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Effect of Hemodialysis on 7-Year Clinical Outcomes After Sirolimus-Eluting Stent Implantation

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Background: Hemodialysis (HD) patients are reported to show poor clinical outcomes after percutaneous coronary intervention (PCI) with sirolimus-eluting stent (SES) compared with non-HD patients and their long-term prognosis remains unclear.

Methods and Results: We prospectively enrolled 489 consecutive patients undergoing PCI with SES and performed a retrospective analysis focusing on HD patients. Median follow-up was 7.0 years (interquartile range, 4.2–7.9) and the follow-up rate was 100%. At the 7-year follow-up, the cumulative incidences of all-cause death, target lesion revascularization (TLR) and major adverse cardiac events (MACE) were significantly higher in HD patients than in non-HD patients (HD vs. non-HD=34.7% vs. 9.6%, 42.6% vs. 10.2% and 75.3% vs. 24.4%, respectively; log-rank P<0.001). Cox-proportional hazard analysis revealed that independent predictors of all-cause death were HD (hazard ratio [HR] 2.88, 95% confidence interval [CI]: 1.39–6.00), insulin-treated diabetes mellitus (HR 2.19, 95% CI: 1.17–4.11), heart failure (HR 2.58, 95% CI: 1.25–5.32) and older age (HR 1.06/1-age, 95% CI: 1.02–1.10). Moreover, HD was an independent predictor of TLR (HR 3.63, 95% CI: 1.85–7.11) and MACE (HR 3.54, 95% CI: 2.19–5.73).

Conclusions: In the present study, Japanese HD patients undergoing PCI with SES showed poorer long-term clinical outcomes than non-HD patients. HD was a strong predictor of long-term adverse events after SES implantation. (*Circ J* 2015; **79:** 2169–2176)

Key Words: Hemodialysis; Long-term outcome; Percutaneous coronary intervention; Sirolimus-eluting stent

Coronary artery disease (CAD) is present in over 50% of patients with end-stage renal disease (ESRD) on hemodialysis (HD).[1] Cardiovascular disease, including heart failure (HF) and myocardial infarction (MI), is the leading cause of death among HD patients and accounts for approximately 30% of all-cause death. ESRD patients, including those on HD, have an increased risk of restenosis and major adverse cardiac events (MACE) after percutaneous coronary intervention (PCI); either balloon angioplasty alone or bare-metal stent (BMS) implantation.[2] A recent report showed advantages of coronary artery bypass grafting (CABG) in HD patients.[3]

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The sirolimus-eluting stent (SES [Cypher, Cordis/Johnson & Johnson, Miami, FL, USA]), one of the most widely used first-generation drug-eluting stents (DES), significantly reduced the rate of target lesion revascularization (TLR) compared with BMS implants in randomized control trials.[4–7] However, all the well-designed studies of DES have excluded HD patients in order to avoid clinical heterogeneity of the study population. Several papers reported that HD patients showed poor clinical outcomes after PCI with SES compared with non-HD patients.[8,9] However, the effect of HD on long-term clinical outcomes after SES implantation has not been fully evaluated, so the goal of the present study was to evaluate the long-term clinical outcomes of HD patients undergoing PCI with SES.

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Methods

Study Design and Population

The study population consisted of 489 consecutive patients who had undergone successful coronary SES implantation registered at the Tokyo Women's Medical University Hospital between August 2004 and December 2005. The median follow-up was 7.0 years (interquartile range, 4.2–7.9). Enrolled patients were divided into 2 groups: the HD group (43 patients [8.8%]) and the non-HD group (446 patients [91.2%]). Their clinical characteristics, including age, sex, coronary risk factors (hypertension, diabetes mellitus [DM], dyslipidemia, smoking habits), HF, peripheral artery disease (PAD), and atrial fibrillation, as well as prior histories of stroke, MI, PCI, or CABG surgery, were reviewed for all patients.

Interventional Procedures

SES deployment was performed according to standard procedures in contemporary practice.[10,11] Balloon or stent size and inflation pressure, usage of intravascular ultrasound (IVUS) and of the rotablator were left to the discretion of each operator. The definition of successful SES implantation was residual stenosis less than 25% with TIMI flow 3 assessed angiographically by eye at the end of the procedure. The endpoint of the PCI procedure was left to each operator's discretion with angiographic and/or IVUS guidance. The minimum lumen diameter and the percentage diameter stenosis after coronary stenting were calculated by using quantitative coronary angiography (QCA) on a single-plane, worst-view angulation. The left ventricular ejection fraction was determined by contrast ventriculography or echocardiography during hospitalization in all participants. All patients received aspirin (81–100 mg/day) before the procedure and additional antiplatelet therapy with ticlopidine (200 mg/day) was instituted. The postprocedural antiplatelet regimen consisted of lifelong aspirin (81–100 mg/day) and ticlopidine (200 mg/day for more than 6 months). The duration of ticlopidine treatment was at the operator's discretion. At 9 months after SES implantation, protocol-mandated angiography was performed. Patients' clinical information during the observation period was obtained from outpatient clinic visits, a review of the medical record, or by telephone interview with the patient.

Endpoints and Study Definitions

The primary endpoints of this study were all-cause death, TLR and MACE. TLR was defined as repeat PCI for a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent. MACE included all-cause death, target vessel revascularization (TVR), and non-fatal MI. TVR was defined as any repeat PCI in the target vessel and MI was defined according to the definition in the ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction.[12] We also examined the incidence of revascularization of non-target vessels or any coronary arteries revascularization during the study period (**Figure S1**). Binary angiographic restenosis was defined as >50% diameter stenosis on QCA analysis at follow-up. Final decision making to perform TLR and/or TVR was left to the attending physicians, who essentially determined it by visual assessment of angiographic stenosis >50% on the target lesion in addition to cardiac ischemia-related symptom and/or positive results on cardiac stress test or myocardial perfusion scintigraphy. With regard to the counting of each event, the authors used the per-patient basis rather than the per-lesion basis.

Statistical Analysis

Categorical variables were compared using χ^2 test. Continuous variables are expressed as mean value±standard deviation, and compared using Student's t-test or Mann-Whitney U-test based on the distributions. A 2-sided P-value of less than 0.05 was considered statistically significant. Event-free survival curves were constructed using Kaplan-Meier curves and were compared between the groups by the log-rank test. Cox-proportional hazard models were used to estimate the risk of HD for adverse clinical outcomes, adjusting for the differences in the patients' characteristics. Covariates that were statistically significant on univariate analysis and/or those that were clinically relevant were included in the multivariate models. To avoid over-fitting problem caused by the limited number of events, we restricted the number of covariates, including age, sex, body mass index, hypertension, DM, dyslipidemia, clinical presentation on admission, number of diseased vessels, HF, prior MI, prior PCI, prior CABG, prior stroke, PAD and medication discharge (angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARB] and statins). Statistical analyses were performed by an independent physician using statistical software (IBM SPSS Statistics version 20.0, Armonk, NY, USA).

Ethical Considerations

The study protocol was based on the regulations of the hospital's ethics committee. All participating patients gave written, informed consent. Patient enrollment was carried out according to the principles of the Declaration of Helsinki.

Results

Baseline Clinical Characteristics

The patients' baseline clinical characteristics are summarized in **Table 1**. Male patients accounted for 86% of the study population, which had an average age of 66 years. DM was apparent in 51% of patients, including 13% with insulin-dependent DM. Patients in the HD group showed significantly lower body mass index (P<0.001) and higher prevalence of insulin-treated DM (P<0.001), HF (P<0.001), PAD (P<0.001), and multivessel disease (P=0.014), while patients in the non-HD group had a significantly higher prevalence of dyslipidemia (P=0.020). In terms of laboratory data, the HD group showed significantly higher levels of C-reactive protein (CRP) (P=0.013) and lower levels of hemoglobin, HDL-cholesterol, and LDL-cholesterol (P<0.001, P=0.005 and P<0.001, respectively) than the non-HD group. Regarding oral medications, the HD group was administered more ACEI/ARB (P=0.022) and less statins (P=0.010) compared with the non-HD group, both on admission and at discharge (**Table 2**).

Angiographic Lesion Profiles and Procedural Parameters

We evaluated 57 lesions in the HD group and 625 in the non-HD group at the initial PCI session (**Table 3**). Numbers of implanted stents, distribution of target vessels, and lesion complexities, including the ratio of chronic total occlusion, were similar between the groups. For the target lesions, IVUS was used in 77%, pre-stenting/post-stenting balloon dilation were performed in 71% and 46%, respectively; the average stent size was 3.0 mm and total stent length was 32 mm. Comparison of these parameters between lesions in the HD and the non-HD group showed no statistically significant differences. On the other hand, there appeared to be significantly more restenotic lesions in the HD group (P=0.001), and stent deployment in ostial lesions and ablation device use were significantly more frequent in the HD group than in the non-HD group (P=0.002

Table 1. Characteristics of Patients Undergoing PCI With SES

Variable	HD group (n=43)	Non-HD group (n=446)	P value
Age, years	65.7±9.9	66.1±10.1	0.80
>75	7 (16%)	103 (23%)	0.31
Male	36 (84%)	386 (87%)	0.61
BMI, kg/m^2	22.5±3.4	24±3.1	<0.001
Hypertension	36 (84%)	345 (77%)	0.34
Diabetes	27 (63%)	223 (50%)	0.11
Insulin treatment	15 (35%)	47 (11%)	<0.001
Dyslipidemia	25 (58%)	332 (74%)	0.020
Current smoker	24 (56%)	284 (63%)	0.35
Clinical presentation			
SAP/UAP/SMI/RMI/NSTEMI/STEMI	15/8/12/3/1/4	176/102/78/22/11/57	0.62
Multivessel disease	36 (84%)	291 (65%)	0.014
Heart failure	9 (21%)	18 (4%)	<0.001
Atrial fibrillation	4 (9%)	53 (12%)	0.84
Prior MI	14 (33%)	116 (26%)	0.36
Prior PCI	15 (35%)	112 (25%)	0.16
Prior CABG	10 (23%)	63 (14%)	0.11
Prior stroke	4 (9%)	40 (9%)	0.94
Peripheral arterial disease	8 (19%)	20 (5%)	<0.001
Laboratory data			
Hemoglobin, g/dl	10.7±1.3	13.8±2.0	<0.001
CRP, mg/L	1.3±2.8	0.6±1.8	0.013
Total cholesterol, mg/dl	158.8±34.6	181.9±36.4	<0.001
HDL-C, mg/dl	38.8±12.0	45.4±12.2	0.005
LDL-C, mg/dl	76.4±55.3	103.7±43.1	<0.001
Triglyceride, mg/dl	145.6±116.3	146.5±97.4	0.45

*eGFR <60 ml/min/1.73 m^2. BMI, body mass index; CABG, coronary artery bypass grafting; CRP, C-reactive protein; HD, hemodialysis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAP, stable angina pectoris; SES, sirolimus-eluting stent; UAP, unstable angina pectoris.

Table 2. Oral Medications Administered to Patients Undergoing PCI With SES

Variable	On admission			At discharge		
	HD group (n=43)	Non-HD group (n=446)	P value	HD group (n=43)	Non-HD group (n=445)	P value
Aspirin	34 (79%)	322 (72%)	0.33	42 (98%)	432 (97%)	0.82
Ticlopidine	13 (30%)	169 (38%)	0.32	42 (98%)	438 (98%)	0.71
Warfarin	1 (2%)	36 (8%)	0.17	2 (5%)	38 (9%)	0.37
Nicorandil	9 (20%)	84 (19%)	0.74	9 (21%)	78 (18%)	0.58
CCB	23 (53%)	206 (46%)	0.36	22 (51%)	177 (40%)	0.15
β-blocker	19 (44%)	204 (46%)	0.84	37 (86%)	344 (77%)	0.19
ACEI/ARB	30 (70%)	230 (52%)	0.022	38 (88%)	326 (73%)	0.03
Statin	11 (26%)	205 (46%)	0.010	25 (58%)	368 (83%)	<0.001
Nitrate	22 (51%)	199 (45%)	0.41	17 (40%)	153 (34%)	0.50

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker. Other abbreviations as in Table 1.

and P<0.001, respectively). Overall angiographic follow-up rate at 9 months was 69.3%. Target lesion length, baseline reference vessel diameter, or acute lumen gain were not significantly different between the groups (Table 4). However, the minimal lesion diameter was significantly larger at baseline and smaller at the 9-month follow-up in the HD group (P=0.014, P=0.002, respectively) and resulted in a significantly higher late lumen loss and binary restenosis rate (both P<0.001).

Clinical Follow-up at 7 Years

The clinical outcomes are presented in Figure 1. At the 7-year follow-up, the cumulative incidences of all-cause death, TLR, TVR and MACE rates were all significantly higher in the HD group than in the non-HD group.

Figure 1A shows the Kaplan-Meier curves for all-cause death. The ratio of all-cause death was significantly higher in the HD group than in the non-HD group throughout the obser-

Table 3. Lesion Characteristics and Procedural Parameters for Patients Undergoing PCI With SES

Variable	HD group (n=57)	Non-HD group (n=625)	P value
Target vessel			
LAD	23 (40.4%)	275 (44%)	
LCx	10 (17.5%)	140 (22.4%)	
RCA	24 (42.1%)	184 (29.4%)	0.21
LMT	0 (0%)	15 (2.4%)	
Other	0 (0%)	11 (1.8%)	
ACC/AHA classification			
A	0 (0%)	32 (5.1%)	
B1	3 (5.3%)	73 (11.7%)	0.13
B2	32 (56.1%)	309 (49.4%)	
C	22 (38.6%)	211 (33.8%)	
De novo lesion	48 (84.2%)	593 (94.9%)	0.001
Restenotic lesion	9 (15.8%)	32 (5.1%)	0.001
Bifurcation lesion	12 (21.1%)	167 (26.7%)	0.35
Ostial lesion	7 (12.3%)	22 (3.5%)	0.002
Chronic total occlusion	0 (0%)	37 (5.9%)	0.06
Moderate/severe calcification	45 (78.9%)	225 (36.0%)	<0.001
IVUS use	45 (78.9%)	483 (77.3%)	0.77
Rotablator use	13 (22.8%)	14 (2.2%)	<0.001
Maximum deployment pressure, atm	16.9±3.3	16.5±2.8	0.46
Pre-dilatation	42 (73.7%)	440 (70.4%)	0.60
Stent diameter, mm	3.02±0.38	3.00±0.37	0.79
Total stent length, mm	32.5±16.3	29.5±15.0	0.12
No. of stents/lesion	1.42±0.65	1.28±0.54	0.07
Post dilatation	24 (42.1%)	288 (46.1%)	0.56

LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; IVUS, intravascular ultrasound; RCA, right coronary artery. Other abbreviations as in Table 1.

Table 4. QCA Results at Baseline and 9-Month Follow-up of Patients Undergoing PCI With SES

Variable	HD group (n=57)	Non-HD group (n=625)	P value
Lesion length, mm	22.8±14.2	22.2±13.9	0.72
Reference vessel diameter, mm	2.90±0.76	2.70±0.60	0.18
Minimal lesion diameter, mm			
Before procedure	1.04±0.50	0.84±0.52	0.014
After procedure	2.73±0.64	2.64±0.53	0.35
At 9-month follow-up	2.04±0.94	2.45±0.71	0.002
Diameter stenosis, %			
Before procedure	64.5±14.6	69.5±17.8	0.08
After procedure	12.8±9.9	12.8±9.7	0.97
At 9-month follow-up	35.6±25.8	18.9±17.8	<0.001
Acute lumen gain, mm	1.69±0.60	1.80±0.66	0.26
Late lumen loss, mm	0.81±0.80	0.33±0.51	<0.001
Binary restenosis	11 (19.3%)	32 (5.1%)	<0.001

QCA, quantitative coronary angiography. Other abbreviations as in Table 1.

vation period (log-rank; P<0.001). After 1 year, the event rate per year was 4.6% in the HD group and 1.2% in the non-HD group. At 7 years, the survival rate was 65.3% in the HD group and 90.5% in the non-HD group. **Figure 1B** shows the Kaplan-Meier curves for TLR, which was significantly higher in the HD group (log-rank; P<0.001). After 1 year, the event rate per year was 4.1% in the HD group and 0.8% in the non-HD group. At 7 years, the TLR-free rate was 57.4% in the HD group and 89.8% in the non-HD group. **Figure 1C** shows the Kaplan-Meier curves for TVR, which was significantly higher in the HD group (log-rank; P<0.001). After 1 year, the event rate per year was 5.4% in the HD group and 1.9% in the non-HD group. At 7 years, the TLR-free rate was 42.4% in the HD group and 82.2% in the non-HD group. **Figure 1D** shows the frequency of MACE in the 2 groups. The occurrence of MACE was significantly higher in the HD group (log-rank;

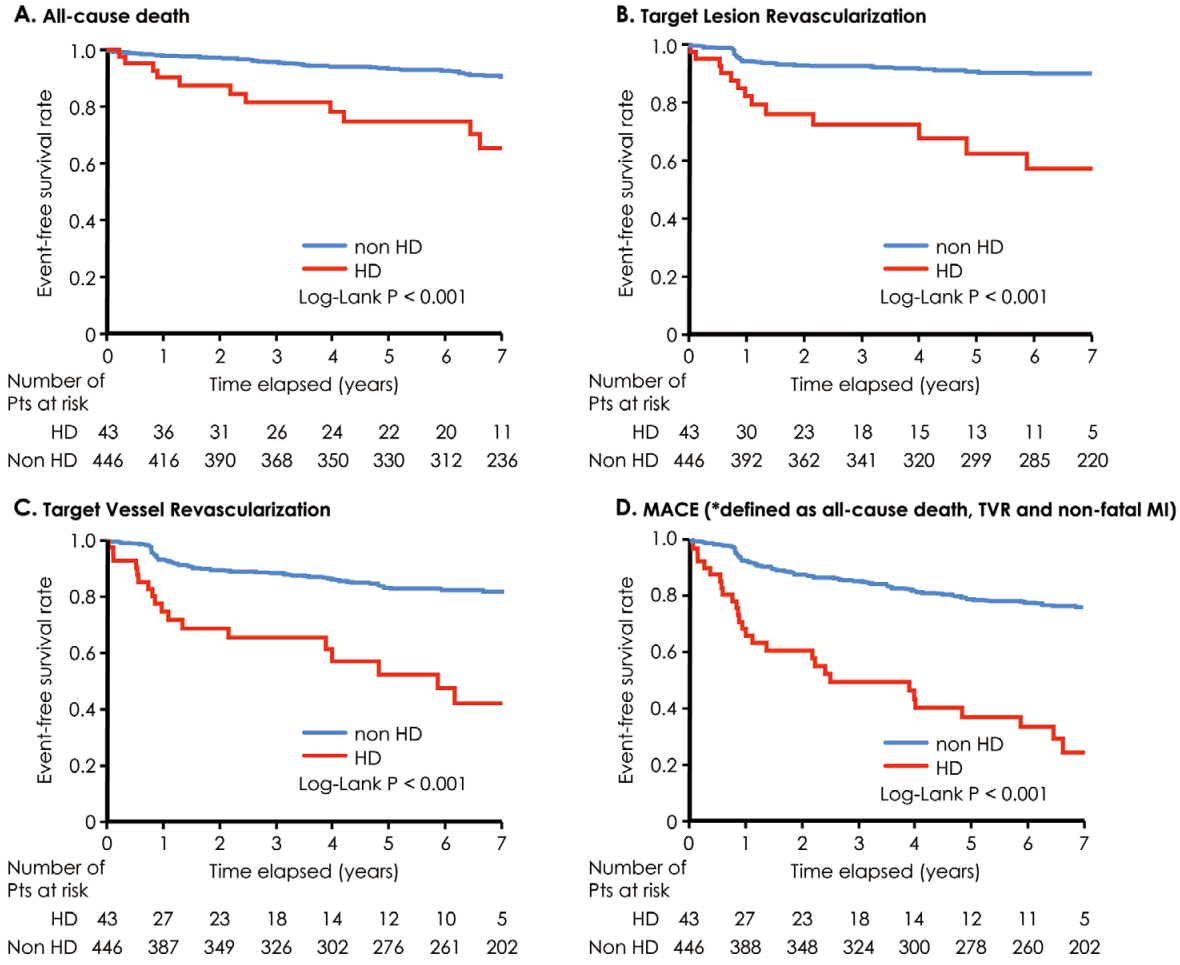

Figure 1. (A–D) Kaplan-Meier curves of clinical events. HD, hemodialysis; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization.

P<0.001). After 1 year, the event rate per year was 7.0% in the HD group and 2.8% in the non-HD group. At 7 years, the MACE-free rate was 24.7% in the HD group and 75.7% in the non-HD group. There were no significant trends in the number of events across lesion locations.

Causes of death in each group were shown in Table 5.

Table 5. Cause of Death in Patients Undergoing PCI With SES

	HD group (n=43)	Non-HD group (n=446)
Cardiac death	4 (9.3%)	13 (3.9%)
Heart failure	0 (0%)	7 (1.6%)
MI	1 (2.3%)	2 (0.4%)
Arrhythmia	2 (4.6%)	1 (0.7%)
Non-cardiac death	14 (32.6%)	28 (6.3%)
Fatal bleeding	3 (7.0%)	5 (1.1%)
Malignancy	0 (0%)	13 (2.9%)
Infection	5 (11.6%)	6 (1.3%)
Other	6 (14.0%)	4 (0.9%)

Abbreviations as in Table 1.

Dual Antiplatelet Therapy (DAPT) Discontinuation and Stent Thrombosis

DAPT was terminated within 1 year in 12.3% of HD patients and in 14.6% of non-HD patients and in up to 35.4% and 39.7%, respectively, at 7 years (Figure 2). In only 6 cases (1.2% of all patients; 1 HD patient vs. 5 non-HD patients=2.3% vs. 1.1%), definite/probable stent thrombosis was detected during the observation period; in the HD group, 1 early thrombosis appeared at 19 days after SES deployment, and in the non-HD group, 2 early (day 0 and 4) and 3 very late (day 1,035, 1,099, and 1,452) cases were detected. All 6 patients continued to receive DAPT at the time of stent thrombosis.

Predictors of Clinical Events

Cox-proportional hazard analysis revealed that independent predictors of all-cause death were HD, insulin-treated DM, HF and older age. Moreover, HD was an independent predictor of TLR and MACE. Insulin-treated DM was also an independent predictor of TLR (Table 6).

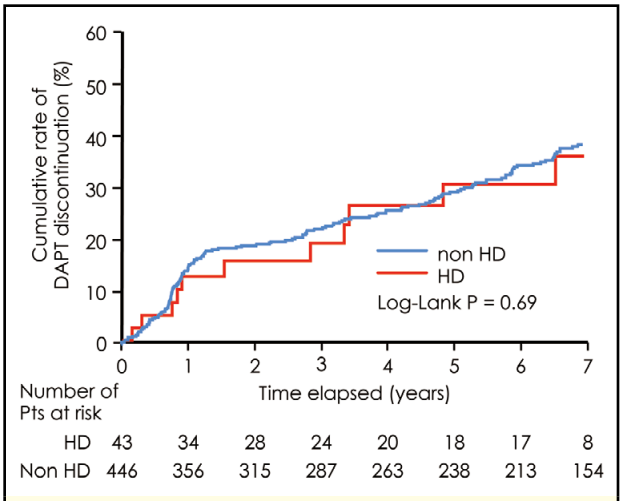

Figure 2. Cumulative rate of discontinuation of dual antiplatelet therapy (DAPT) after implantation of sirolimus-eluting stents up to the 7 years. HD, hemodialysis.

Table 6. Cox Multivariate Analysis of Independent Predictors of All-Cause Death, TLR and MACE in Patients Undergoing PCI With SES

	HR	95% CI	P value
All-cause death			
HD	2.88	1.39–6.00	0.01
Heart failure	2.58	1.25–5.32	0.01
Insulin-treated DM	2.19	1.17–4.11	0.02
Higher age (/1-age)	1.06	1.02–1.10	<0.001
TLR			
HD	3.63	1.89–7.11	<0.001
Insulin-treated DM	1.92	1.02–3.4	0.05
MACE			
HD	3.54	2.19–5.73	<0.001

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiac events; TLR, target lesion revascularization. Other abbreviations as in Table 1.

Discussion

This study is noteworthy given the long-term (7 years) follow-up of SES in HD patients in a real-world clinical setting. The main findings of the present study were: (1) HD patients with CAD and SES implantation had poorer long-term clinical outcomes than non-HD patients; (2) the independent predictors of all-cause death in patients treated with SES were HD, insulin-treated DM, and prior stroke; and (3) HD patients had a higher prevalence of severe comorbidities, such as insulin-treated DM, HF, and PAD than non-HD patients.

Clinical and Angiographic Characteristics

The present study showed, in agreement with previous reports, that HD patients had a higher prevalence of insulin-dependent DM and HF, both known to be negative prognostic factors, and PAD, indicating extensive atherosclerosis, compared with non-HD patients.[13,14] It is important to clarify the significance of the association of each risk factor with outcomes in HD patients, because most risk factors related to clinical outcomes are modifiable by medical interventions and lifestyle improvements.

Diabetes is one of the strongest risk factors for CAD, and CAD, indeed, is the leading cause of mortality in diabetic patients. Moreover, DM is the most common etiology of chronic kidney disease and renal replacement therapy.[15,16] Namely, the majority of HD patients also have DM, and the prognostic significance of DM in HD patients is serious. In addition, chronic kidney disease treated with maintenance HD is frequently accompanied by chronic HF. Researchers in the Czech Republic reported that the mortality for both diseases was high, and the incidence of HF was 97% with a 50% 3-year mortality.[17] One of the possible reasons for such a high mortality rate was that only a small proportion of HD patients with chronic HF received appropriate treatment.[18] Overall, the clinical profiles of HD patients are obviously worse than those of non-HD patients; therefore, intensive care should be considered for the former's prognostic outcomes.

In terms of angiographic findings, the HD group included more multivessel coronary stenoses, probably because of the higher prevalence of insulin-treated DM in HD patients.[19] Nakamura et al reported that HD and insulin-treated DM were strong independent predictors of mortality and TLR in DM patients at 3 years.[8] Our results of long-term clinical outcomes were consistent with those mid-term results. The HD group also included heavier calcified lesions than in the non-HD group. As in the previous papers, our results supported that the presence of heavy calcification is a strong factor of deterioration in PCI outcome.[9] Baseline minimal lesion diameter was larger in the HD group, suggesting that PCI in small vessels of HD patients may have been intentionally avoided because of procedural complexity and predictable poor long-term prognosis of target lesions. Nevertheless, the angiographic results at follow-up were exceedingly worse in the HD group, and possibly led to the poorer clinical outcomes observed in those patients.

Lipid Profiles and Inflammation

The present study showed that HD patients had lower values of HDL-cholesterol as well as LDL-cholesterol than did the non-HD patients, and fewer HD patients received statin treatment even at the end of their hospitalization. These findings were consistent with previous reports about poor prognosis in HD patients[20] that assumed one of the reasons for the higher event rate was lower rates of administration of statins with anti-inflammatory effects. HD patients showed higher CRP values on admission to hospital in the present study. Moreover, low HDL-cholesterol levels have been reported as predictive of negative clinical outcomes in patients achieving LDL-cholesterol targets with statins after PCI.[21] The therapeutic benefits of contemporary medical treatment with statins for the prognosis of HD patients has still not been elucidated and needs to be optimized in terms of patients' lipid control.

Long-Term Efficacy

Accumulated evidence has clarified that the risk of CAD in patients with maintenance HD appears to be far greater than in the general population, and CAD is the leading cause of death in patients with severe renal dysfunction. Previous studies demonstrated that stent implantation, compared with balloon angioplasty without stents, reduced the incidence of MACE in HD patients.[22] However, even in the BMS era, clinical outcomes after coronary intervention of patients with HD remained poor compared with the non-HD population.[23,24] The RAVEL study demonstrated the superiority of SES to BMS in selected patients, because of the safety and efficacy observed in long-

term clinical outcomes.[25] Nevertheless, several reports showed no differences in all-cause death, TLR and MACE rates between SES and BMS in HD patients and in our study, the incidence of both all-cause death and TLR at 1-year was similar to that in the previous reports.[26,27]

The 2-year follow-up outcomes of the largest randomized double-blinded SIRIUS trial showed that most TLRs were performed within 1 year after SES implantation.[7] Intimal proliferation occurring in the late phase after implantation of DES in an animal model was equivalent to that for a BMS over the long term, indicating a so-called late "catch-up" phenomenon.[28] In addition, the multicenter prospective J-Cypher registry compared HD and non-HD patients implanted with SES to assess the mid-term clinical outcomes at 3 years, claiming that HD appeared to be strongly associated, even more than DM, with mortality and TLR after SES implantation.[29]

To date, several studies have shown shorter-term clinical outcomes, compared with the 7-year follow-up of our study. In our study, a large number of clinical events were apparent within 1 year after SES implantation, as in previous studies. However, our long-term follow-up to 7 years newly revealed that late adverse events beyond the peri-procedural period continued to occur more frequently in HD patients without attenuation, compared with non-HD patients (events rate/year after 1 year; all-cause death: 4.6% vs. 1.2%; TLR, 4.1% vs. 0.8%; TVR: 5.4% vs. 1.9%; MACE: 7.0% vs. 2.8%, respectively), even though HD patients were administered more ACEI/ARB as cardioprotective medications than non-HD patients.

Stent Thrombosis

In the present study, 6 cases (1.2% of all patients; 1 HD patient vs. 5 non-HD patients=2.3% vs. 1.1%) of definite or probable stent thrombosis were observed. Similar to previous reports,[8,30,31] HD is thought to be a predictor of stent thrombosis.[32] One possible reason for this is resistance to thienopyridines and aspirin treatment in patients with HD. HD patients seem to have enhanced platelet activation after coronary stent implantation, even with DAPT, despite suppressed platelet aggregation. Several other multifactorial mechanisms may contribute to platelet reactivity in HD patients besides antiplatelet drugs, resulting in enhanced platelet activation.[33] In fact, all 6 patients continued to receive DAPT at the time of stent thrombosis.

Predictors of Adverse Events

The multivariate analysis revealed that HD, insulin-treated DM, HF and older age were independent predictors for all-cause death. These findings indicate that pathophysiological aspects such as renal dysfunction and insulin-treated DM may highly affect the efficacy of SES. Generally, the deteriorated long-term prognosis in HD patients may be attributable to high comorbid rates of DM, which is also considered as an independent predictor of prognosis.[26] From our long-term observation that HD was the most potent predictor for all-cause death, and the only independent predictor of TLR and MACE, it may be concluded that HD patients with SES implantation may be considered to be at extremely high risk for poor long-term prognosis. Because the cause of death in the HD patients varied, it is very difficult to identify a specific, desirable approach. Focusing on stent thrombosis and fatal bleeding, as well as the duration and regimen of antiplatelet therapy, should be considered on an individual basis and management of treatment adherence is thought to be a crucial issue.

Apart from the development of newer-generation DES, such as biolimus-, everolimus- and zotarolimus-eluting stents, SES have not been used recently in current clinical practice. Still, the results of this study will be helpful for future longer-term follow-up of patients who have existing implanted SES and will also be an essential foundation for evaluating the long-term effects of newer-generation DES.

Study Limitations

The limitations of the present study are that it was an observational cohort study in a single center and that the number of patients at risk in this study was small; there was a lack of definition of the procedural endpoint, for example, optimal stenting criteria which might affect the long-term outcome, especially in HD patients, who generally have complex morphological legions including heavy calcification. Additionally, in most cases, TLR was considered during ad-hoc interventional procedure; therefore, we determined TLR by visual assessment, rather than QCA analysis. Such routine angiographic follow-up could lead to oculo-stenotic reflex; however, the binary in-stent restenosis ratio evaluated by QCA was similar to the TLR ratio at 9-month follow-up on Kaplan-Meier analysis.

Conclusions

HD was an independent predictor of long-term adverse events after implantation of SES, a first-generation DES. HD patients had more complicated clinical backgrounds, which could be one of the reasons for their unfavorable long-term clinical outcomes. Examination of the effect of newer-generation DES on long-term outcomes in this high-risk population is warranted.

Disclosures

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Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier curves of (A) non-target vessel revascularizations, (B) any revascularizations and (C) major adverse cardiac events.

Please find supplementary file(s);
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