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Long-term cardiovascular prognosis after rotational atherectomy in hemodialysis patients: Data from the J2T multicenter registry

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ABSTRACT

Background: Hemodialysis (HD) patients have heavy calcium deposits in their stenotic coronary arteries and worse post-percutaneous coronary intervention (PCI) prognoses than those who do not undergo HD. Rotational atherectomy (RA) facilitates PCI success in severely calcified lesions. We aimed to identify clinical and procedural characteristics that predict HD patients' long-term prognoses after PCI that included RA in the drug-eluting stent (DES) era.

Methods: This study included 302 patients who underwent regular HD from J2T Multicenter Registry database of 1090 consecutive patients who underwent RA to treat de novo calcified lesions at three university hospitals between 2004 and 2015. The primary endpoint was cardiovascular (CV) death.

Results: During the 5-year observation period, 59 CV deaths (19.5%) occurred. The CV death group and non-CV death group had comparable profiles except significantly lower left ventricular ejection fraction, higher brain natriuretic peptide (BNP), lower rate of RA burr upsizing, and lower rate of final thrombolysis in myocardial infarction (TIMI) 3 flow achievement in the CV death group. Cox regression analysis revealed that increasing ablation burr size (hazard ratio [HR]: 0.33; 95% confidence interval [CI]: 0.13–0.81), final TIMI 3 flow (HR: 0.07; 95% CI: 0.02–0.28), lower BNP level, and optimal medication were independently associated with better CV mortality in HD patients.

Conclusion: In the DES era, oral medications at the time of PCI and stepwise calcium ablation were associated with improved long-term CV mortality in HD patients who are scheduled to undergo RA to treat severely calcified coronary artery stenoses, as therapeutic strategies.

1. Introduction

The presence of calcification in the coronary arteries is associated with adverse events in the general population and in patients with coronary artery disease (CAD) who are undergoing coronary revascularization [1–3]. Patients who undergo regular hemodialysis (HD) have heavy calcium deposits in their stenotic coronary arteries and have worse prognoses following percutaneous coronary intervention (PCI) compared with patients who do not undergo HD [4]. Technically, PCI within a heavily calcified coronary artery may lead to failures in device delivery, an increased risk of coronary dissection as a consequence of high-pressure balloon dilatation, or the insufficient expansion of the deployed stent [5].

Rotational atherectomy (RA) is an effective strategic option that facilitates the technical success of PCI in severely calcified lesions by ablating calcified plaques [6–8]. Although the findings from several studies have shown improved clinical outcomes in patients who underwent PCI that included RA followed by drug-eluting stent (DES) implantation, the adverse event rates remain high [9–14]. Furthermore, the findings from many studies have shown that HD is the strongest predictor of major adverse cardiovascular events (MACE) in patients with highly complex, severely calcified lesions that require RA, despite the use of a DES [14,15].

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Few studies, however, have examined the long-term clinical prognoses of HD patients who have undergone RA followed by PCI. Hence, the purpose of this study was to identify clinical and procedural characteristics that predict HD patients' long-term clinical prognoses following PCI that included RA in the DES era.

2. Methods

2.1. Study population and endpoints

This study was a subanalysis of data from the J2T ROTA registry that comprises data from a multicenter, retrospective, cohort study that involved 1090 patients who underwent RA for de novo calcified coronary lesions between 2004 and 2015. The development of the J2T ROTA registry complied with the ethical guidelines for epidemiological studies, and the relevant review boards of the three participating hospitals approved this study's protocol. The data were collected at each site using a standardized case report form that recorded the patients' demographic and clinical characteristics, and the procedural and follow-up data. The follow-up data were obtained at the time of registry enrollment, and were based on patients' medical records and on physician or patient interviews. The investigators had full access to the data and controlled their analyses. The study's inclusion and exclusion criteria, design, procedural details, and complete results have been published [16]. Of the patients who were enrolled in the registry, 302 patients who underwent regular HD (HD group) were compared with 788 patients who did not undergo HD (non-HD group) with respect to their baseline characteristics and long-term prognoses. The current study's primary endpoint was cardiovascular (CV) mortality after the index PCI. CV death included death caused by an acute myocardial infarction, arrhythmias, heart failure, stroke, CV procedures, CV hemorrhages, and other CV causes, and sudden cardiac death. The current study's composite secondary endpoint was MACE that included any death, acute coronary syndrome (ACS), stent thrombosis, target vessel revascularization (TVR), and stroke. In this study, the endpoints were analyzed on a per-patient basis. At the next step, we compared baseline clinical, angiographic, and procedural profiles, and long-term prognoses between patients who achieved the primary endpoint during the observation period and those who did not.

2.2. Statistical analyses

The data are expressed as the means and the standard deviations, percentages and numbers, and as the medians and the interquartile ranges in the tables, and as the means and the standard errors of the means in the figures.

The independent Student's *t*-test and the non-parametric equivalent Mann-Whitney-*U* test were used to compare the two groups, and the analysis of variance and Kruskal-Wallis test were used to compare among the ≥3 groups with respect to the continuous variables, and the chi-squared test and Fischer's exact test were used to compare the groups with respect to the categorical variables, as appropriate. Kaplan-Meier plots were constructed to determine the cumulative incidence of clinical events from the index procedure, and the differences between the two groups were assessed using the log-rank test, and the difference among ≥3 groups were assessed using the log-rank trend test. Univariate Cox hazard regression analyses were performed, and variables that reached a level of significance of $p < 0.10$ and were considered clinically significant were included in the multivariable model. Multivariable Cox hazard regression analysis was performed to exclude the confounding factors and identify independent risk factors for CV death in the HD patients. Age, body mass index (BMI), diabetes, left ventricular ejection fraction (LVEF), multivessel disease, the log brain natriuretic peptide (BNP) levels, C-reactive protein (CRP) levels, the administration of aspirin, β-blockers, and calcium-channel blockers (CCB) at discharge, a long stent use that was defined as a total stent length ≥ 23 mm, an RA burr that was upsized, and a final thrombolysis in myocardial infarction (TIMI) 3 flow were used to adjust the multivariable model. To clarify potential modification effects between variables, product terms were entered in the model to confirm such interactions. Additionally, to evaluate the contribution of the optimal medical therapy (OMT) that was defined as the combination of at least one anti-platelet drug, one statin, one β-blocker, and one ACEi/ARB on CV death, another model of multivariate Cox hazard regression analysis was performed using the numbers of OMT as a covariant, instead of the administration of aspirin and β-blockers. A scoring system for predicting CV death was developed using the independent predictive factors' coefficients. The enhanced discriminatory abilities of the risk scores were evaluated by comparing the areas under the receiver operating characteristic (ROC) curves (AUROC) that involved using binary values in two prediction models for CV death using the method developed by DeLong et al. [17] A two-sided p-value <0.05 was considered statistically significant. The statistical analyses were performed using R software, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients' baseline clinical characteristics, angiographic findings, and procedural parameters

3.1.1. HD patients versus non-HD patients

Compared with those in the non-HD group, the patients in the HD group were significantly younger, had lower BMIs and LVEFs, and their rates of diabetes, hypertension, atrial fibrillation, and coronary artery bypass grafting (CABG) were higher (Supplemental Table 1). Patients in the HD group had significantly lower low-density lipoprotein-cholesterol (LDL-C) levels, higher CRP levels and lower hemoglobin levels compared with those in the non-HD group. Regarding the medications prescribed at discharge, the patients in the HD group were more likely to receive cilostazol and less likely to receive angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB) than the patients in the non-HD group.

The HD group contained fewer patients with multivessel disease, and their right coronary arteries were more frequently treated, and contained fewer patients who had small or long stents deployed compared with those in the non-HD group (Supplemental Table 1). Systems with larger specifications were selected for the patients in the HD group because of limitations associated with blood access. The groups were comparable regarding the maximum RA burr size used but upsizing the RA burr occurred significantly more frequently in the HD group compared with that in the Non-HD group (41% vs. 31%, $p = 0.001$). Among the first-generation DESs implanted, paclitaxel-eluting stents (PES) were used more frequently than sirolimus-eluting stents (SES) in the HD group. The final TIMI 3 flow was comparable, at 96% in both groups.

3.1.2. CV death versus non-CV death in HD patients

During the 5-year observation period, 59 CV deaths (19.5%) occurred. The CV death group ($n = 59$) and non-CV death group ($n = 243$) had comparable profiles except significantly lower LVEFs, higher BNP, lower rate of RA burr upsizing, and lower rate of final TIMI 3 flow achievement in the CV death group (Table 1). In terms of implanted stents, patients in both groups were implanted with stents that were comparable in diameters and lengths; however, the CV death group showed significantly higher rate of PES use and relatively lower rate of SES.

3.2. In-hospital and long-term outcomes

Supplemental Table 2 shows the patients' in-hospital outcomes. During hospitalization, there were comparable rates of adverse events that included death, myocardial infarction, cardiac tamponade, major bleeding, intra-aortic balloon pumping or percutaneous cardiopulmonary support, and emergency surgery in the HD and non-HD groups.

During the 5-year period after the PCIs, 118 CV deaths occurred, comprising 59 deaths (19.5%) in the HD group and 59 deaths (7.5%) in the non-HD group (Supplemental Table 2). The Kaplan-Meier curves show continuous increases in the CV death rates in both groups throughout the observation period (Fig. 1). The event rates per year were 5.0% in the HD group and 2.0% in the Non-HD group. The HD group had a significantly higher CV mortality rate than that in the non-HD group (log-rank test: $p < 0.001$; hazard ratio [HR]: 4.66; 95% confidence interval [CI]: 3.03–7.18).

The rates of MACE (66.9% vs. 37.2%, $p < 0.001$), including any death (40.4% vs. 17.9%, $p < 0.001$), TVR (32.1% vs. 17.3%, $p < 0.001$), and stroke (7.0% vs. 3.8%, $p = 0.036$) were significantly higher in the HD group compared the non-HD group (Supplemental Table 1). The rates of ACS (7.9% vs. 6.4%, $p = 0.35$) and stent thrombosis (2.3% vs. 0.9%, $p = 0.07$) did not differ significantly between the HD and non-HD groups. The results from the log-rank tests that followed the Kaplan-Meier analyses were consistent with the aforementioned data (Supplemental Fig. 1).

3.3. Predictors of CV death in HD patients

The variables that had p values <0.10 according to the univariate Cox analyses of CV death were age, BMI, diabetes, LVEF, multivessel disease, the log BNP level, CRP level, the prescription of aspirin, β-blockers, and CCBs at discharge, a long stent use, RA burr upsizing, and a final TIMI 3 flow (Table 2). The multivariable Cox hazard analysis determined that the log BNP level (HR: 2.33; 95% CI: 1.23–4.41), the use of aspirin (HR:

Table 1
Patients' Clinical Profiles and Angiographic Parameters.

Variables	All HD	CV death (+)	CV death (-)	p value
	n = 302	n = 59	n = 243	
Age, mean ± SD, years	65.0 ± 10.1	66.4 ± 9.2	64.7 ± 10.3	0.42
Male, n (%)	245 (81%)	47 (80%)	198 (81%)	0.72
BMI, mean ± SD, kg/m^2	22.6 ± 3.7	22.0 ± 3.6	22.7 ± 3.7	0.15
Diabetes, n (%)	200 (66%)	44 (75%)	156 (64%)	0.17
Insulin use, n (%)	92 (30%)	18 (31%)	74 (30%)	> 0.99
Hypertension, n (%)	264 (87%)	52 (88%)	212 (87%)	> 0.99
Dyslipidemia, n (%)	169 (56%)	28 (47%)	141 (58%)	0.15
Current smoker n (%)	68 (23%)	10 (17%)	58 (24%)	0.30
Family history of CAD, n (%)	54 (18%)	11 (19%)	43 (18%)	0.85
ACS presentation, n (%)	55 (18%)	12 (20%)	43 (18%)	0.71
Prior MI, n (%)	74 (25%)	17 (29%)	57 (23%)	0.40
Prior PCI, n (%)	100 (33%)	19 (32%)	81 (33%)	> 0.99
Prior CABG, n (%)	53 (18%)	12 (20%)	41 (17%)	0.57
Atrial fibrillation, n (%)	64 (21%)	13 (22%)	51 (21%)	0.86
LVEF, mean ± SD, %	48.2 ± 13.5	43.6 ± 14.2	49.4 ± 13.2	0.004
Low LVEF (<40%), n (%)	84 (28%)	26 (44%)	58 (24%)	0.006
Laboratory data				
Hemoglobin, mean ± SD, g/dL	10.8 ± 1.5	10.7 ± 1.6	10.8 ± 1.4	0.76
Total cholesterol, mean ± SD, mg/dL	161.7 ± 37.9	163.5 ± 45.7	161.3 ± 36.1	0.99
Triglycerides, mean ± SD, mg/dL	129.4 ± 90.9	103.7 ± 54.9	135.3 ± 96.4	0.009
HDL-C, mean ± SD, mg/dL	47.1 ± 17.6	49.4 ± 19.5	46.5 ± 17.1	0.52
LDL-C, mean ± SD, mg/dL	91.6 ± 33.3	96.7 ± 35.2	90.3 ± 32.8	0.20
HbA1c, mean ± SD, %	6.07 ± 0.96	6.08 ± 0.94	6.07 ± 0.97	0.92
CRP, mean ± SD, mg/dL	1.10 ± 2.32	1.49 ± 3.01	1.00 ± 2.10	0.18
BNP, mean ± SD, pg/mL	1,006 ± 1,362	1,476 ± 1,664	887 ± 1,254	0.006
Medical therapy at discharge				
Aspirin, n (%)	284 (94%)	52 (88%)	232 (95%)	0.06
Thienopyridines, n (%)	274 (91%)	54 (92%)	220 (91%)	> 0.99
DAPT, n (%)	259 (86%)	48 (81%)	211 (87%)	0.30
Cilostazol, n (%)	32 (11%)	7 (12%)	25 (10%)	0.81
Statins, n (%)	122 (40%)	22 (37%)	100 (41%)	0.66
ACEi/ARB, n (%)	171 (57%)	30 (51%)	141 (58%)	0.31
β-blocker, n (%)	146 (48%)	23 (39%)	123 (51%)	0.11
OMT, kinds	2.44 ± 0.96	2.25 ± 1.06	2.49 ± 0.93	0.10
Calcium-channel blocker, n (%)	143 (47%)	22 (37%)	121 (50%)	0.08
Nitrates/nicorandil, n (%)	136 (45%)	30 (51%)	106 (44%)	0.38
Target vessel				
LAD, n (%)	176 (58%)	33 (56%)	143 (59%)	
Circumflex, n (%)	43 (14%)	12 (20%)	31 (13%)	
RCA, n (%)	83 (27%)	14 (24%)	69 (28%)	0.32
LMT, n (%)	27 (9%)	5 (8%)	22 (9%)	> 0.99
Multivessel disease, n (%)	204 (68%)	46 (78%)	158 (65%)	0.06
Chronic total occlusion, n (%)	15 (5%)	0	15 (6%)	-
Stent diameter, mm	3.01 ± 0.43	2.94 ± 0.41	3.03 ± 0.43	0.17
Small diameter stent use[a], n (%)	47 (16%)	12 (20%)	35 (14%)	0.31
Stent length, mm	36.7 ± 18.6	36.6 ± 18.0	36.8 ± 18.8	0.97
Long stent use[b], n (%)	208 (69%)	45 (76%)	163 (67%)	0.20
Guiding catheter size, mean ± SD, Fr.	6.81 ± 0.60	6.78 ± 0.59	6.81 ± 0.60	0.68
6 Fr, n (%)	88 (29%)	18 (31%)	70(29%)	
7 Fr, n (%)	181 (60%)	35 (59%)	146 (60%)	
8 Fr, n (%)	30 (10%)	5 (8%)	25 (10%)	0.93
First burr size, mean ± SD, mm	1.54 ± 0.19	1.57 ± 0.17	1.53 ± 0.19	0.12
1.25 mm, n (%)	49 (16%)	5 (8%)	44 (18%)	
1.5 mm, n (%)	171 (57%)	35 (59%)	136 (56%)	
1.75 mm, n (%)	66 (22%)	16 (27%)	50 (21%)	
2.0 mm, n (%)	15 (5%)	3 (5%)	12 (5%)	
2.15 mm, n (%)	1 (0.3%)	0	1 (0.4%)	
2.25 mm, n (%)	0	0	0	0.41
Max. burr size, mean ± SD, mm	1.68 ± 0.23	1.66 ± 0.22	1.69 ± 0.24	0.38
1.25 mm, n (%)	18 (6%)	2 (3%)	16 (7%)	
1.5 mm, n (%)	119 (39%)	29 (49%)	91 (37%)	
1.75 mm, n (%)	97 (32%)	17 (29%)	80 (33%)	
2.0 mm, n (%)	54 (18%)	9 (15%)	46 (19%)	
2.15 mm, n (%)	9 (3%)	1 (2%)	8 (3%)	
2.25 mm, n (%)	3 (1%)	1 (2%)	2 (1%)	0.64
RA burr upsizing, n (%)	124 (41%)	17 (29%)	107 (44%)	0.04
Scoring balloon after RA, n (%)	27 (9%)	1 (2%)	26 (11%)	0.04
Stent type				
Bare-metal stent, n (%)	33 (11%)	10 (17%)	23 (9%)	0.11
1st-generation DES, n (%)	152 (50%)	32 (54%)	120 (49%)	0.56
SES, n (%)	71 (24%)	8 (14%)	63 (26%)	0.06
PES, n (%)	83 (27%)	24 (41%)	59 (24%)	0.01
2nd-generation DES, n (%)	103 (34%)	15 (25%)	88 (36%)	0.13
Co-Cr EES, n (%)	70 (23%)	12 (20%)	58 (24%)	0.61

Table 1 (*continued*)

Variables	All HD	CV death (+)	CV death (-)	p value
	n = 302	n = 59	n = 243	
Pt-Cr EES, n (%)	25 (8%)	4 (7%)	21 (9%)	0.80
Final TIMI 3 flow, n (%)	290 (96%)	52 (88%)	238 (98%)	0.003

ACEi = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; CAD = coronary artery disease; Co-Cr = cobalt-chromium; CRP = C-reactive protein; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stent; HD = hemodialysis; HDL-C = high-density lipoprotein-cholesterol; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LDL-C = low-density lipoprotein-cholesterol; LMT = left main trunk; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; Pt-Cr = platinum-chromium; RA = rotational atherectomy; RCA = right coronary artery; SD = standard deviation; SES = sirolimus-eluting stent; TIMI = thrombolysis in myocardial infarction.

[a] **Deployed stent diameter <2.5 mm.**

[b] **Total length of deployed stent >23 mm.**

0.24; 95% CI: 0.08–0.72), β-blockers (HR: 0.31; 95% CI: 0.13–0.70), and CCBs (HR: 0.23; 95% CI: 0.10–0.55), an RA burr upsizing (HR: 0.33; 95% CI: 0.13–0.81), and a final TIMI 3 flow (HR: 0.07; 95% CI: 0.02–0.28) were independently associated with CV death. Additionally, the numbers of OMT was independently associated with CV death (1-drug increase; HR: 0.64; 95% CI: 0.43–0.96), even after the adjustment of age, BMI, diabetes, LVEF, multivessel disease, the log BNP level, CRP level, and CCBs at discharge, a long stent use, RA burr upsizing, and a final TIMI 3 flow (Supplemental Table 3). From the viewpoint of slow flow/no-reflow phenomenon in the clinical settings, a modification effect between RA burr upsizing and achieving final TIMI 3 flow was also examined, and there was no significant interaction between them (P for interaction = 0.706).

The six variables from the multivariate model were weighted equally for CV mortality, and four risk strata were defined as follows: low risk with a score of 0–1; mild risk with a score of 2; moderate risk with a score of 3, and high risk with a score ≥ 4. The distribution of the risk scores for CV mortality within HD patients peaked at a score of 2 points (Supplemental Fig. 2A). The ROC analysis determined a BNP cutoff value of 380 pg/mL. The patients with the higher risk scores were significantly older, and had lower BMIs, lower LVEFs, and higher CRP levels at baseline (Supplemental Table 4). The diverse comorbidities were evenly distributed among the four subgroups. Positive correlations existed between CV mortality and the risk scores ($p < 0.001$) (Supplemental Fig. 2B). A risk score of ≥3 had a sensitivity of 72.0% and a specificity of 61.0% for predicting CV mortality (Supplemental Fig. 2C). The Kaplan-Meier analysis validated this risk stratification (log-rank test for trend: $p < 0.001$) (Fig. 2).

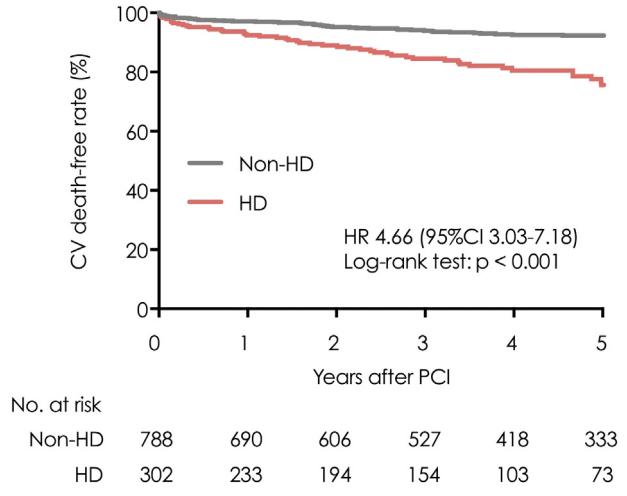

Fig. 1. Cardiovascular (CV) Mortality in the Patients Who Did and Did Not Undergo Hemodialysis (HD). Comparisons of CV mortality after percutaneous coronary intervention between the HD patients and the non-HD patients. CV = cardiovascular; CI = confidence interval; HD = hemodialysis; HR = hazard ratio; PCI = percutaneous coronary intervention.

3.4. RA burr size selection

Based on the results of Cox hazard analysis that the RA burr upsizing strategy was an independent predictor for CV mortality, to focus on the RA burr size selection, we compared baseline profiles and long-term prognoses between patients who received step-by-step upsizing burr strategy and those who received single burr strategy. The two groups had comparable clinical profiles. Interestingly, the step-up burr group had a significantly smaller size of 'initial' RA burr and a significantly larger size of 'final' RA burr, when compared to the single burr group (both $p < 0.001$) (Supplemental Table 5). The Kaplan-Meier curves show the lower tendency of CV mortality rate in the step-up burr group than that in the single burr group (log-rank test: p = 0.07; HR: 1.66; 95% CI: 0.98–2.79). Additionally, in the overall population, maximum RA burr size did not affect the achievement of final TIMI 3 flow (p = 0.65) (Supplemental Fig. 5).

3.5. Effect of treatment period

To understand the effect of the treatment period on the strategies of PCI with RA, HD patients were divided into two groups; the first DES generation (2004–2009; *n* = 157) and the second DES generation (2010–2015; *n* = 145). The 2004–2009 group had a significantly higher BNP level and LDL-C value; however, the administration rates of OMT after PCI were comparable except aspirin prescription (97% vs. 91%, p =

Table 2
Univariate and multivariate analyses of cardiovascular death in the hemodialysis patients.

Variables	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.04	1.01–1.07	0.005			
Male	0.78	0.41–1.47	0.45			
BMI	0.93	0.86–1.01	0.07			
Diabetes	1.70	0.94–3.05	0.08			
LVEF	0.97	0.95–0.99	0.002			
Multivessel disease	2.16	1.15–4.07	0.017			
log BNP	2.77	1.56–4.94	<0.001	2.33	1.23–4.41	0.009
CRP	1.14	1.04–1.25	0.006			
Aspirin	0.41	0.19–0.92	0.029	0.24	0.08–0.72	0.010
Statin	0.74	0.44–1.26	0.27			
ACEi or ARB	0.65	0.39–1.09	0.102			
β-Blocker	0.55	0.33–0.93	0.026	0.31	0.13–0.70	0.005
Calcium-channel blocker	0.53	0.31–0.90	0.019	0.23	0.10–0.55	<0.001
Long stent use	1.78	0.95–3.32	0.07			
Small diameter stent use	1.50	0.79–2.84	0.21			
RA burr maximum size	0.63	0.21–1.90	0.41			
RA burr upsize	0.61	0.35–1.08	0.09	0.33	0.13–0.81	0.016
Final TIMI 3	0.16	0.07–0.35	<0.001	0.07	0.02–0.28	<0.001

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CRP = C-reactive protein; LVEF = left ventricular ejection fraction; RA = rotational atherectomy; TIMI = thrombolysis in myocardial infarction.

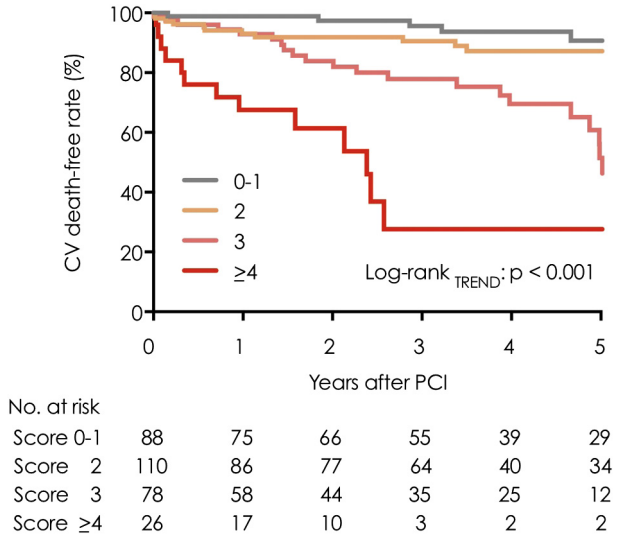

Fig. 2. Cardiovascular (CV) Mortality in the Hemodialysis (HD) Patients Categorized According to the Risk Score. The risk scores for CV death consisted of rotational atherectomy burr upsizing, a final thrombolysis in myocardial infarction 3 flow, the brain natriuretic peptide level, and optimal medication among the HD patients. Visualization of the time-to-event analysis was achieved using Kaplan-Meier estimates of CV mortality after percutaneous coronary intervention. The differences among the patients who had been categorized according to their risk scores were assessed using log-rank tests. The patients with higher risk scores had the greatest CV mortality during the observational period ($p < 0.001$). CV = cardiovascular; PCI = percutaneous coronary intervention.

0.023) between the groups (Supplemental Table 6). Regarding angiographic findings, the 2010–2015 group received RA with significantly smaller burrs followed with the implantation of significantly smaller or longer stents. As a result, the 2010–2015 group showed a significantly higher CV mortality than the 2004–2009 group (Log-rank test: $p = 0.007$; HR: 1.90; 95% CI: 1.12–3.25) (Supplemental Fig. 4).

4. Discussion

The principal findings from this study are that long-term CV mortality was worse in patients who underwent regular HD compared with those who did not undergo HD, and in the HD group, an increase in the RA burr size, a final TIMI 3 flow, the BNP level, and the prescription of aspirin, β-blockers, and CCBs were independent predictors of CV death. The present study's data are derived from a study that included one of the largest sets of observational data and the longest follow-up period, and to the best of our knowledge, this is the first study to investigate long-term mortality and its contributory factors in a substantially sized sample of patients who underwent regular HD and PCI that involved RA. If a technical modification of the existing device in addition to OMT and CCBs could improve their prognoses, the outlook for these high-risk patients would be better.

4.1. Profiles of the HD and Non-HD patients

While the HD patients were over 15 years younger than those who did not undergo HD, all of the HD group's clinical characteristics, except the lipid profiles, were worse than those in the non-HD group. Regarding the laboratory data, low hemoglobin and high BNP levels were noteworthy characteristics of the HD patients. The impaired renal function and improved lipid profiles in the patients who underwent regular HD may have been associated with the lower prescription rates for ACEi/ARBs and statins, respectively. In addition to atherosclerosis, ectopic calcification is a major cause of coronary artery narrowing in HD patients [18,19]. It is possible that the calcified stenoses were more evenly distributed among the three vessels within the HD group.

4.2. Prognoses

Several studies' findings have shown higher rates of complications in association with the use of atherectomy devices during PCI [20–22]. Regarding the safety of RA, PCI with RA was associated with low and similar periprocedural complication rates in both patient groups in the current study, which indicates that the present practice of undertaking PCI with RA has matured technically to some extent. On the contrary, we showed that after PCI that involved RA, the long-term CV prognosis for the HD patients was worse than that for the patients who did not undergo HD. Therefore, long-term prognoses should be considered at the time of the procedure.

The results from the original study of the J2T registry data showed that age, HD, diabetes, multivessel disease, a low LVEF, CRP, and the administration of statins were related to CV mortality [16]. These factors are frequently associated with mortality, and the current study's results are consistent with those from previous studies [9,14,16,23,24]. However, the predictors of CV death in the HD patients were largely different from those in the whole population. Rather than the commonly reported risk factors, unusual factors, including a final TIMI 3 flow and an RA burr upsizing, remained significant after the multivariate analysis, which may have been associated with the extremely high risk of CV mortality in the HD patients.

Although the HD patients' prognoses were worse than those for the non-HD patients, there was a subpopulation of HD patients that had a lower risk of CV death. The results from the multivariate analysis determined there were six independent predictors of CV death, and if an HD patient had ≤2 risk factors at the time of the PCI, their long-term prognosis was comparable with that for a patient in the non-HD population. On the contrary, mortality began to increase at one year after PCI with RA in the HD patients who had risk scores of 3, and the survival rate declined at a very early stage after PCI with RA in the HD patients who had risk scores of ≥4.

4.3. Medications

Evidence is accumulating that supports recommending OMT as an initial treatment strategy for all patients with CAD [25,26]. Nevertheless, patients whose symptoms persist, despite the administration of OMT or those with angiographically significant CAD, undergo PCI or CABG [27–29]. Since atherosclerosis progresses even after revascularization [30,31], patients should continue OMT after revascularization [32–34]. The findings from this study are consistent with those from prior studies regarding the long-term outcomes for patients administered OMT [32–34]. Notably, however, statins did not affect the primary endpoint in the HD patients in this study.

Statins reduce the CV event and mortality rates in patients with CAD and in those at a high risk of CV disease [35,36]. However, in the current study, statin treatment did not predict CV mortality after PCI that involved RA in the HD patients, despite it doing so in the population overall. The results from a large-scale registry study are consistent with those from the current study [37], which suggest that HD patients may be refractory to treatment with lipid-lowering therapy. Since the LDL-C levels were lower in the HD patients compared with the non-HD population at the time of PCI, there seemed to be little scope for improving the HD patients' clinical prognoses by administering lipid-lowering therapy. On the contrary, only 40% of this patient population that was at a very high risk of atherosclerosis was prescribed statins. Such low statin prescription rates may have been associated with the higher CRP levels at the time of PCI, which may have led to the poorer clinical prognoses after RA in the HD group. Moreover, preexisting conditions that prevent the administration of OMT including antiplatelets and β-blockers, or CCBs worsen the prognosis, but if there is no specific reason to the contrary, we should consider prescribing OMT, even if

complete revascularization is achieved. In particular, we should reassess whether OMT was administered to the patients with risk scores ≥3.

4.4. RA burr upsizing

Initial atherectomy with a large RA burr may generate large amounts of debris from the ablated calcified plaque, which often results in the slow-flow phenomenon through a distal artery embolism [38]. The use of intravascular ultrasound to determine the appropriate size of the RA burr and increasing the burr size should be considered, if possible. Thus, a phased ablation approach could reduce the amount of debris generated per burr stroke and lower the chance of a distal artery embolism. The finding that increasing the RA burr size was independently associated with better CV mortality suggested that the sufficient ablation of a calcified plaque was required for a good outcome. Additionally, given that a final TIMI 3 blood flow was a predictor of CV death and that the maximum burr size was unrelated to the primary endpoint, an appropriate and phased size selection of the RA burr may be warranted to avoid impaired coronary blood flow at the end of the session and to improve the clinical outcomes in this very high-risk population. Patients in the step-up burr strategy group had significantly smaller initial burr size and also larger final burr size than the single burr strategy group, suggesting that operators may have planned to increase burr size step by step. The step-up burr strategy group finally achieved successful RA by significantly larger burr size; while the rates of final TIMI 3 flow were comparable between the groups. Additionally, Cox multivariate analysis in HD patients showed that maximum burr size did not matter with regard to long-term CV mortality, and also the step-up burr strategy affected the prognosis, independent of the achievement of final TIMI 3 flow. Collectively, starting RA with smaller burr size and upsizing with care may lead to sufficient calcium ablation without increases in no-reflow phenomenon. However, this retrospective analysis only reported the numbers of used RA burrs, regardless of whether the changes in the RA burr sizes were scheduled or unintended. Therefore, a prospective study with a large number of patients that compares step-up atherectomies and single atherectomies with a large RA burr is warranted to validate this study's findings.

4.5. Study limitations

The current study's results should be interpreted in the context of its limitations. First, this study was a retrospective and observational analysis of data from a registry with a limited sample size. The findings from quantitative coronary angiography were not available for this study; hence, it is difficult to determine the contributions of a target lesion's diameter and length to the endpoint. The analysis of the angiographic findings did not involve a core laboratory, and the indications for RA, PCI, or clinical follow-up depended on the established daily practices at each hospital. The routine angiography follow-up rates, namely, 63.9% of the HD patients and 74.6% of the non-HD patients ($p < 0.001$), could have introduced bias in relation to the TVR rates. When the first RA burr caused slow flow/no-reflow phenomenon, the operator may have not performed the subsequent upsizing of RA burr. This is another limitation for concluding the association between the stepwise ablation and the prognosis. Medication should have been changed during the 5-year observation time. However, we only analyzed medication regimen at the time of PCI. Glycoalbumin was not recorded to evaluate the status of diabetes in this registry. Glycohemoglobin as an alternative is reported to be underestimated in HD patients. However, neither of glycohemoglobin or hemoglobin levels affected the results. Finally, almost 10% of the enrolled patients had undergone bare-metal stent implantations in this study, even in the DES era, and newly released small size DES revealed more aggressive PCI with RA to small vessels and resulted in the poorer prognosis in the latter phase of the entry period. However, the multivariate analysis determined that the stent type or its size did not affect the results.

5. Conclusion

In the DES era, oral medications at discharge, a better neurohormonal status, an achievement of good coronary blood flow, and a sufficient stepwise ablation of calcium were associated with better long-term CV mortality in HD patients who are scheduled to undergo RA to treat severely calcified coronary artery stenoses.

Clinical perspectives

HD patients frequently have heavily calcified coronary stenoses and poorer post-PCI prognoses than non-HD patients. Although PCI with RA is a promising option for achieving technical success in severely calcified lesions, few studies have investigated the long-term clinical prognoses for HD patients after PCI with RA. The long-term CV mortality was higher in the HD patients than in the non-HD patients, and increasing the RA burr size, a final TIMI 3 flow, the BNP level, and the prescription of aspirin, β-blockers, and CCBs were independent predictors of CV death in the HD patients. There was a positive correlation between CV mortality and risk scores. Prospective, large-scale studies that compare step-up atherectomy and single atherectomy with a large RA burr are warranted to validate this study's findings.

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Study registration

The study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) with the identifier UMIN000030517.

https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034833.

Conflict of interest statement

Juntendo University School of Medicine (Dr. Okai, Dr. Dohi, Dr. Okazaki, Dr. Tamura, Dr. Miyauchi, and Dr. Daida) and Teikyo University School of Medicine (Dr. Nakashima, Dr. Okabe, Dr. Nagura, Dr. Nara, Dr. Kawashima, Dr. Kyono, and Dr. Kozuma) received institutional research funds from Boston Scientific Japan. Dr. Kyono and Dr. Kozuma have received modest honoraria for lecture from Boston Scientific Japan. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.022.

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