.031$). Abbreviations: ESUS=embolic stroke of undetermined source; RRT=renal replacement therapy.

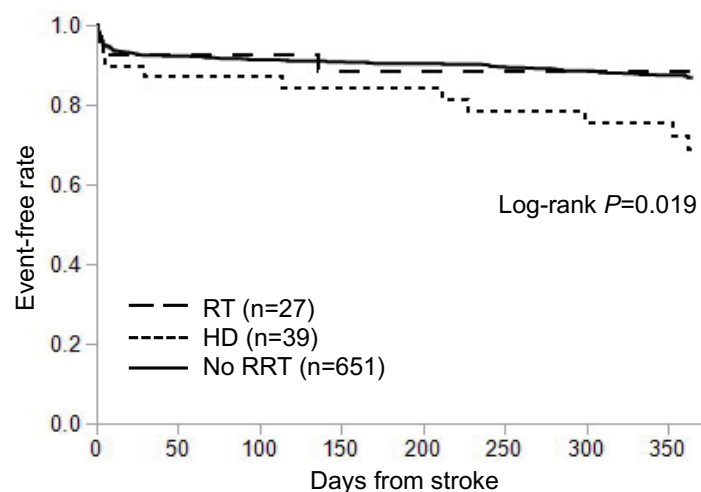


Fig. 2. Kaplan-Meier curves for major cardiovascular events

Abbreviations: HD=hemodialysis; RRT=renal replacement therapy; RT= renal transplantation.

and 6 patients, respectively, for anticoagulation of the extracorporeal circuit. There were no significant associations of the type of anticoagulant for HD with a specific subtype of ischemic stroke.

The data on medication use at discharge and surgery are presented in [Supplementary Table 4](#). The usage rates of antiplatelet and anticoagulant agents were 74.1% and 32.1% in the RT group and 59.0% and 46.5% in the HD group, respectively. Among the RT and HD patients with 74.1% and 87.2% prevalence of hypertension, ≥ 1 antihypertensive agents were used in 61.5% and 82.1%, respectively at discharge.

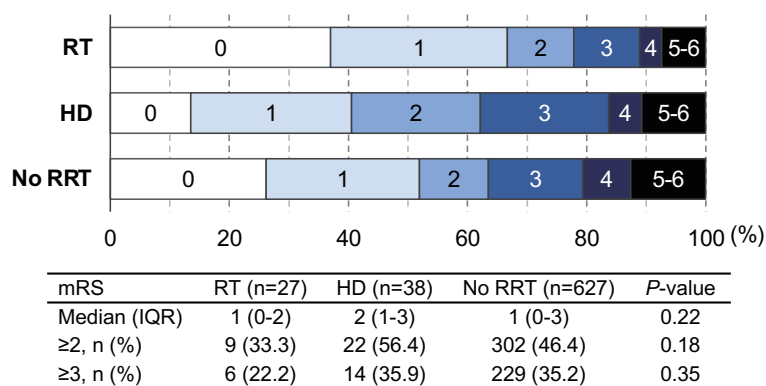
One-Year Event Risk

Among the 717 patients, 96 had at least one vascular event within one year, giving an event rate of 13.4% (95% confidence interval, 11.1%–16.1%). As shown in [Fig. 2](#) and [Table 3](#), patients in the HD group had a significantly higher risk of MACE than those in the non-RRT group. No differences were observed between the MACE risks of the patients in the RT and non-RRT groups. These results were consistent when patients with no RRT history were further divided according to the presence or absence of CKD ([Supplementary Fig. 3](#)). There was no difference in the risk of all-cause mortality across the three groups.

Table 3. Event risk at one year

| | Event rate, n (%/year) | Log rank <i>P</i> -value | Adjusted HR (95% CI) | <i>P</i> -value |
|-----------------------------|------------------------|--------------------------|----------------------|-----------------|
| Primary outcome | | | | |
| Major cardiovascular events | | | | |
| No RRT | 82 (13.1) | - | 1.00 (ref) | - |
| Renal transplant | 3 (11.3) | 0.82 | 0.92 (0.29-2.98) | 0.89 |
| Hemodialysis | 10 (28.2) | 0.019 | 2.14 (1.11-4.14) | 0.020 |
| Secondary outcome | | | | |
| Stroke | | | | |
| No RRT | 71 (11.3) | - | 1.00 (ref) | - |
| Renal transplant | 3 (11.3) | 0.97 | 1.09 (0.33-3.54) | 0.89 |
| Hemodialysis | 6 (15.8) | 0.39 | 1.49 (0.65-3.45) | 0.35 |
| Ischemic stroke | | | | |
| No RRT | 64 (10.1) | - | 1.00 (ref) | - |
| Renal transplant | 3 (11.3) | 0.83 | 1.13 (0.35-3.70) | 0.84 |
| Hemodialysis | 5 (13.2) | 0.55 | 1.39 (0.56-3.47) | 0.48 |
| All-cause death | | | | |
| No RRT | 46 (7.3) | - | 1.00 (ref) | - |
| Renal transplant | 1 (3.7) | 0.49 | 0.57 (0.08-4.22) | 0.58 |
| Hemodialysis | 4 (10.4) | 0.48 | 1.57 (0.58-4.39) | 0.39 |

Abbreviations: CI=confidence interval; HR=hazard ratio; RRT=renal replacement therapy.

**Fig. 3.** Modified Rankin Scale score at one year

Abbreviations: HD=hemodialysis; IQR=interquartile range; mRS=modified Rankin Scale; RRT=renal replacement therapy; RT=renal transplantation.

There were 3 and 5 patients who experienced recurrent stroke in the RT and HD groups, respectively. Subtypes of the index and recurrent strokes were coincident, except for 1 patient in the HD group who had atherothrombosis at first and then developed cardioembolism during follow-up ([Supplementary Table 5](#)). [Supplementary Table 6](#) shows comparisons of the 1-year MACE risk between each immunosuppressive agent users and non-users among the RT patients. Cyclosporine and mizoribine tended to raise the risk of MACE with no statistical differences, whereas tacrolimus and mycophenolate

mofetil were associated with a lower risk. In the HD group, 32 (84.2%) and 6 (15.8%) patients used unfractionated heparin and low-molecular-weight heparin during the HD procedure, respectively. As shown in [Supplementary Table 7](#), the event rates of MACE and ischemic stroke were not significantly different between the anticoagulant drugs.

One-Year Functional Prognosis

[Fig. 3](#) shows the distributions of the mRS scores at one-year follow-up. The percentages of patients with poor functional outcomes tended to be lower in

Table 4. Multivariable analysis for disability at one year

| | OR (95% CI) | P-value |
|-----------------------------|------------------|---------|
| Age, per 1 year increase | 1.05 (1.04-1.07) | < 0.001 |
| Male | 0.98 (0.68-1.39) | 0.91 |
| RRT | | |
| No RRT | 1.00 (ref) | - |
| Renal transplant | 1.11 (0.41-3.04) | 0.83 |
| Hemodialysis | 1.33 (0.64-2.76) | 0.44 |
| NIHSS, per 1 point increase | 1.16 (1.11-1.20) | < 0.001 |

Disability was defined as an modified Rankin Scale score of ≥ 3 at 1 year after index stroke.

Abbreviations: CI=confidence interval; OR=odds ratio; RRT=renal replacement therapy; NIHSS=National Institute of Health Stroke Scale.

the RT group, although the difference was not statistically significant. The inter-group difference was significant when the patients with no RRT were subdivided into those with CKD and those without CKD (**Supplementary Fig. 4**). The multivariable analysis showed that RT or HD was not independently associated with poor functional prognosis at one year; age and NIHSS were independent determinants of disability (**Table 4**).

Discussion

Our main findings were as follows: (1) ESUS and cardioembolism were the most frequent stroke subtypes in RT and HD patients, respectively; (2) the one-year risk of MACE in stroke patients with RT was significantly lower than that in the HD patients and as low as that in the non-RRT patients; and (3) the one-year functional outcomes tended to be better in RT patients than in HD patients. While both risk factor management and appropriate antithrombotic therapies are essential at all stages of CKD¹³, the benefits of targeted therapies may differ in the RT and HD patients, given the substantial disparities in characteristics and outcomes of stroke between them.

Ischemic Stroke Subtype

Our results are consistent with a prior study reporting that 66% of ischemic strokes after RT were cryptogenic and 31% were likely to be embolic strokes¹⁴. The underlying mechanisms of ESUS can be classified as cardioembolic and non-cardioembolic¹⁵. Although we performed a standardized cardiac workup, latent paroxysmal atrial fibrillation might be a cause of ESUS in RT patients. Another possibility is embolism from subclinical non-stenotic atherosclerotic lesions. The atherosclerotic process is generally accelerated after RT, resulting in thromboembolic events¹⁶. Several studies have reported an increase in the prevalence of atherosclerotic wall changes in RT

patients^{17, 18}. In our study, ipsilateral 30–50% stenosis of the extracranial carotid artery was found in 15% of RT patients, which was comparable to that in HD patients. Additionally, the serum homocysteine levels were significantly higher in the RT patients than in those without a history of RRT, whereas the prevalence of common vascular risk factors (i.e., hypertension, diabetes, or dyslipidemia) were similar. Previous studies demonstrated that an elevated homocysteine concentration was a predictor of increased cardiovascular morbidity or mortality among patients with end-stage kidney disease^{19, 20}. High concentrations of homocysteine are known to have deleterious effects on the vascular endothelium through oxidant stress and promote atherosclerosis and thrombus formation^{21, 22}. Moreover, homocysteine showed a predilection towards the promotion of platelet adhesion to endothelial cells and was also associated with higher levels of prothrombotic factors²³. Recent studies indicated that ESUS cases result from non-stenotic atherosclerosis, atrial cardiopathy, patent foramen ovale, etc., which are generally regarded as low- to moderate-risk embolic sources¹². We speculated that thrombotic tendency may be enhanced by the presence of hyperhomocysteinemia even in such non-high-risk diseases. The treatments for lowering homocysteine concentrations may have cardiovascular benefits in RT patients, although further studies are needed to verify this.

Cardioembolism was the most common subtype in patients undergoing HD, presumably because of their high prevalence of atrial fibrillation. This is consistent with the report of a previous study⁵, whereas some studies found that small vessel occlusion was the most frequent subtype for those receiving HD^{6, 24}. As renal function declines, patients are more likely to develop atrial fibrillation²⁵. The prevalence of atrial fibrillation was reported to be particularly high in HD patients, at 7–27%²⁶⁻²⁸. Most HD patients experience chronic volume overload and its

rapid fluctuation, which can increase the incidence of atrial fibrillation. In addition, the calcification of the cardiac valve by the dysregulation of calcium and phosphate metabolism can cause valvular heart disease, leading to the development of atrial fibrillation²⁹). In our study, the 38.5% prevalence of atrial fibrillation in HD patients was the highest among the groups.

Vascular Event Risk

RT patients have a higher cardiovascular risk than the general population, since they usually have, in addition to traditional risk factors such as hypertension, diabetes, hyperlipidemia, or smoking, nontraditional cardiovascular risk factors, including adverse metabolic effects of immunosuppression, chronic anemia, hyperhomocysteinemia, chronic inflammation, proteinuria, and chronic allograft nephropathy³⁰). The United States Renal Data Systems reported that the three-year incidence of *de novo* cerebrovascular events after RT was 6.8%³¹). Meanwhile, few data are available on the vascular risks in secondary prevention settings. In our study, the one-year MACE risk after stroke was 11.3% in RT patients, which was comparable with that in non-RRT patients (13.1%) and lower than that in HD patients (28.2%). Our patients in the RT group seemed to undergo rigorous preventive treatment during follow-up. Specifically, the usage rates of antiplatelet, anticoagulant, antihypertensive, and lipid-lowering agents were 74%, 32%, 62%, and 56%, respectively. These appropriate interventions may have lowered the MACE risk in RT patients to the level of the patients with no RRT history.

Functional Prognosis

Although RRT modalities were not independent determinants of functional prognosis, RT patients seemed to show better outcomes than HD patients; 22% and 36% were handicapped or dead one year after stroke in RT and HD patients, respectively. To date, few studies have assessed disability after stroke among RT recipients. Toyoda *et al.* reported that HD was an independent indicator for an mRS of ≥ 3 at 4 weeks⁴). The case fatality of stroke in RT patients has been reported to be very high, with a mortality rate of approximately 40% at one year^{32, 33}). The good prognosis in our study may be partly attributed to the different patient backgrounds as well as the improved secondary prevention measures. In addition, the Japanese RT patients showed excellent long-term outcomes with longer survival periods than the non-Japanese RT patients³⁴), which could be consistent with our results.

Limitations

First, the sample was relatively small, especially for the RRT groups; thus, our analysis is susceptible to type II error. However, this is inevitable given that stroke after RT is a rare condition. We could not perform extensive multivariable adjustments because of the small number of outcome events. Second, we had no data available on the exact change of blood pressure levels during follow-up, which could affect the vascular outcomes. Third, because of the single-center setting, generalizability is limited. The annual MACE rate of 11.3% in the non-RRT group was higher than that reported in previous clinical trials on general stroke populations^{35, 36}). This may be in part due to our consecutive enrollment of patients regardless of their age, general conditions, or comorbidities, and clinical trials usually select patients whose systemic condition is fair. In addition, patients were included within one week of onset, ensuring that early recurrent events were captured. It is plausible that our patients represent the “real world” stroke cohort rather than those who would be included in clinical trials. Our results should be interpreted with caution and reproduced in larger multicenter studies.

Conclusions

RT patients were more likely to have ESUS and were at a lower risk of recurrent vascular events than HD patients. Our study provides useful information for developing optimal secondary prevention strategies for patients undergoing RT as well as HD.

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None.

Conflict of Interest

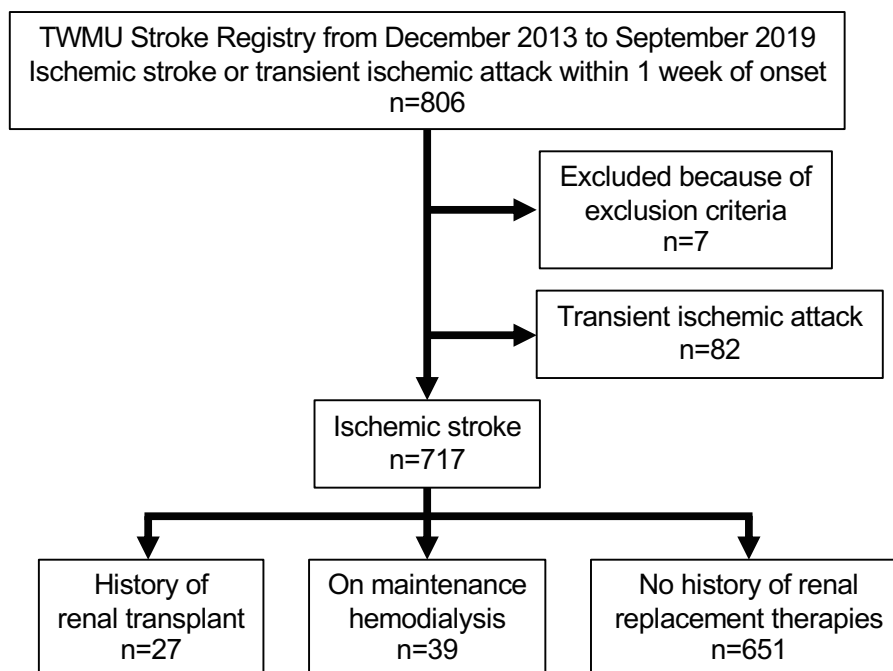
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Supplementary Fig. 1. Study flowchart

Supplementary Table 1. Usage of immunosuppressive agents among 27 patients after renal transplant

| | No. of patients (%) |
|-----------------------|---------------------|
| Prednisolone | 23 (85.2) |
| Tacrolimus | 21 (77.8) |
| Mycophenolate mofetil | 21 (77.8) |
| Cyclosporine | 2 (7.4) |
| Mizoribine | 2 (7.4) |
| Everolimus | 1 (3.7) |

Supplementary Table 2. Baseline characteristics

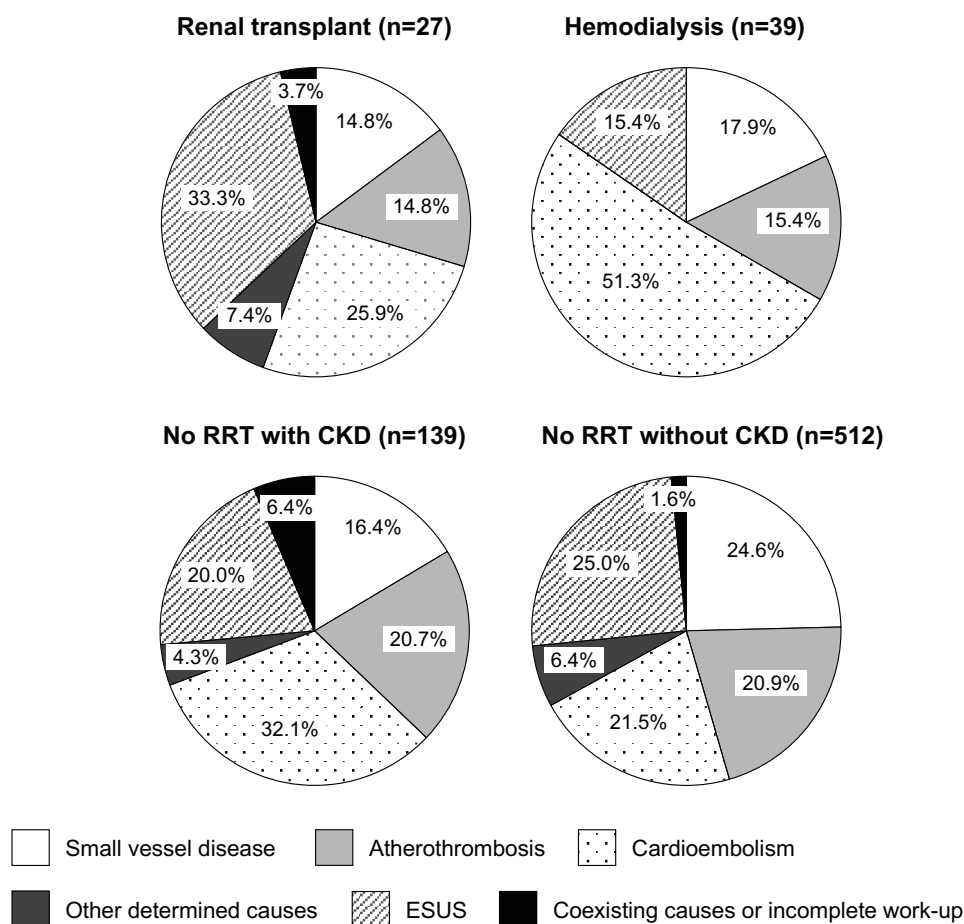
| | Renal transplant (n = 27) | Hemodialysis (n = 39) | No RRT (n = 651) | | P-value* |
|---|------------------------------|--------------------------|------------------------------------|--------------------------|----------|
| | | | With CKD [†] (n = 139) | Without CKD (n = 512) | |
| Age, y | 59 ± 12 | 67 ± 13 | 76 ± 10 | 70 ± 13 | < 0.001 |
| Male | 22 (81.5) | 23 (59.0) | 89 (64.0) | 300 (58.6) | 0.069 |
| Medical history | | | | | |
| Hypertension | 20 (74.1) | 34 (87.2) | 123 (88.4) | 360 (70.3) | < 0.001 |
| Diabetes mellitus | 12 (44.4) | 19 (48.7) | 70 (50.4) | 180 (35.2) | 0.006 |
| Dyslipidemia | 14 (51.9) | 18 (46.1) | 84 (60.4) | 224 (43.8) | 0.005 |
| Current smoking | 3 (11.1) | 3 (7.7) | 17 (12.2) | 103 (20.2) | 0.024 |
| Atrial fibrillation | 6 (22.2) | 15 (38.5) | 46 (33.1) | 96 (18.8) | 0.006 |
| Chronic heart failure | 2 (7.4) | 12 (30.8) | 33 (23.7) | 32 (6.3) | < 0.001 |
| Stroke | 4 (14.8) | 10 (25.6) | 31 (22.3) | 99 (19.3) | 0.61 |
| Coronary artery disease | 2 (7.4) | 8 (20.5) | 37 (26.6) | 55 (10.7) | < 0.001 |
| Peripheral artery disease | 2 (7.4) | 8 (20.5) | 15 (10.8) | 15 (2.9) | < 0.001 |
| Investigations | | | | | |
| Intracranial artery > 50% stenosis | 5 (18.5) | 13 (33.3) | 44 (32.1) | 140 (27.5) | 0.39 |
| Extracranial artery > 50% stenosis | 2 (7.4) | 4 (10.3) | 29 (21.5) | 67 (13.1) | 0.059 |
| Extracranial artery 30%-50% stenosis | 4 (14.8) | 6 (15.4) | 18 (13.3) | 66 (12.9) | 0.97 |
| Complex aortic atheroma | 2 (20.0) | 4 (33.3) | 12 (40.0) | 39 (25.3) | 0.39 |
| Laboratory data | | | | | |
| Creatinine mg/dL | 2.4 ± 2.5 | 7.6 ± 2.7 | 1.6 ± 0.1 | 0.8 ± 0.1 | < 0.001 |
| LDL-c, mg/dL | 111 ± 41 | 98 ± 38 | 110 ± 47 | 119 ± 36 | 0.001 |
| HDL-c, mg/dL | 50 ± 22 | 51 ± 15 | 53 ± 19 | 56 ± 17 | 0.097 |
| Triglycerides, mg/dL | 139 ± 64 | 117 ± 58 | 137 ± 92 | 130 ± 97 | 0.64 |
| HbA1c, % | 6.0 ± 0.7 | 6.2 ± 1.7 | 6.6 ± 1.3 | 6.9 ± 6.0 | 0.71 |
| Homocysteine, nmol/mL | 15.2 (11.6-19.4) | 21.5 (14.5-26.9) | 12.7 (10.4-16.8) | 8.8 (6.9-11.7) | < 0.001 |
| hsCRP, mg/mL | 1.3 (0.2-2.3) | 5.2 (1.5-14.8) | 2.6 (0.5-8.4) | 1.2 (0.4-4.8) | 0.83 |
| IL-6, pg/mL | 4.0 (1.48-11.3) | 9.3 (4.3-13.5) | 5.2 (2.5-11.0) | 3.1 (1.7-7.1) | 0.73 |
| BNP, pg/mL | 99 ± 168 | 728 ± 790 | 219 ± 25 | 114 ± 186 | < 0.001 |
| NIHSS | 2 (1-4) | 4 (2-6) | 3 (2-6) | 3 (1-5) | 0.42 |

Figures are expressed as n (%), mean ± standard deviation, or median (interquartile range).

*Comparisons among four groups. [†]CKD was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m².

Comparisons among patients with renal transplant, hemodialysis and no RRT.

Abbreviations: BNP=brain natriuretic peptide; CKD=chronic kidney disease; HDL-c=high density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; IL-6=interleukin- 6; LDL-c=low density lipoprotein cholesterol; NIHSS=National Institute of Health Stroke Scale; RRT=renal replacement therapy.



Supplementary Fig. 2. Etiologic subtype of ischemic stroke

Distributions of etiologic subtype were significantly different between the groups ($P=0.002$).

Abbreviations: CKD=chronic kidney disease; ESUS=embolic stroke of undetermined source; RRT=renal replacement therapy.

Supplementary Table 3. Immunosuppressive agent use in ESUS and Non-ESUS patients in the renal transplant group

| | ESUS (n = 9) | No ESUS (n = 18) | P-value |
|-----------------------|--------------|------------------|---------|
| Prednisolone | 7 (77.8) | 16 (88.9) | 0.45 |
| Tacrolimus | 7 (77.8) | 14 (77.8) | 1.00 |
| Mycophenolate mofetil | 7 (77.8) | 14 (77.8) | 1.00 |
| Cyclosporine | 0 | 2 (11.1) | 0.19 |
| Mizoribine | 1 (11.1) | 1 (5.6) | 0.61 |
| Everolimus | 0 | 1 (5.6) | 0.36 |

ESUS=embolic stroke of undetermined source.

Supplementary Table 4. Medication use at discharge and surgical treatments

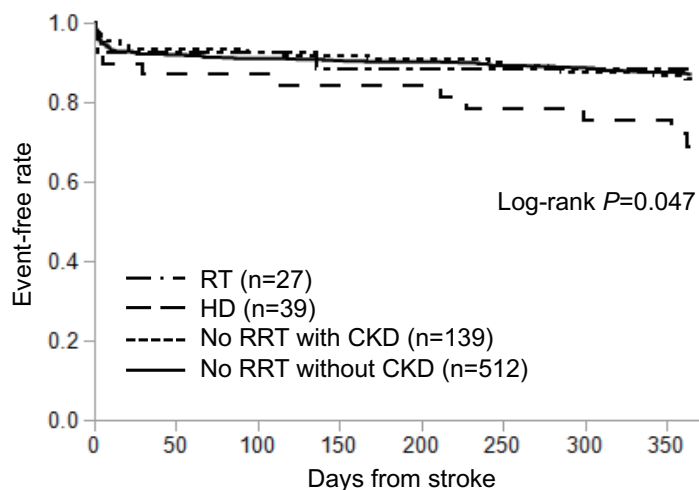
| | Renal transplant (<i>n</i> = 27) | Hemodialysis (<i>n</i> = 39) | <i>P</i> -value* | No RRT (<i>n</i> = 651) | <i>P</i> -value† |
|-----------------------------------|--------------------------------------|----------------------------------|------------------|-----------------------------|------------------|
| Antiplatelet agent, | 20 (74.1) | 23 (59.0) | 0.20 | 457 (70.3) | 0.31 |
| Single | 9 (33.3) | 16 (41.0) | 0.53 | 267 (41.1) | 0.72 |
| Dual or triple | 11 (40.7) | 7 (18.0) | 0.042 | 190 (29.2) | 0.12 |
| Anticoagulant agent | 9 (32.1) | 20 (46.5) | 0.15 | 237 (32.8) | 0.72 |
| Warfarin | 6 (22.2) | 20 (51.2) | 0.016 | 87 (13.5) | <0.001 |
| Direct oral anticoagulant agent | 3 (11.1) | 0 | 0.018 | 128 (19.9) | <0.001 |
| Antihypertensive agent | 16 (61.5) | 32 (82.1) | 0.067 | 357 (54.9) | 0.002 |
| Ca channel blocker | 11 (40.7) | 22 (56.4) | 0.21 | 192 (29.5) | 0.002 |
| ACEI/ARB | 8 (29.6) | 18 (46.2) | 0.17 | 190 (29.1) | 0.10 |
| Beta blocker | 6 (22.2) | 15 (38.4) | 0.16 | 99 (15.2) | 0.002 |
| Diuretics | 2 (7.4) | 6 (15.4) | 0.32 | 78 (12.0) | 0.60 |
| Alpha blocker | 0 | 4 (10.3) | 0.036 | 18 (2.8) | 0.046 |
| RAS inhibitor | 2 (7.4) | 1 (2.6) | 0.36 | 4 (0.6) | 0.039 |
| Lipid lowering agent | 15 (55.6) | 25 (64.1) | 0.49 | 404 (62.2) | 0.76 |
| Statin | 14 (51.9) | 22 (56.4) | 0.71 | 443 (60.7) | 0.55 |
| Others | 4 (14.8) | 9 (23.1) | 0.40 | 247 (38.0) | 0.006 |
| Glucose lowering agent or insulin | 7 (25.9) | 14 (35.9) | 0.39 | 283 (28.1) | 0.57 |
| Carotid endarterectomy | 0 | 0 | - | 11 (1.7) | 0.34 |
| Carotid artery stent | 0 | 0 | - | 17 (2.6) | 0.19 |

Figures are expressed as *n* (%).

*Comparisons between patients with renal transplant and hemodialysis.

†Comparisons among patients with renal transplant, hemodialysis, and no RRT.

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; RAS=renin angiotensin aldosterone system; RRT=renal replacement therapy.

**Supplementary Fig. 3.** Kaplan-Meier curves for major cardiovascular events

Abbreviations: CKD=chronic kidney disease; HD=hemodialysis; RRT=renal replacement therapy; RT=renal transplantation.

Supplementary Table 5. Etiologic subtype of initial and recurrent ischemic stroke in patients receiving renal replacement therapy

| | Index stroke subtype | Recurrent stroke subtype |
|------------------------|------------------------|--------------------------|
| Renal transplant group | | |
| Patient 1 | Atherothrombosis | Atherothrombosis |
| Patient 2 | Other determined cause | Other determined cause |
| Patient 3 | Coexisting cause | Coexisting cause |
| Hemodialysis group | | |
| Patient 1 | Cardioembolism | Cardioembolism |
| Patient 2 | Cardioembolism | Cardioembolism |
| Patient 3 | Atherothrombosis | Cardioembolism |
| Patient 4 | ESUS | ESUS |
| Patient 5 | Small vessel disease | Small vessel disease |

Abbreviations: ESUS=embolic stroke of undetermined source.

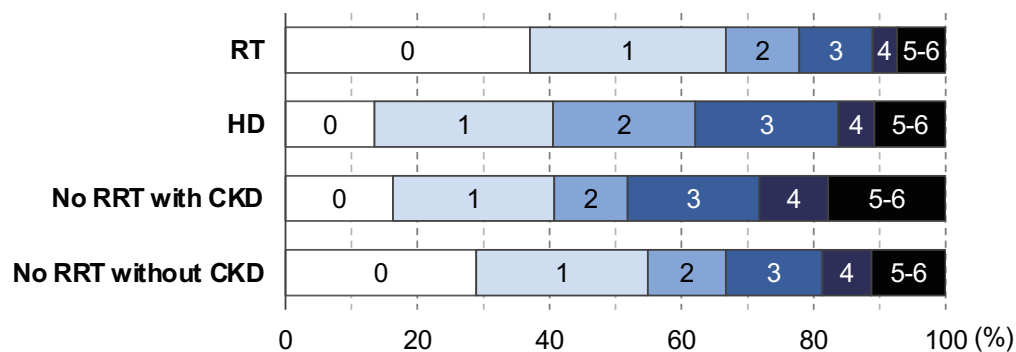
Supplementary Table 6. Risk of major adverse cardiovascular events at one year by the use of each immunosuppressive agent

| | Event rate, <i>n</i> (%/year) | Log rank <i>P</i> -value |
|-----------------------|-------------------------------|--------------------------|
| Prednisolone | | |
| No (<i>n</i> = 4) | 0 | |
| Yes (<i>n</i> = 23) | 3 (13.0) | 0.48 |
| Tacrolimus | | |
| No (<i>n</i> = 6) | 2 (33.3) | |
| Yes (<i>n</i> = 21) | 1 (5.0) | 0.038 |
| Mycophenolate mofetil | | |
| No (<i>n</i> = 6) | 2 (33.3) | |
| Yes (<i>n</i> = 21) | 1 (5.0) | 0.038 |
| Cyclosporine | | |
| No (<i>n</i> = 25) | 2 (8.2) | |
| Yes (<i>n</i> = 2) | 1 (50.0) | 0.057 |
| Mizoribine | | |
| No (<i>n</i> = 25) | 2 (8.2) | |
| Yes (<i>n</i> = 2) | 1 (50.0) | 0.057 |
| Everolimus | | |
| No (<i>n</i> = 26) | 3 (11.7) | |
| Yes (<i>n</i> = 1) | 0 | 0.73 |

Supplementary Table 7. Event risk at one year by the type of anticoagulant used for hemodialysis

| | Event rate, <i>n</i> (%/year) | | Log rank <i>P</i> -value |
|-----------------------------|-------------------------------|----------------------|--------------------------|
| | UFH (<i>n</i> = 32) | LWMH (<i>n</i> = 6) | |
| Major cardiovascular events | 9 (30.0) | 1 (20.0) | 0.49 |
| Ischemic stroke | 5 (16.0) | 0 | 0.32 |

Abbreviations: LWMH=low-molecular-weight heparin; UFH = unfractionated heparin



| mRS | RT (n=27) | HD (n=38) | No RRT (n=627) | | P-value |
|--------------|-----------|-----------|----------------|----------------|---------|
| | | | CKD (n=135) | No CKD (n=492) | |
| Median (IQR) | 1 (0-2) | 2 (1-3) | 2 (1-4) | 1 (0-3) | 0.001 |
| ≥2, n (%) | 9 (33.3) | 22 (56.4) | 80 (57.6) | 222 (43.4) | 0.006 |
| ≥3, n (%) | 6 (22.2) | 14 (35.9) | 65 (46.8) | 164 (32.0) | 0.007 |

Supplementary Fig. 4. Modified Rankin Scale score at one year

Abbreviations: CKD=chronic kidney disease; HD=hemodialysis; IQR=interquartile range; mRS=modified Rankin Scale; RRT=renal replacement therapy; RT=renal transplantation.