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Impact of Multivascular Disease on Cardiovascular Mortality and Morbidity in Patients Receiving Hemodialysis: Ten-Year Outcomes of the Q-Cohort Study

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Aim: Multivascular disease, indicating concurrent arteriosclerotic lesions in a number of different vascular beds, is an independent risk factor for recurrent ischemic events in the general population. However, the impact of multivascular disease on the risk of developing cardiovascular disease has not been fully evaluated in patients receiving hemodialysis.

Methods: A total of 3,504 hemodialysis patients were prospectively followed for 10 years. In this study, multivascular disease was defined as the coexistence of coronary artery disease and stroke. We examined the relationship between multivascular disease and the occurrence of composite cardiovascular endpoint, consisting of cardiovascular death, nonfatal coronary artery disease, nonfatal stroke, and peripheral artery disease.

Results: The proportion of participants with multivascular disease was 5.7% (n=200) at baseline. During follow-up (median, 106.6 months; interquartile range, 50.1–121.8 months), 1,311 patients experienced the composite endpoint, which was defined as at least one of the following: cardiovascular death (n=620), nonfatal coronary artery disease (n=318), nonfatal stroke (n=340), and peripheral artery disease (n=257). Compared with the group with no history of cardiovascular disease, the risk of experiencing the composite endpoint increased significantly with higher numbers of injured vascular beds in patients with single vascular disease (hazard ratio, 1.68; 95% confidence interval, 1.49–1.89) and in those with multivascular disease (hazard ratio, 2.11; 95% confidence interval, 1.71–2.60). In a multivariable analysis, multivascular disease was an independent predictor of cardiovascular events, in addition to diabetes, aging, and hypertension.

Conclusions: This study clearly demonstrated that multivascular disease was a powerful predictor for cardiovascular mortality and morbidity in patients receiving hemodialysis.

Key words: Cardiovascular disease, End-stage kidney disease, Atherosclerosis.

Introduction

Globally, arteriosclerotic disease, including coronary artery disease (CAD), stroke, and peripheral arterial disease (PAD), is a main cause of mortality[1-3]. A previous study reported that 13% of patients with acute coronary syndrome had confirmed previous arterial disease in different vascular territories[4-6]. Furthermore, the global Reduction of Atherothrombosis for Continued Health (REACH) registry found that 15.9% of those with symptomatic atherothrombosis had polyvascular disease (PVD) characterized by

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lesions in multiple vascular beds and that the recurrent cardiovascular event rate increased with higher numbers of affected vascular beds[4, 6-12]. These epidemiological studies suggest that PVD is one of the most potent predictors of the future development of cardiovascular disease (CVD) events among patients with arteriosclerosis.

Arteriosclerotic disease is also common among patients receiving dialysis and is of great importance as a major cause of death and comorbidity in these patients. A nationwide survey in Japan revealed that 4.3% and 7.2% of the annual hemodialysis-related deaths were attributed to CAD and stroke, respectively[13]. It is widely recognized that patients receiving hemodialysis are a high-risk group for recurrent cardiovascular events due to their heavy arteriosclerotic burden[14, 15]. Nevertheless, the impact of multivascular disease on cardiovascular risk has not been fully elucidated in this population. A better understanding of the determinants of future cardiovascular events in patients receiving hemodialysis would be useful for clinicians to detect high-risk patients with CVD recurrence and to establish promising therapeutic strategies. Furthermore, identifying patients with a high risk of future CVD events would allow future trials assessing the efficacy of novel treatments to focus on patients most likely to benefit. The purpose of this study was to clarify the impact of multivascular disease on cardiovascular mortality and morbidity using data from a long-term longitudinal cohort of patients receiving hemodialysis.

Methods

Study Population

The details of the design of the Q-Cohort study have been described previously[16-18]. From the Q-Cohort study, we enrolled 3,598 outpatients >18 years of age who received hemodialysis at 39 dialysis facilities in Japan between December 31, 2006, and December 31, 2007, as the cohort in the current study. Participants were followed until December 31, 2016. We excluded participants with missing data for one or more baseline characteristics (n=81) and outcome information (n=13). After exclusions, we enrolled 3,504 patients as the final study population.

The study protocol was approved by the Clinical Research Ethics Committee of the Institutional Review Board at Kyushu University (Approval Number 20-31) and all participating institutions. Written informed consent was obtained from all participants at the start of the study. The present study was performed in accordance with the Ethics of Clinical Research (Declaration of Helsinki). This study is registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN ID: 000000556). The authors had no conflicts of interest to declare to the patients in this study.

Covariates

The main exposure was the presence of multivascular disease at baseline, and potential confounders were as follows: age; sex; dialysis duration; presence of diabetes mellitus; predialysis systolic blood pressure; hemoglobin concentration; serum albumin, Ca×iP products, intact PTH, total cholesterol, and log-transformed C-reactive protein; Kt/V (patient clearance, dialysis time, urea space); body mass index (BMI); and the use of renin–angiotensin system blockade and vitamin D-receptor activators. We selected cardiovascular risk factors for analysis based on the previous studies in the REACH Registry and our hemodialysis cohort[6, 8, 19, 20]. In the present study, multivascular disease was defined as the coexistence of CAD and stroke due to the lack of information about PAD at baseline. Thus, the definition of multivascular disease in this study did not include PAD as a component. CAD was defined as myocardial infarction and angina treated with coronary vasodilators. Valvular heart disease, coronary vasospastic angina, PAD, and arrhythmias were excluded from the definition of CAD. Stroke was also defined as a symptomatic and clinically diagnosed patient with cerebral hemorrhage and ischemic infarction. Moreover, since our database lacked information on aortic aneurysm, carotid atherosclerosis, ischemic colitis, and others, these were not included in the past history of CVD. These data were collected by reviewing patients' medical records. We could not detect when previous vascular disease at baseline occurred due to the lack of medical record information. The risk factors for CVD consisted of older age, diabetes, hypertension, hypercholesterolemia, and obesity. Older age was defined as ≥ 65 years for men and ≥ 70 years for women[8]. Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or current use of antihypertensive agents. Hypercholesterolemia was defined as serum total cholesterol ≥ 220 mg/dL, and obesity was defined as BMI ≥ 25 kg/m^2 according to the Asia–Pacific definition[21]. Blood samples were collected before starting each dialysis session, and hematological and serum biochemical parameters were determined using standard methods[16]. The corrected serum calcium concentration calculation was based on the serum albumin concentration, which was based on Payne's formula: corrected calcium concentration (mg/dL) = observed total calcium concentration (mg/dL) + (4.0 − serum albumin concentration [g/dL]).

Outcomes

The primary outcome was a composite cardiovascular endpoint defined as a composite of the three-point major adverse cardiovascular event score (MACE; cardiovascular death, nonfatal CAD, and nonfatal stroke) and PAD. CAD was defined as myocardial infarction, hospitalization for unstable angina, and/or coronary intervention (coronary artery bypass surgery or angioplasty). Stroke was defined as a persistent symptomatic neurological deficit diagnosed using brain imaging. PAD was defined as critical limb ischemia requiring amputation or revascularization. Research collaborators consisting of local physicians at each dialysis facility annually evaluated participants' health status. When the patient moved to another dialysis facility where a collaborator of this study was not present, we performed follow-up surveys through email or telephone.

Statistical Analysis

Participants were divided into four risk category groups according to the number of CVD risk factors and injured vascular beds (<3 risk factors, ≥ 3 risk factors, single vascular disease, and multivascular disease), and the linear trends in the mean values and frequencies of covariates across baseline risk categories were determined using a linear regression or logistic regression model. Survival was assessed using the Kaplan–Meier method and compared using log-rank tests. Multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for each risk factor for developing cardiovascular events were calculated using a Cox proportional hazards model. All models were adjusted for potential risk factors for CVD including age; sex; dialysis duration; presence of diabetes mellitus; predialysis systolic blood pressure; hemoglobin concentration; serum albumin, Ca×iP products, intact-PTH, total cholesterol, and log-transformed C-reactive protein; Kt/V; BMI; and the use of renin–angiotensin system blockade and vitamin D-receptor activators. To evaluate the influence of diabetes on the onset of CVD events, we performed a stratified analysis according to the presence or absence of diabetes and vascular lesions. Statistical analyses were performed using the SAS software package (ver. 9.3; SAS Institute, Cary, NC) and the STATA software package (ver. 14.0; Stata Corp., College Station, TX). Two-tailed $P<0.05$ was considered statistically significant.

Results

Table 1 summarizes patients' baseline characteristics. Of the 3504 patients, 2329 (66.5%) had no prior vascular disease at baseline; 2010 of these patients (57.4%) had <3 CVD risk factors, and 319 patients (9.1 %) had ≥ 3 CVD risk factors. The proportion of patients with previous vascular disease at baseline was 33.5% ($n=1,175$), of which 975 patients (27.8%) had single vascular disease, and 200 patients (5.7%) had multivascular disease. Among the patients with multivascular disease, 34 had cerebral hemorrhage and CAD, 155 had ischemic infarction and CAD, and 11 had other cerebrovascular disease plus CAD. The baseline characteristics of the overall population were an average age of 64.2 years, 59.4% men, and a mean dialysis duration of 5.3 years. The proportion of patients with hypertension was 85.6%, and diabetes was present in 29.3% of the patients. Obesity and hypercholesterolemia were present in 9.6% and 5.0% of the patients, respectively.

During follow-up, 1,735 patients had all-cause death, and 1,311 patients experienced at least 1 composite endpoint, including 1,224 patients with a 3-point MACE score, 620 with cardiovascular death, 318 with nonfatal CAD, 340 with nonfatal stroke, and 257 with PAD. A total of 620 cardiovascular deaths included 226 sudden deaths. **Fig. 1** shows the 10-year incidence of cardiovascular events during follow-up according to the baseline risk category. With increasing numbers of arteriosclerotic risk factors and injured vascular beds (<3 risk factors, ≥ 3 risk factors, single vascular disease, or multivascular disease), there was a significant increase in the rate of cardiovascular death (12.0%, 23.2%, 24.9%, and 31.0%, respectively; P for trend <0.001), nonfatal CAD death (7.7%, 8.5%, 12.0%, and 9.5%, respectively; P for trend <0.001), nonfatal stroke (8.0%, 12.9%, 11.5%, and 13.0%, respectively; P for trend <0.001), PAD (4.9%, 10.0%, 10.1%, and 14.0%, respectively; P for trend <0.001), three-point MACE (26.6%, 43.0%, 46.2%, and 51.0%, respectively; P for trend <0.001), and the composite endpoint (28.8%, 45.8%, 49.4%, and 54.5%, respectively; P for trend <0.001). During a 10-year follow-up, 222 patients developed new-onset multivascular disease.

The 5-year and 10-year event-free survival rate for the composite endpoint was 79.0% and 64.7% in patients with <3 risk factors, 58.3% and 39.1% in those with ≥ 3 risk factors, 56.7% and 36.4% in those with single vascular disease, and 45.3% and 17.2% in those with multivascular disease, respectively **(Fig. 2)**. **Table 2** lists the multivariable-adjusted HR of outcomes according to the baseline categories. Patients with <3 risk factors were considered the reference group. Compared with patients with <3 risk factors, those with ≥ 3 risk factors, single vascular disease, or multivascular disease had a 1.18-fold, 1.74-fold, and 2.23-fold increased risk of developing the composite

Table 1. Patients' Baseline Characteristics According to the Baseline Risk Category

	All patients (n = 3,504)	No previous vascular disease at baseline		Previous vascular disease at baseline	
		< 3 risk factors (n = 2,010)	≥ 3 risk factors (n = 319)	Single vascular disease (n = 975)	Multivascular disease (n = 200)
Age (years)	64.2 (55.9–72.8)	60.0 (52.5–68.8)	71.3 (65.0–76.5)	67.8 (59.3–75.0)	71.8 (65.5–78.4)
Gender (male) (%)	59.4	57.4	51.1	64.2	68.5
Dialysis duration (years)	5.3 (2.1–11.3)	5.9 (2.2–12.3)	5.8 (3.0–5.8)	5.7 (2.2–11.7)	5.3 (2.8–9.2)
History of cardiovascular disease (%)	22.4	0.0	0.0	100.0	100.0
Hypertension (%)	85.6	81.7	99.1	88.7	87.5
Hypercholesterolemia (%)	5.0	2.2	19.4	6.2	4.0
Diabetes mellitus (%)	29.3	15.5	79.6	36.9	49.5
Obesity (%)	9.6	5.0	38.6	10.2	6.0
Predialysis systolic blood pressure (mmHg)	153 (138–168)	150 (136–166)	165 (152–180)	155 (140–170)	155 (136–172)
Serum albumin (g/dL)	3.8 (3.6–4.1)	3.9 (3.6–4.1)	3.9 (3.6–4.2)	3.8 (3.5–4.0)	3.7 (3.4–4.0)
Hemoglobin concentration (g/dL)	10.6 (9.8–11.3)	10.6 (9.9–11.3)	10.6 (10.0–11.3)	10.6 (9.8–11.3)	10.5 (9.7–11.2)
Serum corrected calcium (mg/dL)	9.4 (8.9–9.9)	9.4 (8.9–9.9)	9.2 (8.7–9.8)	9.3 (8.9–9.8)	9.4 (8.9–9.9)
Serum phosphorus (mg/dL)	4.9 (4.1–5.6)	4.9 (4.2–5.7)	4.8 (4.2–5.8)	4.8 (4.0–5.6)	4.8 (4.0–5.4)
Serum total cholesterol (mg/dL)	152 (131–178)	153 (132–176)	152 (130–194)	152 (130–179)	149 (127–174)
C-reactive protein (mg/dL)	0.13 (0.06–0.30)	0.13 (0.05–0.30)	0.10 (0.05–0.30)	0.14 (0.08–0.40)	0.20 (0.10–0.59)
Kt/V (single-pool)	1.56 (1.42–1.71)	1.56 (1.43–1.76)	1.49 (1.30–1.77)	1.56 (1.42–1.67)	1.56 (1.43–1.58)
Body mass index (kg/m^2)	20.9 (19.1–22.7)	20.6 (19.1–22.3)	22.8 (21.5–24.7)	20.9 (18.9–22.8)	20.9 (18.9–22.3)
Use of RASB (%)	43.2	39.8	50.2	46.5	49.5
Use of VDRA (%)	70.1	72.5	71.8	65.6	64.5

Abbreviations: RASB, renin-angiotensin system blockade; VDRA, vitamin D-receptor activator; Kt/V, (patient clearance, dialysis time, urea space)
Values are given as the median (interquartile range) or percentage. Risk factors were older age, diabetes, hypertension, hypercholesterolemia, and obesity. Older age was defined as ≥ 65 years for men and ≥ 70 years for women. Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or current use of antihypertensive agents. Hypercholesterolemia was defined as serum total cholesterol ≥ 220 mg/dL. Obesity was defined as body mass index ≥ 25 kg/m^2.

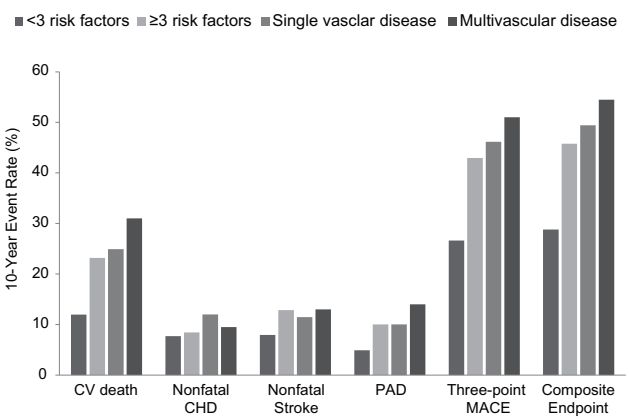

Fig. 1. Rate of cardiovascular events during the 10-year follow-up according to the baseline risk category

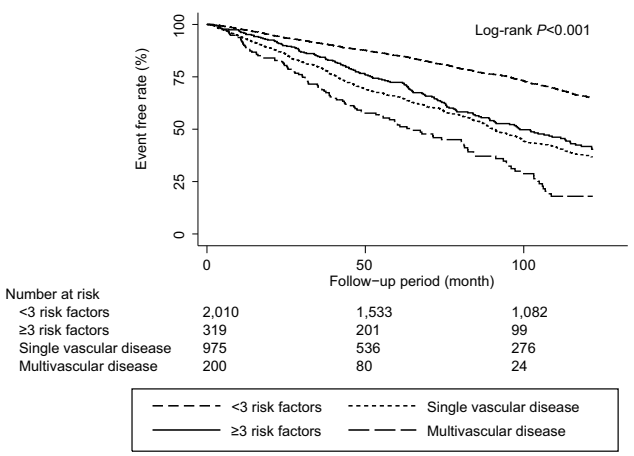

Fig. 2. Kaplan–Meier curves for the composite endpoint consisting of cardiovascular death, nonfatal coronary arterial disease, nonfatal stroke, and peripheral artery disease

endpoint, respectively. A similar linear upward trend among baseline categories was seen for the risk of cardiovascular death, nonfatal stroke, PAD, and three-point MACE, but not for nonfatal CAD.

Table 3 summarizes the multivariable independent predictors of the composite endpoint. Among the predictors, multivascular disease was an independent predictor, in addition to potential risk factors for

Table 2. Multivariable-Adjusted Hazard Ratios for Outcomes According to the Baseline Risk Category

	No previous vascular disease at baseline		Previous vascular disease at baseline	
	< 3 risk factors (n = 2,010)	≥ 3 risk factors (n = 319)	Single disease (n = 975)	Multivascular disease (n = 200)
	Hazard Ratio (95% CI)[a]			
Cardiovascular Death, n = 620	1.00 (reference)	1.31 (0.97–1.77)	1.88 (1.55–2.27)	2.43 (1.80–3.29)
Nonfatal CAD, n = 318	1.00 (reference)	0.71 (0.45–1.13)	1.51 (1.17–1.96)	1.43 (0.87–2.36)
Nonfatal Stroke, n = 340	1.00 (reference)	1.50 (1.00–2.23)	1.54 (1.39–3.34)	2.16 (1.39–3.34)
PAD, n = 257	1.00 (reference)	0.80 (0.51–1.26)	1.51 (1.11–2.04)	2.19 (1.39–3.45)
Three-point MACE, n = 1,224	1.00 (reference)	1.24 (1.00–1.53)	1.78 (1.55–2.03)	2.29 (1.82–2.87)
Composite Endpoint, n = 1,311	1.00 (reference)	1.18 (0.96–1.46)	1.74 (1.53–1.98)	2.23 (1.79–2.77)

Abbreviations: CI, confidence interval; CAD, coronary artery disease; PAD, peripheral arterial disease; MACE, major adverse cardiovascular events.
Three-point MACE was defined as a composite of cardiovascular death, nonfatal CAD, and nonfatal stroke.
The composite endpoint was defined as a composite of the three-point MACE and PAD.
[a]Adjusted for age, sex, dialysis duration, diabetes, systolic blood pressure, hemoglobin concentration, serum albumin, Ca × iP products, intact-PTH, total cholesterol, and log-transformed C-reactive protein, Kt/V (patient clearance, dialysis time, urea space), body mass index, and use of renin-angiotensin system blockade and vitamin D-receptor activators.

Table 3. Multivariable Independent Predictors of Composite endpoint in the Cox regression Model

Variable	Hazard Ratio (95% CI)[a]	P-value
Multivascular disease (vs. no vascular disease)	2.11 (1.71-2.60)	< 0.01
Single-vascular disease (vs. no vascular disease)	1.68 (1.49-1.89)	< 0.01
Diabetes (vs. no)	1.56 (1.38-1.77)	< 0.01
Age (per 10 year increment)	1.36 (1.29-1.44)	< 0.01
Use of RASB (%)	1.30 (1.16-1.46)	< 0.01
Men (vs. women)	1.14 (1.01-1.29)	0.04
Log-transformed serum C-reactive protein (per 1 log [mg/dL] increment)	1.12 (1.08-1.16)	< 0.01
Systolic blood pressure (per 10 mmHg increment)	1.04 (1.01-1.07)	< 0.01
Use of VDRA (%)	0.88 (0.78-0.99)	0.03
Serum albumin (per 1 g/dL increment)	0.86 (0.74-0.99)	0.04

Abbreviations: CI, confidence interval; RASB, renin-angiotensin system blockade; VDRA, vitamin D receptor activator.
[a]Adjusted for age, sex, dialysis duration, diabetes, systolic blood pressure, hemoglobin concentration, serum albumin, Ca × iP products, intact-PTH, total cholesterol, and log-transformed C-reactive protein, Kt/V (patient clearance, dialysis time, urea space), body mass index, and use of RASB and VDRA.

cardiovascular events such as diabetes, aging, and hypertension. Compared with patients with no history of vascular disease, the risk of experiencing the composite endpoint increased significantly with increased numbers of injured vascular beds (HR, 1.68; 95% CI, 1.49–1.89 in patients with single vascular disease; HR, 2.11; 95% CI, 1.71–2.60 in patients with multivascular disease). As shown in **Table 4**, multivascular disease was an independent risk factor for composite CVD events regardless of whether blood pressure and RASB use were incorporated into the model. Furthermore, blood pressure and RASB were selected as independent risk factors for composite CVD events in a Cox regression model using a stepwise backward selection method **(Table 5)**. **Table 6** presents the multivariable independent predictors of new-onset multivascular disease. Among the predictors, multivascular disease, single vascular disease, Ca × iP products, and log-transformed C-reactive protein were independently associated with the development of new-onset multivascular disease, in addition to traditional risk factors for cardiovascular events such as diabetes, aging, and hypertension. The influence of the number of injured vascular beds on patients' risk for other cardiovascular events was essentially the same **(Table 7)**.

Fig. 3 illustrates the additional risk of having diabetes with a history of cardiovascular disease at baseline. Overall, the presence of diabetes was associated with an increased risk of cardiovascular events (event rate for the composite endpoint without or with dia-

Table 4. Multivariable-Adjusted Hazard Ratios for Composite Endpoint According to the Baseline Risk Category

	No previous vascular disease at baseline		Previous vascular disease at baseline	
	< 3 risk factors (n = 2,010)	≥ 3 risk factors (n = 319)	Single-vascular disease (n = 975)	Multivascular disease (n = 200)
	Hazard Ratio (95% CI) [a]			
Model 1	1.00 (reference)	1.22 (0.99-1.50)	1.80 (1.58-2.04)	2.24 (1.80-2.79)
Model 1 + systolic blood pressure	1.00 (reference)	1.21 (0.98-1.48)	1.78 (1.56-2.02)	2.24 (1.80-2.79)
Model 1 + RASB	1.00 (reference)	1.18 (0.95-1.45)	1.76 (1.54-2.00)	2.21 (1.77-2.75)
Model 1 + systolic blood pressure + RASB	1.00 (reference)	1.17 (0.95-1.45)	1.75 (1.53-1.99)	2.21 (1.78-2.75)

Abbreviations: CI, confidence interval; CAD, coronary artery disease; PAD, peripheral arterial disease; MACE, major adverse cardiovascular events; RASB, renin-angiotensin system blockade; VDRA, vitamin D receptor activator.
Three-point MACE was defined as a composite of cardiovascular death, nonfatal CAD, and nonfatal stroke.
The composite endpoint was defined as a composite of the three-point MACE and PAD.
Model 1 was adjusted for age, sex, dialysis duration, diabetes, hemoglobin concentration, serum albumin, Ca × iP products, intact-PTH, total cholesterol, and log-transformed C-reactive protein, Kt/V (patient clearance, dialysis time, urea space), body mass index, and use of VDRA.

Table 5. Multivariable Independent Predictors of Composite Endpoint in the Cox regression Model using Backward selection method

Variable	Hazard Ratio (95% CI) [a]	P value
Multivascular disease (vs. no vascular disease)	2.18 (1.77-2.68)	< 0.01
Single-vascular disease (vs. no vascular disease)	1.70 (1.51-1.92)	< 0.01
Diabetes (vs. no)	1.55 (1.38-1.75)	< 0.01
Age (per 10 year increment)	1.34 (1.27-1.41)	< 0.01
Use of RASB (%)	1.30 (1.16-1.46)	< 0.01
Log-transformed serum C-reactive protein (per 1 log [mg/dL] increment)	1.12 (1.08-1.16)	< 0.01
Systolic blood pressure (per 10 mmHg increment)	1.04 (1.02-1.07)	< 0.01
Serum albumin (per 1 g/dL increment)	0.85 (0.74-0.99)	0.03

Abbreviations: CI, confidence interval; RASB, renin-angiotensin system blockade.
[a] Variables were selected by using a Cox proportional hazard model and a stepwise backward method with $P < 0.05$ for remaining variables to determine the predictors of composite endpoint.

Table 6. Multivariable Independent Predictors of New-onset Multivascular Disease in the Cox regression Model

Variable	Hazard Ratio (95% CI) [a]	P value
Multivascular disease (vs. no vascular disease)	2.59 (1.38-4.89)	< 0.01
Diabetes (vs. no)	2.29 (1.70-3.09)	< 0.01
Single-vascular disease (vs. no vascular disease)	1.82 (1.24-2.68)	< 0.01
Use of RASB (%)	1.81 (1.36-2.41)	< 0.01
Age (per 10 year increment)	1.33 (1.17-1.52)	< 0.01
Log-transformed serum C-reactive protein (per 1 log [mg/dL] increment)	1.16 (1.06-1.27)	< 0.01
Ca × iP products (per 10 increment)	1.15 (1.03-1.30)	0.02
Systolic blood pressure (per 10 mmHg increment)	1.13 (1.07-1.21)	< 0.01

Abbreviations: CI, confidence interval; CAD, coronary artery disease; RASB, renin-angiotensin system blockade; VDRA, vitamin D receptor activator.
Multivascular disease was defined as a composite of cardiovascular death, nonfatal CAD, and nonfatal stroke.
[a] Adjusted for age, sex, dialysis duration, diabetes, systolic blood pressure, hemoglobin concentration, serum albumin, Ca × iP products, intact-PTH, total cholesterol, and log-transformed C-reactive protein, Kt/V (patient clearance, dialysis time, urea space), body mass index, and use of RASB and VDRA.

Table 7. Multivariable Predictors of Cardiovascular Events in the Cox regression Model

Variable	Cardiovascular Death (n = 620)	Nonfatal CAD (n = 318)	Nonfatal Stroke (n = 340)	PAD (n = 257)	Three-point MACE (n = 1,224)	Composite Endpoint (n = 1,311)
	Hazard Ratio (95% CI) [a]					
Multivascular disease (vs. no vascular disease)	2.23 (1.68–2.97)	1.55 (0.95–2.53)	1.93 (1.26–2.95)	2.39 (1.56–3.66)	2.13 (1.72–2.65)	2.11 (1.71–2.60)
Single vascular disease (vs. no vascular disease)	1.75 (1.47–2.08)	1.63 (1.28–2.08)	1.40 (1.10–1.78)	1.61 (1.23–2.10)	1.69 (1.49–1.91)	1.68 (1.49–1.89)
Age (per 10-year increment)	1.67 (1.54–1.82)	1.07 (0.96–1.18)	1.19 (1.07–1.32)	1.36 (1.20–1.54)	1.37 (1.29–1.45)	1.36 (1.29–1.44)
Men (vs. women)	1.11 (0.93–1.34)	1.28 (0.98–1.67)	1.04 (0.81–1.33)	1.00 (0.76–1.33)	1.15 (1.01–1.31)	1.14 (1.01–1.29)
Dialysis duration (per 5-year increment)	1.06 (1.00–1.13)	0.99 (0.90–1.08)	0.91 (0.83–1.00)	1.05 (0.94–1.17)	0.99 (0.95–1.04)	1.00 (0.96–1.04)
Diabetes (vs. no)	1.73 (1.45–2.08)	1.44 (1.12–1.86)	1.18 (0.92–1.52)	3.41 (2.57–4.53)	1.50 (1.32–1.71)	1.56 (1.38–1.77)
Systolic blood pressure (per 10-mmHg increment)	0.98 (0.94–1.02)	1.10 (1.04–1.15)	1.10 (1.05–1.16)	1.04 (0.98–1.10)	1.04 (1.02–1.07)	1.04 (1.01–1.07)
Serum albumin (per 1-g/dL increment)	0.64 (0.52–0.79)	1.26 (0.92–1.71)	0.93 (0.69–1.24)	1.10 (0.79–1.53)	0.86 (0.74–1.00)	0.85 (0.73–0.99)
Hemoglobin concentration (per 1-g/dL increment)	0.97 (0.90–1.04)	1.09 (0.98–1.21)	1.07 (0.97–1.18)	0.91 (0.81–1.02)	1.01 (0.96–1.07)	1.01 (0.96–1.06)
Serum total cholesterol (per 10-mg/dL increment)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (1.00–1.01)	1.00 (0.99–1.01)	1.00 (1.00–1.01)	1.00 (1.00–1.01)
Log-transformed serum C-reactive protein (per 1-log [mg/dL] increment)	1.09 (1.04–1.15)	1.15 (1.06–1.24)	1.08 (1.01–1.15)	1.24 (1.13–1.35)	1.12 (1.08–1.16)	1.12 (1.08–1.16)
Kt/V (single-pool) (per 1 increment)	0.83 (0.59–1.18)	1.23 (0.74–2.05)	1.49 (0.93–2.39)	0.65 (0.37–1.13)	1.09 (0.85–1.40)	1.05 (0.83–1.34)
Body mass index (per 1-kg/m^2 increment)	0.95 (0.92–0.98)	1.07 (1.03–1.11)	0.98 (0.94–1.02)	1.03 (0.99–1.07)	0.99 (0.97–1.01)	1.00 (0.98–1.02)
Use of RASB (%)	1.19 (1.01–1.40)	1.57 (1.25–1.99)	1.11 (0.89–1.39)	1.78 (1.37–2.33)	1.28 (1.14–1.44)	1.30 (1.16–1.46)
Use of VDRA (%)	0.81 (0.68–0.96)	0.97 (0.76–1.24)	1.09 (0.85–1.39)	0.64 (0.50–0.83)	0.91 (0.80–1.03)	0.88 (0.78–0.99)

Abbreviations: CI, confidence interval; CAD, coronary artery disease; PAD, peripheral arterial disease; MACE, major adverse cardiovascular events; RASB, renin-angiotensin system blockade; VDRA, vitamin D-receptor activator.
Three-point MACE was defined as a composite of cardiovascular death, nonfatal CAD, and nonfatal stroke.
The composite endpoint was defined as a composite of the three-point MACE and PAD.
[a] Adjusted for age, sex, dialysis duration, diabetes, systolic blood pressure, serum albumin, hemoglobin concentration, Ca × iP products, intact-PTH, total cholesterol, and log-transformed C-reactive protein, Kt/V (patient clearance, dialysis time, urea space), body mass index, and use of RASB and VDRA.

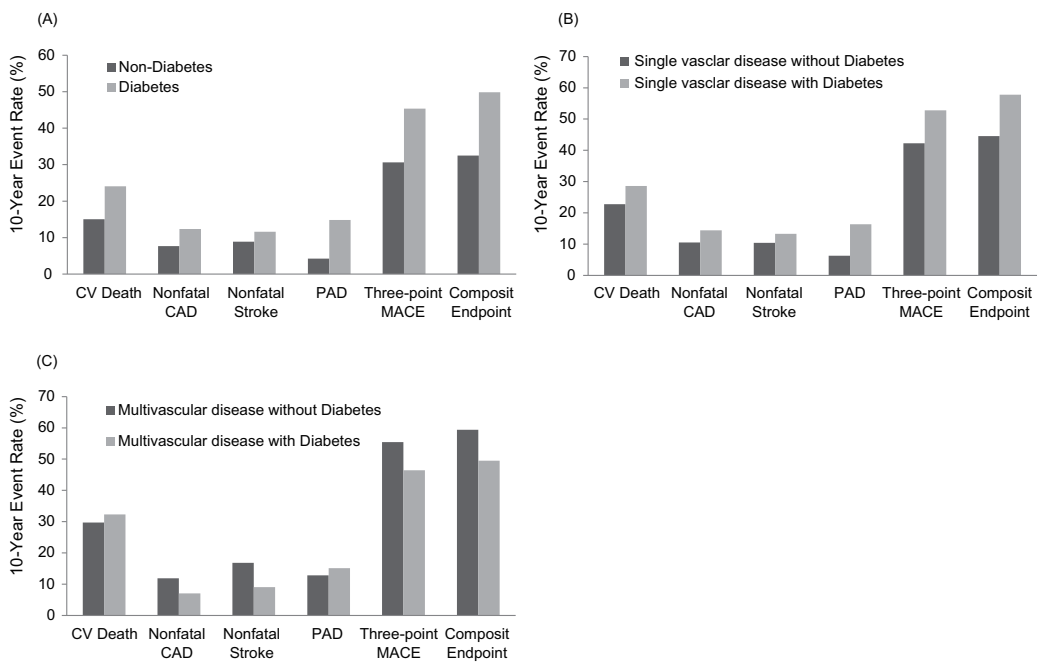

Fig. 3. Rate of cardiovascular events during the 10-year follow-up according to the presence or absence of diabetes

Abbreviations: CV, cardiovascular; CAD, coronary artery disease; PAD, peripheral arterial disease; MACE, major adverse cardiovascular events.
Three-point MACE was defined as a composite of cardiovascular death, nonfatal CAD, and nonfatal stroke. The composite endpoint was defined as a composite of the three-point MACE and PAD.

betes: 32% vs. 50%, respectively). Similarly, the presence of diabetes was also associated with additional risk in patients with single vascular disease (event rate for the composite endpoint without or with diabetes: 45% vs. 58%, respectively). In contrast, the presence of diabetes did not enhance the risk of cardiovascular events in patients with multivascular disease (event rate for the composite endpoint without or with diabetes: 59% vs. 49%, respectively).

Discussion

This study clearly demonstrated that multivascular disease was a powerful predictor of cardiovascular mortality and morbidity among patients receiving hemodialysis. We found that 5.7% of patients had multiple vascular disease locations at baseline. The event-free survival rate for the composite endpoint decreased significantly as the number of risk factors for arteriosclerosis and vascular lesions increased. Moreover, the risk of developing cardiovascular events increased linearly as the number of affected vascular beds increased, even after adjusting for all potential confounders. Future novel anti-atherosclerotic drugs are probably expensive and may have additional adverse effects. Therefore, it is desirable and cost-effective to provide these treatments to individuals at highest ischemic risk. Our simple risk stratification, which combines risk factors and the number of affected vascular beds, can help identify individuals at highest risk for cardiovascular events. These findings could lead to future clinical trials focusing on the patients most likely to benefit from novel therapeutic interventions. Furthermore, the ability of multivascular disease to predict future CVD events might be useful to quickly identify CVD high-risk individuals among patients receiving dialysis, whose clinical features vary widely.

The results of the present study provided a detailed overview of typical patients with cardiovascular disease receiving hemodialysis. Approximately 33.5% of registered patients receiving hemodialysis in our study also had vascular disease in one or two vascular beds at baseline. The remaining 66.5% of patients had no history of vascular events. Approximately 15% of our patients with no history of vascular disease at baseline had multiple arteriosclerotic risk factors. Recent findings from the global REACH Registry focused on the insufficient management of multiple risks in the general population with atherothrombotic disease, emphasizing the need for further improvement in treatment strategies[10, 22].

This study examined the association between multivascular disease and CVD outcomes. The multivariable-adjusted model in the current study incorporated blood pressure and RASB use as confounders. Our sensitivity analysis showed that the presence of multivascular disease was an independent risk factor for composite CVD events, with or without blood pressure and RASB use **(Table 4)**. In addition, blood pressure and RASB use were shown to remain in the model as statistically independent risk factors for CVD using a stepwise backward selection method **(Table 5)**. However, it should also be noted that blood pressure and RASB use may not be suitable potential confounders in patients with multivascular disease, because the presence of multivascular disease can affect blood pressure level. For example, blood pressure level would automatically become lower in patients with poor cardiac function. Some clinicians might make effort to maintain blood pressure level a little bit higher in patients with carotid artery stenosis and so on. Thus, blood pressure may not be a confounder in multivascular disease states. Although blood pressure management can be important before developing multivascular disease, once a multivascular disease occurs, the contribution of blood pressure control to the outcome might be diluted. Further investigation is needed to clarify the significance of blood pressure management in multivascular disease status.

It is well known that the process of atherosclerosis is somewhat different between the general population and chronic kidney disease (CKD) patients. In other words, atheroembolism is the leading cause of PVD in the general population, but CKD-MBD factors are rather important in CKD patients[23]. Therefore, we performed an additional analysis to detect risk factors associated with new-onset of PVD during the 10-year follow-up period in the current cohort. The results showed that Ca x iP products were an independent risk factor for new-onset PVD in the present cohort, focusing on the importance of CKD-MBD factors in the atherosclerotic process in hemodialysis patients.

In the present study, the risk of developing cardiovascular events increased linearly with increasing numbers of affected vascular beds compared with patients who had no previous vascular disease and no multiple risk factors. Missault *et al.* reported that up to 65% of patients with CAD or with a history of stroke have coexisting PAD[24]. In addition, the effect of concurrent PAD on the cardiovascular event rate in stroke patients in the Japanese REACH Registry was larger than that in patients with concurrent CAD[9]. CKD was reported to be associated with intracranial artery stenosis in the middle-aged and elderly population[25]. The prevalence of severe carotid stenosis has been reported to be more than doubled in patients with PAD compared with patients with CAD[26], sug-

gesting that coexisting PAD may be a more potent predictor of future CVD development in patients with multiple arteriosclerotic lesions. In a general Japanese population, a lower ankle–brachial index was associated with an increased risk of incident CKD, independent of traditional cardiovascular risk factors[27]. Unfortunately, data for our cohort lacked information regarding the presence of PAD at baseline. Future research is needed to clarify the effects of differences among injured vascular beds and the combined effect of these differences on the development of future cardiovascular events in patients receiving hemodialysis.

The overall analysis of our cohort showed that the incidence of cardiovascular events was significantly higher in patients with diabetes compared with those without diabetes. This relationship was similar in patients with diabetes with single vascular disease. Conversely, the incidence of nonfatal cardiovascular events in patients with diabetes and PVD was lower compared with patients without diabetes despite the finding that patients with diabetes and PVD had the highest cardiovascular mortality. Our finding that the incidence of cardiovascular events related to the presence of diabetes was higher for fatal events than for nonfatal events in patients with PVD is consistent with a previous observational study of non-dialysis patients[28]. These findings may be the result of underestimating the incidence of nonfatal cardiovascular events due to the high mortality rate in patients with diabetes and PVD. Although intensive management of cardiovascular risk factors is recommended for patients with diabetes, our results suggest the need for more aggressive intervention for patients with diabetes with multiple vascular diseases. In addition, high cardiovascular mortality in patients with diabetes and PVD provides insights into the potential design and interpretation of future clinical trials.

There are several limitations in our study. First, we defined PVD as a combined history of previous CAD and stroke, due to the lack of information on the presence or absence of PAD at baseline. As a result, the effect of PAD may have been underestimated, possibly leading to misclassification of patients, which may have created bias results toward the null hypothesis. Second, although our cohort included large amounts of clinical data, which we used for our analyses, patient data for the duration and severity of previous vascular disease were not available. Finally, the endpoints in this observational cohort were not adjudicated by an independent events committee, as is common in many randomized clinical trials.

In conclusion, our study revealed that PVD was significantly associated with an increased risk of future cardiovascular disease in patients receiving hemodialysis. Evaluating the cross-risk that patients with single vascular disease are more likely to experience further events in other vascular beds would contribute to better understanding of systemic vascular disease and improved prognosis in patients receiving hemodialysis.

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Authors' Contributions

Shigeru Tanaka contributed to the study design, statistical analysis, interpreting the data, and drafting the manuscript. Toshiaki Nakano contributed to the statistical analysis, interpreting the data, and drafting the manuscript. Hiroto Hiyamuta, Masanori Tokumoto, and Kosuke Masutani contributed to acquisition of data and critical revision of the manuscript. Masatomo Taniguchi contributed to study funding, acquisition of data, and critical revision of the manuscript. Kazuhiko Tsuruya, Hiroaki Ooboshi, and Takanari Kitazono contributed to critical revision of the manuscript and supervision of the study. All authors critically reviewed the draft of the manuscript and approved the final version.

Conflict of Interest

The authors declare that they have no relevant financial interests.

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