

Cerebral Microvascular Disease Predicts Renal Failure in Type 2 Diabetes

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ABSTRACT

Abnormalities in small renal vessels may increase the risk of developing impaired renal function, but methods to assess these vessels are extremely limited. We hypothesized that the presence of small vessel disease in the brain, which manifests as silent cerebral infarction (SCI), may predict the progression of kidney disease in patients with type 2 diabetes. We recruited 608 patients with type 2 diabetes without apparent cerebrovascular or cardiovascular disease or overt nephropathy and followed them for a mean of 7.5 years. At baseline, 177 of 608 patients had SCI, diagnosed by cerebral magnetic resonance imaging. The risk for the primary outcome of ESRD or death was significantly higher for patients with SCI than for patients without SCI [hazard ratio, 2.44; 95% confidence interval (CI) 1.36 to 4.38]. The risk for the secondary renal end point of any dialysis or doubling of the serum creatinine concentration was also significantly higher for patients with SCI (hazard ratio, 4.79; 95% CI 2.72 to 8.46). The estimated GFR declined more in patients with SCI than in those without SCI; however, the presence of SCI did not increase the risk for progression of albuminuria. In conclusion, independent of microalbuminuria, cerebral microvascular disease predicted renal morbidity among patients with type 2 diabetes.

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Diabetes is estimated to increase the risk of ESRD by approximately 12-fold,¹ and 20% to 45% of patients with ESRD in most developed countries have type 2 diabetes mellitus.² Furthermore, the presence of nephropathy is known to seriously affect the prognosis of diabetes by increasing the likelihood of cardiovascular death.³ An association has also been reported between elevated urinary albumin excretion rate and diabetic nephropathy,³ and patients with microalbuminuria are defined as having incipient nephropathy.⁴ Nephropathy in type 2 diabetes progresses from microalbuminuria to macroalbuminuria, and from macroalbuminuria to an elevated serum creatinine (Cr) concentration or the need for renal replacement therapy. However, recent clinical studies have shown that renal insufficiency in the absence of microalbuminuria is rela-

tively common in patients with type 2 diabetes.⁵ In addition, GFR was reported to be negatively correlated with the resistive index (RI) of the interlobular renal arteries⁶ in patients with type 2 diabetes. These results have led to the suggestion that glomerular lesions and arteriosclerosis in the kidney independently play important roles in the development of ESRD in type 2 diabetes.

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Although small vessel diseases in the kidney may increase the risk of developing impaired renal function, there is still no established method to assess small vessel disease in the kidney. A linear relationship was observed between the RI and renal vascular resistance.⁷ However, RI is also affected by renal interstitial pressure, indicating that RI is increased in patients with increased interstitial fibrosis,^{7,8} which occurs in various conditions such as chronic pyelonephritis, glomerulosclerosis, and ureteral obstruction. The vascular beds of the kidney and brain have similar hemodynamic properties⁹; therefore, silent cerebral infarction (SCI), small vessel disease in the brain, may be indicative of the presence of small vessel disease in the kidney.

It is therefore possible that the presence of small artery diseases in the brain could indicate an increased risk for worsening kidney function. Accordingly, the goal of the study presented here was to investigate the association between the presence of SCI and renal prognosis in patients with type 2 diabetes.

RESULTS

Of the 659 eligible patients at baseline, follow-up was obtained for 608 (92.3%) patients, and the data analyses were restricted to these patients (Figure 1). Table 1 compares the baseline clinical characteristics of the study population grouped according to whether the patients had SCI (SCI group, *n* = 177) or did not have SCI (non-SCI group, *n* = 431) at baseline. Patients in the SCI group were 6 years older, had diabetes for 2.2 years longer, had higher blood pressure (BP) (systolic BP, 10.3 mmHg; diastolic BP, 2.8 mmHg) and higher albumin-to-Cr ratio (ACR) than patients in the non-SCI group. There were also significant differences in the levels of serum Cr and estimated GFR (eGFR) between the two groups. More patients with SCI had microalbuminuria and diabetic neuropathy. The frequency of smoking was significantly higher in patients with SCI than in patients without SCI. At baseline, the frequency of patients who received lipid-lowering agents

was not different between the two groups (SCI group, 9.6%; non-SCI group, 5.3%). On the other hand, 28 (15.8%) patients in the SCI group and 32 (7.4%) in the non-SCI group were treated with either angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) at baseline. The frequency of patients who were treated with ACE inhibitors or ARBs at baseline was significantly higher in the SCI group than in the non-SCI group. In addition, 95 patients in the SCI group and 179 patients in the non-SCI group were started on ACE inhibitors or ARBs during the follow-up period. Overall, 123 patients in the SCI group (69%) and 211 (49%) in the non-SCI group were treated with ACE inhibitors or ARBs. Although the fasting plasma glucose and glycosylated hemoglobin levels were significantly higher in the SCI group than in the non-SCI group (Table 1), the glycosylated hemoglobin levels were not different between the two groups during the follow-up period (SCI group, 6.99% ± 1.01% versus non-SCI group, 7.08% ± 1.08%).

Over the average 7.5-year follow-up period, 58 patients (34 in the SCI group and 24 in the non-SCI group) reached the primary composite end point of ESRD or death. No patient showed recovery of renal function after starting renal replacement therapy. Twenty-nine patients (13 in the SCI group and 16 in the non-SCI group) died. The causes of death included malignant diseases (five in the SCI group and nine in the non-SCI group), infectious diseases (one in the SCI group and three in the non-SCI group), gastrointestinal bleeding (one in the SCI group and none in the non-SCI group), myocardial infarction (four in the SCI group and none in the non-SCI group), stroke (one in the SCI group and two in the non-SCI group) and sudden death (1 in the SCI group, 2 in the non-SCI group). The frequency of the primary composite outcome of ESRD or death was significantly higher in the SCI group than in the non-SCI group [hazard ratio (HR), 2.44; 95% confidence interval (CI), 1.36 to 4.38] (Figure 2A, Table 2).

The frequency of the secondary renal end point of any dialysis and doubling of the serum Cr concentration was also significantly higher in the SCI group than in the non-SCI group (HR, 4.79; 95% CI, 2.72 to 8.46) (Figure 2B, Table 2). Because no temporary dialysis was reported, all dialysis patients were considered to have progressed to ESRD. In addition, there were no cases of ESRD without doubling of the serum Cr concentration. The decrease in eGFR was greater in the SCI group than in the non-SCI group (Figure 3). During the follow-up period, 70 of 177 patients with SCI and 117 of 431 patients without SCI showed progression of their nephropathy. However, in the multivariate regression model, individuals with baseline SCI did not show an increased risk for progression of nephropathy (95% CI, 0.93 to 1.82)

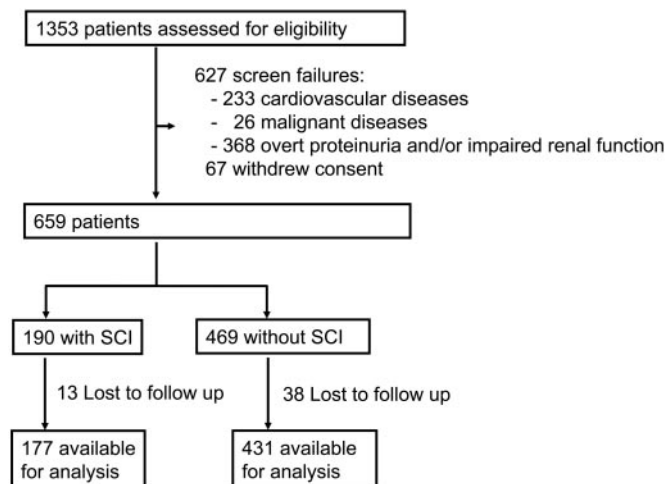


Figure 1. Study profile.

DISCUSSION

The study presented here clearly showed that the presence of SCI increased the risks for the primary outcome of ESRD or death and for the secondary outcome of doubling of serum Cr

Table 1. Baseline clinical characteristics^a

Parameters	SCI Group (n = 177)	P	Non-SCI Group (n = 431)
Age, years	63.3 ± 7.8	<0.001	57.3 ± 8.8
Women, n (%)	74 (41.8)	0.38	197 (45.7)
Duration of diabetes, years	9.8 ± 8.7	0.001	7.6 ± 7.3
History of smoking, n (%)	102 (57.6)	0.007	196 (45.5)
Height, cm	158.5 ± 8.4	0.16	159.6 ± 9.1
Weight, kg	60.1 ± 9.7	0.85	60.2 ± 11.1
Body mass index, kg/m ²	23.9 ± 3.2	0.37	23.6 ± 3.6
BP, mmHg			
systolic	146.8 ± 20.2	<0.001	136.5 ± 19.7
diastolic	81.6 ± 11.2	0.007	78.8 ± 11.3
Fasting plasma glucose, mg/dl	163 ± 44	0.01	176 ± 58
Glycosylated hemoglobin, %	8.3 ± 1.8	0.009	8.7 ± 2.1
Total cholesterol, mmol/L	5.61 ± 1.06	0.60	5.56 ± 1.10
HDL, mmol/L	1.29 ± 0.36	0.35	1.32 ± 0.34
Triglycerides, mmol/L	1.68 ± 0.76	0.52	1.74 ± 1.11
Serum Cr, mmol/L	100.6 ± 21.8	0.04	95.3 ± 20.7
eGFR, mL/min/1.73 m ²	62.6 ± 16.3	<0.001	67.5 ± 16.0
ACR, mg/g ^b	32.9 (28.1 to 38.5)	0.01	25.4 (20.5 to 31.4)
Microalbuminuria, n (%)	95 (53.7)	0.02	188 (43.6)
Any retinopathy, n (%)	70 (39.5)	0.69	155 (36.0)
nonproliferative	47 (26.6)		104 (24.1)
proliferative	23 (13.0)		51 (11.8)
Neuropathy, n (%)	102 (57.6)	0.007	196 (45.5)
Insulin treatment, n (%)	75 (42.4)	0.17	157 (36.4)

^aResults are mean ± SD or number (%) of patients.

^bACR is expressed as the geometric mean and 95% CI.

concentration in patients with type 2 diabetes. Furthermore, the decrease in eGFR was greater in patients with SCI than in those without SCI. These results suggest that the presence of small artery diseases is associated with poor renal prognosis in patients with type 2 diabetes.

The classical clinical courses of type 1 and type 2 diabetes include the development of microalbuminuria, which leads to proteinuria and progressive loss of renal function.^{3,10,11} The typical histologic aberrations in diabetes are glomerular changes, such as thickening of the glomerular basement membrane, progressive accumulation of extracellular matrix in the mesangial area, a nodular form of glomerular sclerosis (Kimelstiel–Wilson lesion), and diffuse mesangial sclerosis. However, recent studies have suggested that renal insufficiency without albuminuria/proteinuria is not uncommon in patients with type 2 diabetes.^{5,12} These findings suggest that several factors (including interstitial fibrosis, ischemic vascular disease, and cholesterol emboli) may contribute to renal impairment in type 2 diabetes. The RI of interlobular renal arteries, which reflects, at least in part, the degree of peripheral intrarenal arterial stiffness, was recently reported to be an independent predictor of deteriorating renal function in patients with type 2 diabetes and microalbuminuria.¹³ Chronic hypoxia in the kidney is well established as one of the main causes of renal failure.¹⁴ Therefore, small artery diseases in the kidneys (arteriosclerosis and/or arteriolosclerosis) may contribute to the worsening of renal function. Because the vascular beds of

the kidney and brain have similar hemodynamic properties,⁹ and because SCI is primarily caused by diseases of the small arteries and arterioles,¹⁵ SCI may be associated with the progression of cardiovascular diseases in addition to renal diseases. The association between impaired kidney function and magnetic resonance imaging (MRI)-detected cerebral infarction was reported in previous cross-sectional studies.^{16–18} In the study presented here, the presence of SCI indicated poor renal prognosis but not the progression of nephropathy, which was defined by the levels of ACR. This is the first prospective study reporting an association between small artery diseases and declining kidney function.

The frequency of patients who were treated with renin-angiotensin system (RAS) blocking agents was higher in the SCI group than in the non-SCI group. Because renal impairment is one of the adverse effects of RAS blocking agents, we examined whether the use of RAS blocking agents affected renal prognosis in the SCI group. However, the frequency of the primary (ESRD or death) and secondary (the composite of any dialysis and doubling of the serum Cr concentration) end points did not differ between the two groups.

Although the MRI slice thickness was not the same at both hospitals, the prevalence of SCI did not differ (the Second Okamoto Hospital, 30.2%; Osaka Rosai Hospital, 26.6%; $P = 0.36$). In addition, in both hospitals the frequency of the end points was significantly higher in the SCI group than in the non-SCI group. Therefore, different slice thickness is unlikely to affect the results.

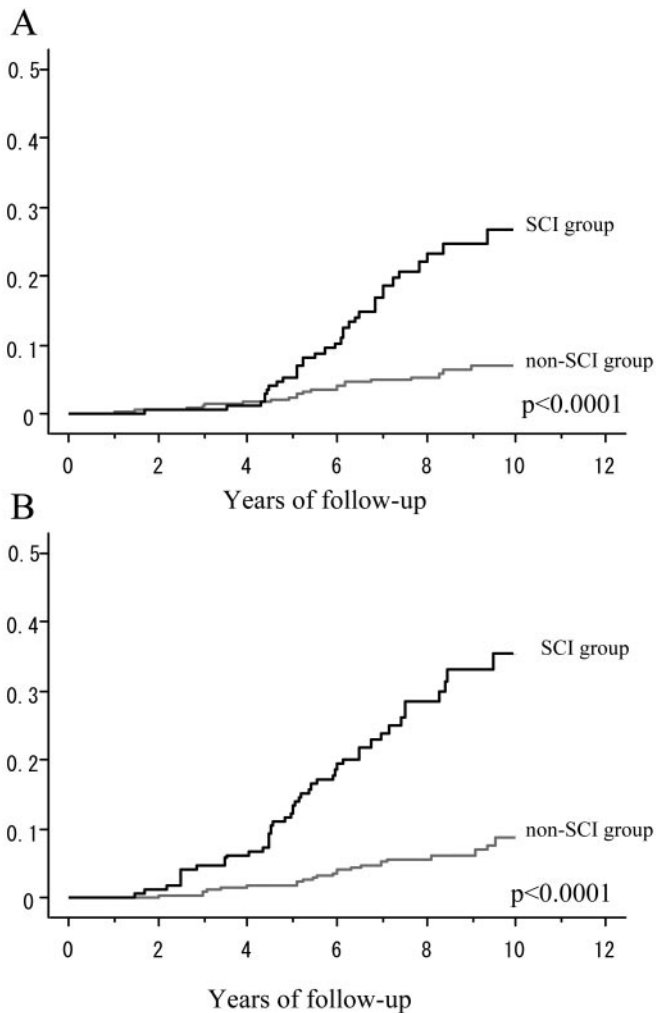


Figure 2. Kaplan–Meier curves for (A) the primary outcome (ESRD or death) and (B) the secondary outcome (dialysis and doubling of serum Cr concentration).

The strengths of this study are the many participating patients with type 2 diabetes and the long-term follow-up. This follow-up study was of adequate size and duration to assess whether the presence of SCIs could affect renal outcomes. The weaknesses of this study are (1) baseline characteristics such as age, BP, and smoking, which are associated with the presence of SCIs and the progression of renal disease, were not the same in both groups; and (2) a selection bias may exist. However, in the multivariate adjusted analysis, the presence of SCIs was a significant risk factor for death and poor renal prognosis and was independent of age, systolic BP, or smoking. In addition, because a high percentage of patients were followed-up (SCI group, 93.2%; non-SCI group, 91.9%), the bias is expected to be minimal in this study. In the study presented here, systolic and diastolic BP were significantly higher in the SCI group than in the non-SCI group at baseline. An elevated BP is associated with SCIs.¹⁹ However, the presence of SCIs increased the risk for progressive kidney dysfunction independently of the baseline BP levels. In addition, there was no interaction between the

existence of SCI and the follow-up time on BP (systolic BP, $P = 0.14$; diastolic BP, $P = 0.54$), indicating that the changes in BP were similar in both groups.

According to population-based studies, the overall prevalence of SCI ranges from 8% to 28%.²⁰ SCI is more common in patients with diabetes than in the general population, and the mean prevalence of SCI in five studies was 38% (range 13 to 82%).^{21–24} In this study, we found SCI in 177 of 608 patients (29%), and the prevalence of SCI was within the previously published range. However, the proportion of patients with reduced eGFR (<60 ml/min/1.73 m²) was greater in our patients (39%) than in an earlier study (22%).²⁵ Nevertheless, because the study presented here was not clinic- or population-based, our patients might have a greater burden of ESRD compared with the general diabetic population.

In the study presented here, although most silent infarcts were multiple lacuna infarcts, we did not exclude patients with relatively large cortical infarcts, which might reflect large artery disease.²⁶ Therefore, intra- and/or extrarenal artery disease may play a role in the progression of kidney disease in our patients. Another limitation of our study is the serum Cr assay used. Because our study was started in 1995, our laboratories did not use a Cr method with calibration traceable to isotope dilution mass spectrometry.

It is important to identify individuals who are at risk of progression of diabetic renal disease. Genomic and proteomic approaches are now widely used to identify candidate molecular markers that correlate with the progression of diabetic nephropathy. In addition, there are many candidate markers that are associated with the progression of experimental nephropathy. However, there is still little evidence in humans to suggest that these markers are more sensitive than changes in urinary albumin excretion. ACR remains the best available noninvasive clinical predictor of this disease to date, although recent clinical studies have shown that renal insufficiency can occur in the absence of microalbuminuria in patients with type 2 diabetes.⁵ As a result, studies are needed to identify new risk markers. The study presented here clearly showed that the presence of SCI indicates poor renal outcomes in patients with type 2 diabetes. Therefore, evaluating SCI may be useful to determine the risk of progression of kidney disease in patients with diabetes. Although, technically noninvasive, brain MRI is associated with greater cost, patient involvement, and inconvenience than other methods. Therefore, new strategies are needed to determine the presence of renal and/or extrarenal microvascular diseases.

Aggressive multifactorial control targeting glycemic levels and BP as well as the use of drugs that block the RAS can prevent the progression of diabetic nephropathy in patients with diabetes and microalbuminuria.^{27–30} Therefore, further studies are needed to determine whether the progression in diabetic nephropathy, the decline in renal function, and/or cardiovascular events can be prevented by such therapies, even in patients with type 2 diabetes and SCI.

In conclusion, patients with type 2 diabetes and SCI had a

Table 2. Incidence of primary and secondary outcomes and its components in patients with type 2 diabetes^a

	Patients with SCI, n (%)	Patients without SCI, n (%)	HR (95% CI) ^b	P
ESRD, death	34 (19.2)	24 (5.6)	2.44 (1.36 to 4.38)	0.003
Death	13 (7.3)	16 (3.7)	1.61 (0.71 to 3.62)	0.25
Doubling ^c	46 (26.0)	24 (5.6)	4.79 (2.72 to 8.46)	<0.0001
Progression ^d	70 (39.5)	117 (27.1)	1.23 (0.88 to 1.73)	0.22

^aACR was logarithmically transformed before analysis.

^bThe HRs were adjusted for gender, age, duration of diabetes, body mass index, smoking status, glycosylated hemoglobin, serum lipid levels (total cholesterol, HDL cholesterol, triglyceride), eGFR, systolic and diastolic BP, and ACR.

^cDoubling, doubling of the serum Cr concentration from baseline.

^dProgression, progression from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria.

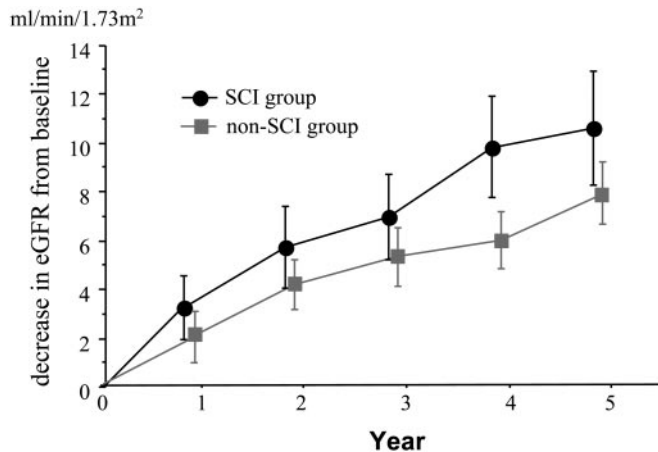


Figure 3. Decreases in the eGFR during the study from baseline. Results are mean \pm 95% CI. A significant ($P < 0.001$) difference was found between the two groups.

worse renal morbidity in comparison to those without SCI. The presence of extrarenal microvascular diseases may be a new predictor of the decline in renal function in patients with type 2 diabetes.

CONCISE METHODS

Patients

Japanese patients with type 2 diabetes, aged 30 to 75 years, who had been admitted to the Second Okamoto Hospital or Osaka Rosai Hospital between January 1995 and December 2000 to control blood glucose and/or examine their diabetic complications, were recruited. The diagnostic criteria for diabetes were elevated plasma glucose levels (fasting, ≥ 7 mmol/L; random value, ≥ 11.1 mmol/L) on two occasions or treatment with oral diabetic drugs and/or insulin. Exclusion criteria included a past history of cerebrovascular events or myocardial infarction, angina treatment, heart failure, uncontrolled arrhythmias, cardiac pacemaker implantation, nondiabetic kidney disease confirmed by renal biopsy, connective tissue disease, malignant disease, current treatment with corticosteroids or immunosuppressive drugs, and obstructive uropathy. Baseline laboratory variables were obtained at admission, and patients with elevated serum Cr concentrations [>1.70 $\mu\text{mol/L}$ (1.5 mg/dl) for men and >147 $\mu\text{mol/L}$ (1.3 mg/dl) for women] and/or overt proteinuria were also excluded from this study.

Of the 1353 patients recruited to the study, 233 had history of myocardial infarction, angina treatment, history of stroke, arrhythmias, and/or pacemaker implantation. In addition, 26 patients had malignant diseases (six hepatoma, eight gastric cancer, three pancreatic cancer, six colon cancer, two lymphoma, and one myeloma). Of the remaining patients, 368 were excluded from the study because of elevated serum Cr concentration and/or overt persistent proteinuria. In addition, of the 726 remaining patients, 67 did not participate in this study (Figure 1). All of the remaining 659 patients gave informed consent to participate in the study and were therefore examined.

At baseline, patients underwent at least two measurements of ACR in morning urine samples on separate occasions. The ACR level in each measurement was classified as follows: <30 mg/g Cr, normoalbuminuria; 30 to 299 mg/g Cr, microalbuminuria; ≥ 300 mg/g Cr, overt proteinuria. Patients in whom the last two or more consecutive tests were within the range indicating microalbuminuria were enrolled as having microalbuminuria. Patients with baseline ACR values ≥ 300 mg/g Cr on at least one occasion were considered to have overt proteinuria and were excluded from the study. The remaining patients were considered to have normoalbuminuria. The eGFR was calculated for each patient from the serum Cr value and age using the abbreviated Modification of Diet in Renal Disease equation,³¹ which was modified by the Japanese coefficient,³² as follows:

$$\text{eGFR (ml/min/1.73 m}^2\text{)} = 194 \times \text{serum Cr}^{-1.094} \times \text{age}^{-0.287} \quad (1)$$

and if female $\times 0.739$. Laboratory serum Cr values were measured using an enzymatic method.

The presence and severity of diabetic retinopathy were assessed by ophthalmologists and were classified as having no abnormalities, nonproliferative retinopathy, or proliferative retinopathy. Diabetic neuropathy was diagnosed in patients who had two or more of the following four factors: the presence of one or more symptoms, the absence of two or more reflexes of the ankles or knee tendons, a vibration-perception threshold that was abnormal for the patient's age, and abnormal autonomic function (loss of heart rate variability with a supine/standing R-R interval ratio on an electrocardiogram <1.04 , postural hypotension with a fall in systolic BP of 20 mmHg or more, or both).^{33,34}

Assessment of Cerebral Infarcts

All patients underwent MRI of the brain. Axial T1- and T2-weighted, and proton density scans were performed using 1.5-Tesla MRI scanners (Second Okamoto Hospital: Gyroscan NT, Philips Medical Sys-

tems, Best, The Netherlands; Osaka Rosai Hospital: Signa Horizon HiSpeed LX, GE Medical Systems, Milwaukee, WI). The slice thickness was 7 mm in scans performed at the Second Okamoto Hospital and 5 mm at the Osaka Rosai Hospital. Infarcts were defined as focal lesions of at least 3 mm in diameter with low signal intensity on T1-weighted images and hyperintensity on T2-weighted images. Proton density scans were used to distinguish infarcts from dilated perivascular spaces. Trained physicians assessed the MRI images of the subjects. A history of stroke and transient ischemic attack was obtained by self report and by reviewing the medical records of all participants. SCI was defined as evidence of one or more infarcts on MRI, without a history of stroke or transient ischemic attack.

Follow-Up

The patients were followed up in the outpatient clinic of the Osaka Rosai Hospital or the Second Okamoto Hospital for management of their BP <130/85 mmHg according to the hypertension treatment guidelines of the World Health Organization/International Society of Hypertension; the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure; and the Japanese Society of Hypertension,^{35,36} and blood glucose (HbA1c <6.5%) by pharmacologic and nonpharmacologic methods. BP was measured using a sphygmomanometer after the patients had been sitting for 5 min. Urinary albumin excretion was measured using an immunoturbidimetry assay (Hitachi 7070E; Hitachi High-Technologies Company Ltd., Tokyo, Japan). The patients were followed-up for an average of 7.5 years. During the follow-up periods, each patient underwent standardized physical examinations and biochemical measurements, including the assessment of ACR and eGFR, every 6 months or more often if necessary. We defined loss to follow-up as the failure of the patient to visit the outpatient clinic after discharge from the hospital.

Outcome Measures

The primary composite outcome was the occurrence of ESRD or death. ESRD was defined as the initiation of long-term renal replacement therapy. Secondary outcomes included the composite of any dialysis and doubling of the serum Cr concentration, changes in eGFR, and the progression of nephropathy (from normoalbuminuria to microalbuminuria or microalbuminuria to macroalbuminuria). The doubling of the serum Cr concentration was defined as two consecutive serum Cr values that were twice the baseline values, and the end point was the time to the first occurrence of a doubling of serum Cr. Patients were designated as being in the stage of microalbuminuria or macroalbuminuria if their urine ACR was 50 to 299 mg/g Cr or ≥ 300 mg/g Cr on two consecutive annual visits, respectively. They were considered to have microalbuminuria or macroalbuminuria if their urine albumin was 50 to 299 mg/g Cr or ≥ 300 mg/g Cr, respectively, at the first of their two measurements.

Statistical Analysis

Results are expressed as mean (SD) or 95% CI as indicated. Comparisons between groups were performed using the χ^2 test or Fisher's exact test for categorical variables and *t* test for continuous variables. Differences in the changes in BP levels between two groups were analyzed using a two-way ANOVA with a repeated measurement model.

Differences in the changes in the eGFR between two groups were analyzed using a linear regression model with repeated measurements. The Kaplan–Meier estimate and the log-rank test were used to compare the event-free survival between patients with SCI and those without SCI. The patient characteristics were uniformly distributed between the patients with and without SCIs, and Cox's proportional hazard regression analysis was used to compare the rate of event development. The validity of the Cox's analysis was tested by log-log plots. HRs were calculated and adjusted for sex, age, duration of diabetes, body mass index, smoking status, glycosylated hemoglobin, serum lipid levels (total cholesterol, HDL cholesterol, triglyceride), eGFR, systolic BP, diastolic BP, and ACR with Cox's proportional hazard model. ACR was logarithmically transformed before analysis. To assess significance, the categorical data were compared between groups with the χ^2 test or Fisher's exact test, and quantitative data were compared between groups with *t* tests or ANOVA. The total number and rate of adverse events were compared for each group.

All tests were two-tailed; a *P* value of <0.05 was considered to be statistically significant.

DISCLOSURES

None.

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