Circulation Reports
Circ Rep 2021; 3: 699–706
doi:10.1253/circrep.CR-21-0129

ORIGINAL ARTICLE
Cardiovascular Intervention

Effects of Patient Background and Treatment Strategy on Clinical Outcomes After Coronary Intervention for Calcified Nodule Lesions

Masatsugu Nozoe, MD, PhD; Shinki Nishioka; Keiji Oi, MD, PhD;
Nobuhiro Suematsu, MD, PhD; Toru Kubota, MD, PhD

Background: The presence of a calcified nodule (CN) is associated with unfavorable clinical outcomes after percutaneous coronary intervention (PCI). This study clarified the optimal management of CNs by reassessing the PCI strategy in association with patient background characteristics and clinical outcomes.

Methods and Results: Among 5,332 consecutive PCI cases managed using intra-coronary imaging, CNs were found in 167 lesions (3.1%). CNs were predominantly located at the proximal or mid-right coronary artery (RCA; 62%). More than half presented clinically as acute coronary syndrome (ACS; 56%). All-cause mortality and the target lesion revascularization (TLR) rate at 1 year were 13% and 23%, respectively. Multivariate analysis revealed that hemodialysis, diabetes, and ACS were independent risk factors for all-cause death, whereas hemodialysis and RCA location were independent risk factors for TLR. Regarding the PCI strategy, not using rotational atherectomy (RA) was significantly associated with restenosis, whereas placing a drug-eluting stent (DES) was not.

Conclusions: Both hemodialysis and RCA location were strong predictors of poor outcomes after PCI for CN. Because not using RA was significantly associated with restenosis, it may be better to use RA whenever possible.

Key Words: Calcified nodule; Hemodialysis; Percutaneous coronary intervention; Right coronary artery; Rotational atherectomy

Plaque rupture, plaque erosion, and calcified nodules (CNs) are the 3 major mechanisms underlying acute coronary syndrome (ACS).[1,2] CNs are pathologically defined as lesions with fibrous cap disruption and luminal thrombus associated with eruptive, dense, calcific nodules, and are considered to be the least frequent cause of ACS compared with plaque rupture and plaque erosion.[1] However, whether CNs are a unique morphology for ACS is unclear. Indeed, a study with intravascular ultrasound (IVUS) demonstrated that CNs were actually not rare, being frequently observed in non-culprit vessels of patients with ACS at rates of 17% per artery and 30% per patient.[3] Furthermore, a study with optical coherence tomography (OCT) demonstrated CNs in 4.2% of all lesions regardless of ACS, with the presence of CNs associated with severe calcification and large hinge movement of the coronary artery.[4]

Percutaneous coronary intervention (PCI) for CNs remains challenging, even in the contemporary drug-eluting stent (DES) era.[5,6] Kobayashi et al reported that the clinical outcomes of ACS with CNs were poor, with a higher incidence of target lesion revascularization (TLR) than in cases of plaque rupture or plaque erosion (27.1% vs. 10.7% and 5.2%, respectively).[7] Morofuji et al reported that the TLR rate was higher in the CN than non-CN group (23.2% vs. 7.9%) in cases with heavily calcified lesions treated with rotational atherectomy (RA) and second-generation DES (CNs observed in 48.5%).[8] Therefore, the optimal PCI strategy for CNs remains unclear.

With the advent of drug-coated balloons (DCBs), stent-less PCI with a DCB is gaining popularity, especially in cases of small coronary artery disease.[9] Because it is not clear whether a DES is indispensable for the treatment of CNs, stent-less PCI with RA and a DCB may be an alternative strategy.[10] Furthermore, the poor clinical outcomes of PCI for CNs may be due to a poor patient background causing CNs in coronary arteries. The clinical significance of CNs may differ depending on patient characteristics and lesion location.

Therefore, the aim of the present study was to clarify the optimal management of CNs by reassessing the PCI strategy in association with patient background characteristics

Received September 23, 2021; accepted September 24, 2021; J-STAGE Advance Publication released online November 5, 2021 Time for primary review: 1 day

Division of Cardiology, Cardiovascular and Aortic Center (M.N., K.O., N.S., T.K.), Department of Clinical Engineering (S.N.), Saiseikai Fukuoka General Hospital, Fukuoka, Japan

Mailing address: Toru Kubota, MD, PhD, FJCS, Division of Cardiology, Cardiovascular and Aortic Center, Saiseikai Fukuoka General Hospital, 1-3-46 Tenjin, Chuo-ku, Fukuoka 810-0001, Japan. E-mail: kubotat01@gmail.com

ISSN-2434-0790

Table 1. Clinical Characteristics of 167 Patients With Calcified Nodules

	Overall	ACS			In-stent restenosis		
		–	+	P value	–	+	P value
No. patients	167	74	93		134	33	
Age (years)	73.1±10.2	72.0±9.5	73.9±10.7	0.235	73.2±10.4	72.6±9.3	0.788
Male sex	120 (71.9)	57 (77.0)	63 (67.7)	0.226	93 (69.4)	27 (81.8)	0.197
Hypertension	141 (84.4)	63 (85.1)	78 (83.9)	1	112 (83.6)	29 (87.9)	0.789
Diabetes	89 (53.3)	44 (59.5)	45 (48.4)	0.164	68 (50.7)	21 (63.6)	0.243
Dyslipidemia	102 (61.1)	50 (67.6)	52 (55.9)	0.151	85 (63.4)	17 (51.5)	0.235
Hemodialysis	55 (32.9)	22 (29.7)	33 (35.5)	0.508	41 (30.6)	14 (42.4)	0.218
Prior PCI	84 (50.3)	45 (60.8)	39 (41.9)	0.019	51 (38.1)	33 (100.0)	<0.001
Prior CABG	15 (9.0)	7 (9.5)	8 (8.6)	1	9 (6.7)	6 (18.2)	0.081
Lesion location (RCA/LCA/SVG)	104/62/1	46/27/1	58/35/0	0.732	74/59/1	30/3/0	<0.001
Multivessel disease	133 (79.6)	59 (79.7)	74 (79.6)	1	105 (78.4)	28 (84.8)	0.478
ACS	93 (55.7)	0 (0.0)	93 (100.0)	<0.001	78 (58.2)	15 (45.5)	0.241
In-stent restenosis	33 (19.8)	18 (24.3)	15 (16.1)	0.241	0 (0.0)	33 (100.0)	<0.001

Unless indicated otherwise, data are given as the mean ± SD or n (%). ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; LCA, left coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; SVG, saphenous vein graft.

and clinical outcomes.

Methods

Study Design

This was a single-center retrospective observational study conducted at Saiseikai Fukuoka General Hospital (Fukuoka, Japan). Consecutive patients who underwent PCI between January 2012 and September 2020 and had CNs in the target lesion were analyzed retrospectively based on clinical records. Major adverse cardiovascular events (MACEs) were defined as a composite of all-cause death, myocardial infarction (MI), stent thrombosis, and TLR.

This study was approved by the Ethics Committee of Saiseikai Fukuoka General Hospital (2021-8-3). The investigation conformed to the principles outlined in the Declaration of Helsinki.

PCI Procedures

All stents used in the present study were second- and third-generation DESs. RA was performed using the Rotablator (Boston Scientific, Natick, MA, USA) at a rotational speed of 160,000±20,000 r.p.m. Excimer laser coronary angioplasty (ELCA) was accomplished using the Spectranetics CVX-300 (Spectranetics, Colorado Springs, CO, USA). All DCBs used were paclitaxel coated (SeQuent Please; B. Braun, Melsungen, Germany).

Coronary Angiography Analyses

Calcification was identified angiographically as readily apparent radiopacities within the vascular wall at the site of the stenosis and classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection), and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).[11] Coronary tortuosity was defined as 2 bends >75° or 1 bend >90° proximal to the target lesion.[4]

Angiographic restenosis was defined as diameter stenosis ≥50% by quantitative coronary angiography within a previously treated segment at the follow-up angiogram.

Intracoronary Imaging Analyses

The intracoronary imaging modalities used in the present study were OCT (Dragonfly; Abbott Vascular, Santa Clara, CA, USA), optical frequency domain imaging (OFDI; FastView; Terumo, Tokyo, Japan), and IVUS (AltaView; Terumo or OptiCross; Boston Scientific). All OCT/OFDI images were analyzed with proprietary software programs (Abbott Vascular or Terumo) in accordance with previously validated criteria for OCT plaque characterization.[12] CNs were defined as superficial calcified plaques with protruding nodular calcium and an attached thrombus on OCT/OFDI,[7] or a convex shape of the luminal side of calcium with an irregular surface on IVUS.[8,13] Cases showing calcium with a smooth luminal surface were excluded as CNs in the present study.

The reference lumen area (RLA) was defined as the mean of the largest lumens proximal and distal to the stenosis within the same segment. To assess asymmetric stent expansion, the stent eccentricity index (SEI) was determined as the minimum stent diameter divided by the maximum stent diameter in each cross-section.[14]

Statistical Analyses

All statistical analyses were performed using EZR 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).[15] Continuous variables are presented as the mean ± SD, unless noted otherwise. Unpaired Student's t-tests were used to compare continuous variables between 2 independent groups. Categorical data are reported as frequencies and percentages and were compared using a Chi-squared or Fisher's exact test. The cumulative incidence risks of adverse clinical events were estimated by the Kaplan-Meier method and compared by the log-rank test. A multivariate analysis was performed using the Cox proportional hazards model for the survival time analysis or logistic regression for binary dependent variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive accuracy of logistic regression analysis.

All tests were 2-tailed, and $P<0.05$ was considered statistically significant.

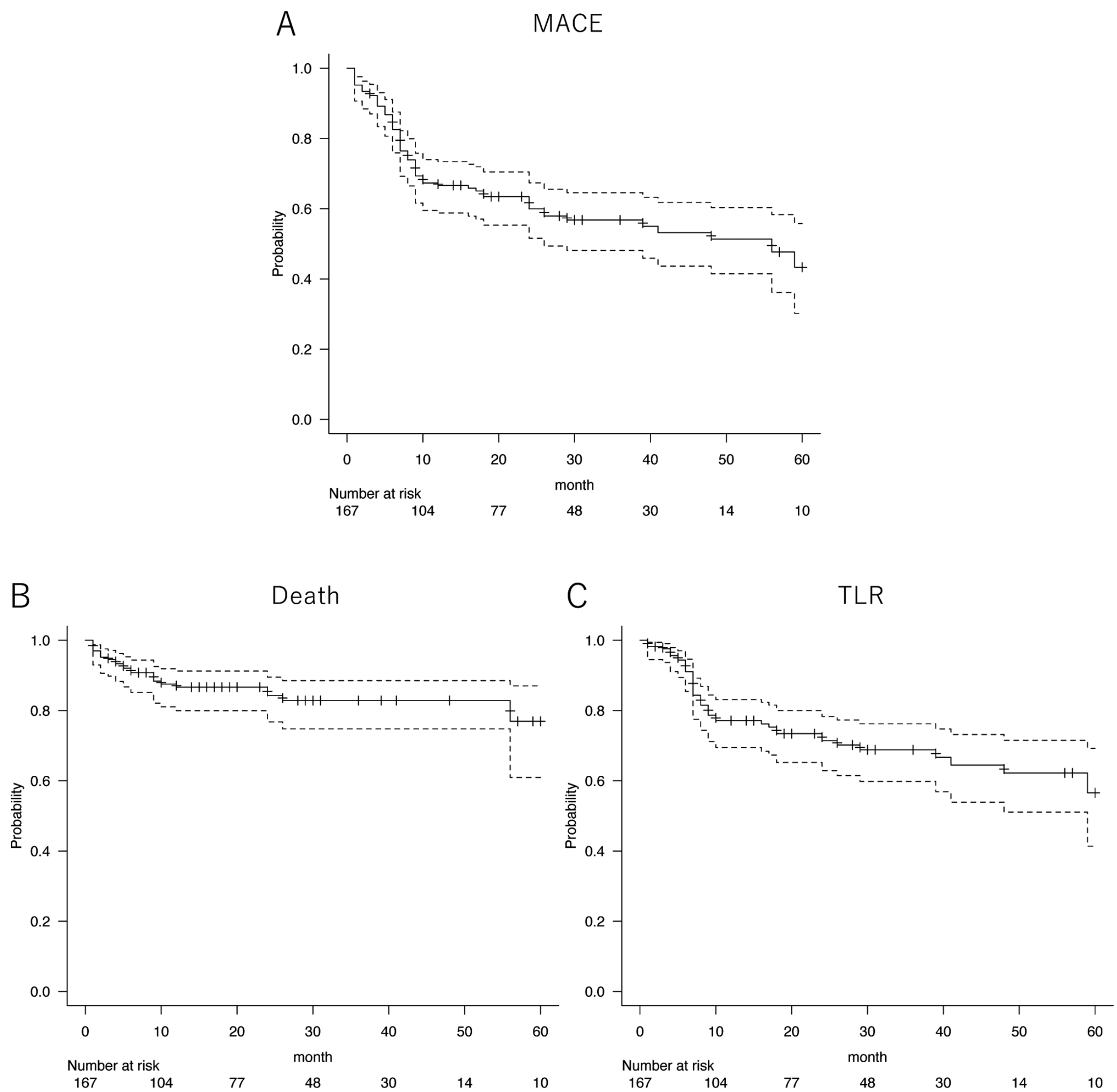

Figure 1. Survival curves (solid lines) for freedom from (**A**) major adverse cardiovascular events (MACEs), (**B**) all-cause death, and (**C**) target lesion revascularization (TLR) with 95% confidence intervals (dashed lines).

Results

Clinical Characteristics of Patients With CNs

Among 5,332 consecutive PCI cases evaluated using intracoronary imaging (IVUS, n=2,953; OCT/OFDI, n=2,454; both IVUS and OCT/OFDI, n=75), CNs were found in 167 lesions (3.1%; IVUS, n=110; OCT/OFDI, n=47; both IVUS and OCT/OFDI, n=10). The clinical characteristics of patients with CNs are summarized in **Table 1**. The mean age was 73 years, 72% were men, 33% were on hemodialysis, and 53% had diabetes. CNs were predominantly located at the proximal or mid-right coronary artery (RCA; n=104 [62%]), followed by the left coronary artery (LCA; n=62 [37%]) and saphenous vein graft (SVG; n=1 [1%]). The case of the CN located at the SVG was reported previously.[16]

More than half the patients with CNs presented clinically with ACS (56%); the CNs were de novo in 134 cases (80%) and the result of in-stent restenosis (ISR) in 33 cases (20%). Most of ISR CN cases occurred after PCI for de novo CNs. There were no significant differences in age, sex, rates of hemodialysis or diabetes, and lesion location between ACS and non-ACS patients. In contrast, although there were no significant differences in age, sex, rates of hemodialysis or mellitus, and ACS between de novo and ISR patients, ISR CNs were more frequently observed in the RCA (90.9%) than de novo CNs (55.2%; P<0.001).

Clinical Outcomes After PCI for CNs

Adverse clinical event-free survival curves after PCI are shown in **Figure 1**. The median follow-up period was 15 months. At 1 and 2 years, the cumulative incidence of MACEs after PCI was 33% and 40%, respectively, the all-cause mortality was 13% and 16%, respectively, and the TLR rate was 23% and 29%, respectively. Over 5 years,

Table 2. Results of Univariate and Multivariate Analyses of Factors Affecting All-Cause Death- and TLR-Free Survival in 167 Patients With Calcified Nodules

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
MACE						
Patient age	0.971	0.949–0.994	0.013			
Male sex	2.574	1.350–4.907	0.004	2.239	1.155–4.341	0.017
Diabetes	2.001	1.221–3.281	0.006			
Hemodialysis	3.930	2.438–6.336	0.000	3.272	2.000–5.351	0.000
RCA location	1.457	0.867–2.449	0.155	1.849	1.101–3.106	0.020
ACS	1.542	0.950–2.504	0.080	2.080	1.245–3.475	0.005
In-stent restenosis	1.405	0.823–2.410	0.212			
All-cause death						
Patient age	0.986	0.947–1.026	0.485			
Male sex	3.178	0.946–10.67	0.614			
Diabetes	3.846	1.434–10.31	0.007	3.187	1.152–8.821	0.026
Hemodialysis	7.807	3.192–19.09	0.000	6.766	2.683–17.06	0.000
RCA location	0.596	0.268–1.328	0.205			
ACS	1.877	0.798–4.414	0.149	2.494	1.015–6.129	0.046
In-stent restenosis	0.577	0.172–1.935	0.373			
TLR						
Patient age	0.964	0.937–0.991	0.010			
Male sex	2.344	1.091–5.035	0.029			
Diabetes	1.508	0.838–2.715	0.171			
Hemodialysis	2.825	1.563–5.106	0.001	3.149	1.739–5.701	0.000
RCA location	2.738	1.277–5.872	0.010	3.093	1.437–6.655	0.004
ACS	1.398	0.775–2.525	0.266			
In-stent restenosis	1.978	1.066–3.668	0.031			

ACS, acute coronary syndrome; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; RCA, right coronary artery; TLR, target lesion revascularization.

there were 8 cases (38%) of sudden cardiac death, 2 cases (10%) of heart failure, and 11 cases (52%) of non-cardiac death. MACE consisted of 3 cases of ST-elevation MI (STEMI) and 7 cases of non-STEMI, all of which were restenosis at the target lesions and treated with PCI. Therefore, all MI cases were counted as TLR as well. No stent thrombosis without MI or TLR was observed.

As summarized in **Table 2**, univariate analysis indicated that MACEs were significantly associated with younger age, male sex, diabetes, and hemodialysis, whereas all-cause death was significantly associated with diabetes and hemodialysis, and TLR was significantly associated with a younger age, male sex, hemodialysis, RCA location, and ISR lesions. Multivariate analysis with a Cox proportional hazards model including age, sex, diabetes, hemodialysis, RCA location, ACS, and ISR lesions revealed that male sex, hemodialysis, RCA location, and ACS were significantly associated with MACEs, whereas diabetes, hemodialysis, and ACS were significantly associated with all-cause death, and hemodialysis and RCA location were significantly associated with TLR. A younger age, male sex, and ISR lesions were not associated with TLR after multivariate analysis. These results suggest that both hemodialysis and RCA location are strong predictors of poor outcomes after PCI for CNs (**Figure 2**). CNs not in the RCA in cases without hemodialysis had significantly better clinical outcomes than those in the RCA with hemodialysis (MACE, P<0.0001; all-cause death, P=0.032; TLR, P<0.0001).

PCI Strategy and Restenosis

The relationship between the PCI strategy and restenosis was investigated in a subset of patients (91 de novo CNs) whose patency was assessed by coronary angiography (n=68), coronary computed tomography angiography (n=15), or stress myocardial perfusion scintigraphy (n=8) within 2 years after PCI. As summarized in **Table 3**, the mean age of this subset of patients was 74 years, 69% were men, 25% were on hemodialysis, 46% had diabetes, and 54% had ACS. Because 29 of the 91 target lesions were diagnosed as having restenosis, the restenosis rate was 32%. Target lesions were located in the RCA in 53 (58%) cases, the left main trunk (LMT) to left anterior descending artery (LAD) in 34 (38%) cases, and in the left circumflex artery (LCX) in 4 (4%) cases; 42% of patients had a history of PCI and 79% of patients had multivessel coronary artery disease. Target lesions were severe with ≥99% stenosis in 42% of cases, tortuous in 41% of cases, and severely calcified in 66% of cases. RA, a scoring balloon, a DES, a DCB, and ECLA were used in 57%, 31%, 80%, 13%, and 2% of patients, respectively. There were no marked differences in the aforementioned clinical characteristics between patients with and without DES implantation or between patients with and without RA (data not shown). Although hemodialysis was more frequently observed in LCA lesions (37% vs. 17% for RCA; P=0.049), all other clinical characteristics were not markedly different between RCA and LCA lesions.

Univariate analysis indicated that a younger age, diabe-

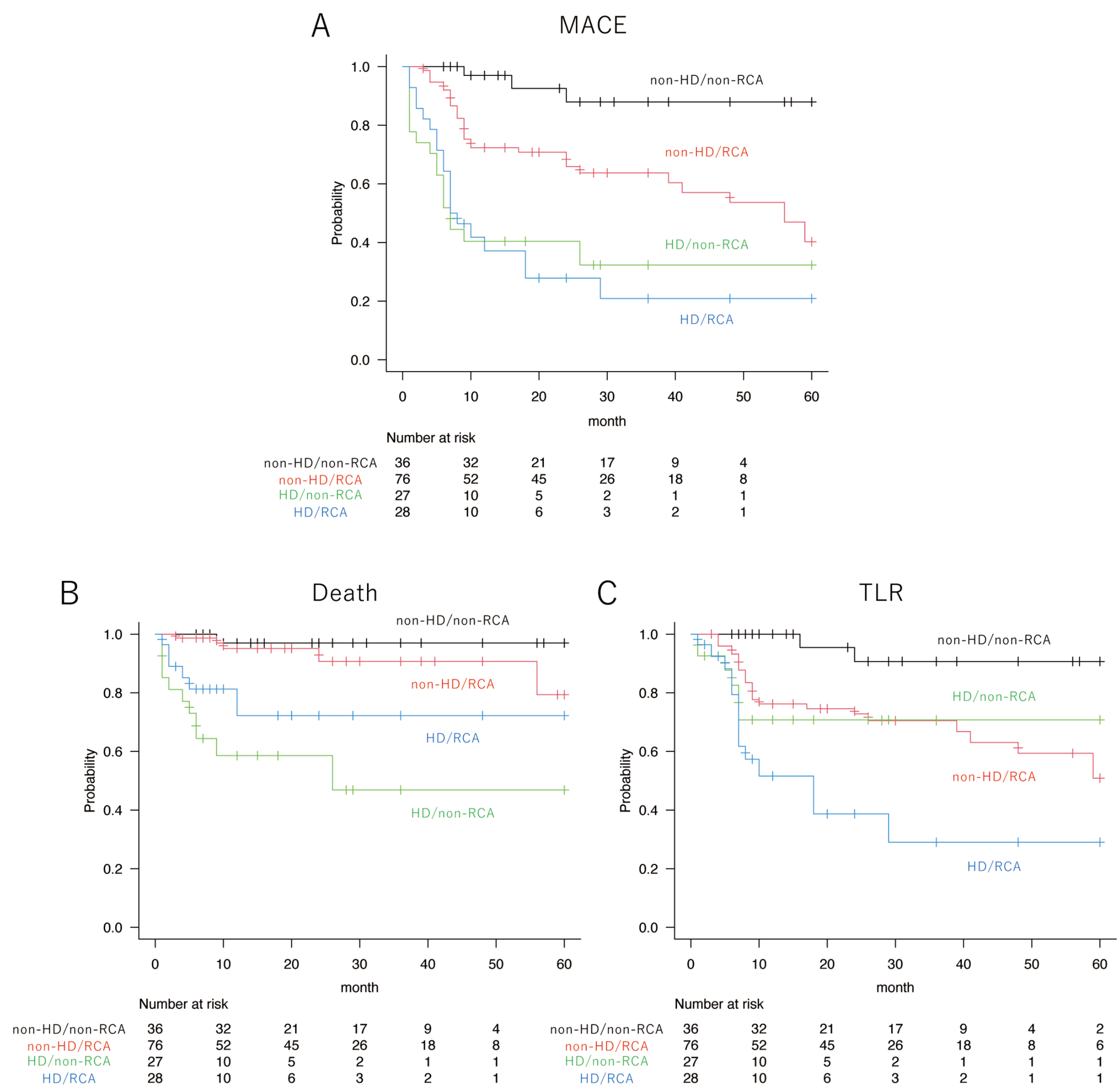

Figure 2. Survival curves for freedom from (**A**) major adverse cardiovascular events (MACEs), (**B**) all-cause death, and (**C**) target lesion revascularization (TLR) stratified by hemodialysis (HD) and right coronary artery (RCA) location.

tes, RCA location, severe stenosis, lesion tortuosity, and not using RA were significantly associated with restenosis ($P<0.05$). Although rates of male sex, hemodialysis, a history of PCI, and DES implantation tended to be higher in the restenosis than non-restenosis group, no significant differences were noted. Multivariate analysis with logistic regression including age, diabetes, RCA location, severe stenosis, lesion tortuosity, RA, hemodialysis, and DES revealed that hemodialysis, diabetes, RCA location, and not using RA were independent predictors of restenosis (**Table 4**). The area under the curve in ROC analysis was 0.778 (95% confidence interval 0.677–0.878).

Among the 73 cases of DES implantation, neither stent brand, stent size, stent length, minimum stent area (MSA), MSA/RLA, nor SEI was associated with restenosis (**Table 5**). Among 52 cases of PCI with RA, neither burr size nor DES implantation was associated with restenosis (data not shown). Among 29 patients with restenosis, 8 (27.6%) presented with ACS, with all 8 having been treated with a DES. In contrast, among 18 patients without DES implantation, 3 (17%) developed restenosis, but none of them presented with ACS (1 had stable effort angina and 2 had silent myocardial ischemia). These results suggest that DES implantation may not be mandatory to prevent restenosis or ACS in PCI of CNs.

Discussion

The major findings of this study were that: (1) CNs were observed in 3.1% of patients who underwent PCI; (2) both hemodialysis and RCA location were strong predictors of poor outcomes after PCI for CN; and (3) restenosis was

Table 3. Clinical Characteristics of 91 Patients With De Novo Calcified Nodules

	Overall	Restenosis		
		No	Yes	P value
No. patients	91	62	29	
Age (years)	74.1±9.7	75.5±9.6	71.1±9.5	0.044
Male sex	63 (69.2)	39 (62.9)	24 (82.8)	0.087
Hypertension	78 (85.7)	53 (85.5)	25 (86.2)	1
Diabetes	42 (46.2)	23 (37.1)	19 (65.5)	0.014
Dyslipidemia	64 (70.3)	47 (75.8)	17 (58.6)	0.139
Hemodialysis	23 (25.3)	12 (19.4)	11 (37.9)	0.072
Prior PCI	38 (41.8)	22 (35.5)	16 (55.2)	0.11
Prior CABG	4 (4.4)	4 (6.5)	0 (0.0)	0.302
Lesion location (RCA/LMT-LAD/LCX)	53/34/4	31/28/3	22/6/1	0.048
Multivessel disease	72 (79.1)	49 (79.0)	23 (79.3)	1
ACS	49 (53.8)	33 (53.2)	16 (55.2)	1
Lesion characteristics				
≥99% stenosis	38 (41.8)	21 (33.9)	17 (58.6)	0.039
Tortuous	53 (58.2)	31 (50.0)	22 (75.9)	0.024
Mild/moderate/severe calcification (n)	8/23/60	7/18/37	1/5/23	0.217
Treatment strategy				
Rotational atherectomy	52 (57.1)	41 (66.1)	11 (37.9)	0.014
Scoring balloon	37 (40.7)	25 (40.3)	12 (41.4)	1
Drug-eluting stent	73 (80.2)	47 (75.8)	26 (89.7)	0.162
Drug-coated balloon	12 (13.2)	10 (16.1)	2 (6.9)	0.325
ELCA	2 (2.2)	1 (1.6)	1 (3.4)	0.538

Unless indicated otherwise, data are given as the mean ± SD or n (%). ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ELCA, excimer laser coronary angioplasty; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 4. Results of a Multivariate Analysis Concerning the Association With Restenosis in 91 De Novo Calcified Nodules

Factor	OR	95% CI	P value
Intercept	0.133	0.033–0.528	0.004
Hemodialysis	3.520	1.000–12.40	0.049
Diabetes	3.330	1.170–9.490	0.024
Right coronary artery	4.290	1.240–14.90	0.022
Rotational atherectomy	0.291	0.103–0.823	0.020

CI, confidence interval; OR, odds ratio.

significantly associated with hemodialysis, diabetes, RCA location, and not using RA.

The prevalence of CNs has varied among studies. CNs are pathologically defined as lesions with fibrous cap disruption and luminal thrombus associated with eruptive, dense, calcific nodules.[1] CNs are considered the least frequent cause of ACS, compared with plaque rupture and plaque erosion. Indeed, using OCT to identify culprit lesion morphologies among 417 ACS patients, Kobayashi et al reported that the prevalence of CN, plaque rupture, and plaque erosion was 6%, 45%, and 41%, respectively.[7] However, using IVUS to investigate non-culprit segments of coronary arteries in 697 ACS patients. Xu et al reported that the prevalence of CNs was 17% per artery and 30% per patient,[3] suggesting that CNs may be more prevalent than previously recognized. Using OCT to evaluate 124 ISR lesions, Isodono et al reported that CN-like ISR was observed in 11 cases (9%).[17] Furthermore, using IVUS to evaluate heavily calcified lesions requiring RA in 264 patients, Morofuji et al identified CNs in 128 lesions (48.5%).[8] In the present study, in which every PCI lesion was included (regardless of ACS or ISR) but non-target lesions were excluded, the prevalence of CNs was 3.1%. CNs should not to be confused with nodular calcification, which does not have fibrous cap disruption or luminal thrombus.[18] Variations in the prevalence of CNs among studies may be explained, in part, by differences in the definition of CN. In the present study, CNs were defined as superficial calcified plaques with protruding nodular calcium and an attached thrombus on OCT/OFDI[7] or a convex shape of the luminal side of calcium with an irregular surface on IVUS,[8,13] and cases of nodular calcification with a smooth luminal surface were excluded.

In the present study, we demonstrated that both hemodialysis and RCA location were strong predictors of poor outcomes after PCI for CNs. As shown in **Figure 2**, non-

Table 5. Clinical Characteristics of 73 Patients With Stent Implantation

	Overall	Restenosis No	Restenosis Yes	P value
No. patients	73	47	26	
Age (years)	73.7±10.1	75.2±10.2	71.1±9.5	0.101
Male sex	49 (67.1)	27 (57.4)	22 (84.6)	0.021
Hypertension	63 (86.3)	41 (87.2)	22 (84.6)	0.737
Diabetes	32 (43.8)	16 (34.0)	16 (61.5)	0.029
Dyslipidemia	54 (74.0)	39 (83.0)	15 (57.7)	0.026
Hemodialysis	18 (24.7)	8 (17.0)	10 (38.5)	0.052
Prior PCI	30 (41.1)	15 (31.9)	15 (57.7)	0.047
Prior CABG	1 (1.4)	1 (2.1)	0 (0.0)	1
Lesion location (RCA/LMT-LAD/LCX)	43/27/3	23/22/2	20/5/1	0.038
Multivessel disease	59 (80.8)	37 (78.7)	22 (84.6)	0.758
ACS	37 (50.7)	22 (46.8)	15 (57.7)	0.465
Lesion characteristics				
≥99% stenosis	30 (41.1)	16 (34.0)	14 (53.8)	0.137
Tortuous	45 (61.6)	26 (55.3)	19 (73.1)	0.209
Mild/moderate/severe calcification (n)	6/18/49	6/14/27	0/4/22	0.042
Rotational atherectomy	35 (47.9)	26 (55.3)	9 (34.6)	0.142
Drug eluting stent				
Stent size (mm)	3.14±0.37	3.13±0.38	3.16±0.38	0.742
Stent length (mm)	40.2±18.9	40.9±18.6	39.0±19.8	0.688
RLA (mm^2)	7.41±2.73	7.32±2.70	7.58±2.85	0.706
MSA (mm^2)	6.46±2.37	6.30±2.24	6.77±2.65	0.448
MSA/RLA	0.88±0.13	0.88±0.13	0.87±0.13	0.855
Stent eccentricity index	0.78±0.10	0.79±0.10	0.75±0.10	0.088

Data given as mean±SD or numbers (%) unless otherwise mentioned. MSA, minimum stent area; RLA, reference lumen area. Other abbreviations as in Table 3.

RCA CNs in patients not on hemodialysis had significantly better clinical outcomes than CNs in the RCA in patients undergoing hemodialysis. Because most non-RCA CNs in the present study were in the LCA, except for 1 lesion in the SVG, CNs in the LCA seem to have a better prognosis than those in the RCA. Although the presence of CNs in target lesions has been shown to be associated with unfavorable clinical outcomes after PCI,[7,8] the clinical significance of CNs may not be the same, differing depending on patient or lesion characteristics.

CNs are typically observed in the proximal to mid-portions of a highly calcified tortuous RCA with a hard bending motion.[4] In addition, some CNs are found predominantly in the bifurcating regions of the LMT, tending to show large necrotic core volumes.[19] Morofuji et al reported that an RCA lesion was an independent risk factor for MACEs in patients with heavily calcified lesions requiring RA, in addition to CNs, ostial lesions, a reduced left ventricular ejection fraction, and hemodialysis.[8] Isodono et al reported that ISR CNs were predominantly observed in the RCA (9/11),[17] as in the present study (30/33), which may also support the hypothesis that CNs in the RCA are a strong predictor of TLR after PCI.

Stent underexpansion has been considered a predictor of stent failure, including TLR and stent thrombosis, especially in cases with heavily calcified lesions.[20] Indeed, Kobayashi et al reported that vessel size and a post-stent minimum lumen area were smaller in ACS patients with than without CNs at the culprit lesion, which may be one reason for the increased incidence of TLR in lesions with CNs.[7] However, Morofuji et al reported that although a greater MSA was achieved in the CN group with frequent use of a larger burr and stent, TLR and stent thrombosis occurred more frequently.[8] In the present study, neither stent brand, stent size, stent length, MSA, MSA/RLA, nor SEI was associated with restenosis, due, in part, to the fact that RA and imaging modalities are aggressively used at Saiseikai Fukuoka General Hospital to avoid stent underexpansion. Therefore, there must be some other reason besides stent underexpansion to explain the poor clinical outcomes after PCI for CNs.

We demonstrated that not using RA was an independent predictor of restenosis after PCI for CNs. Although the precise mechanisms underlying the benefit of RA for lesions with CNs were unclear, debulking of the CN itself rather than lesion expansion may be important when treating CNs. Furthermore, the need for DES implantation was not validated in the present study. The use of DES was not associated with a reduced TLR, and a DES had been implanted in all 8 patients who developed ACS after PCI. In addition, once ISR occurs after PCI, the presence of a DES may complicate the treatment strategy by limiting aggressive debulking and luminal expansion. Recently, Nagai et al reported findings suggesting that stent-less PCI with RA and a DCB may be an effective option for managing complex calcified lesions, regardless of the presence of CNs.[10] Similarly, based on the findings of the present study, we propose that stent-less PCI with RA and a DCB may be a feasible option for treating lesions with CNs.

Study Limitations

Several limitations warrant mention in the present study. First, because this study was a single-center retrospective observational study, the results are not definitive; instead, they are hypothesis generating. The clinical significance of the CN location and optimal PCI strategy with RA and a DES or DCB should be further investigated in future studies. Second, imaging data from the present study were obtained by either IVUS or OCT/OFDI at the discretion of the individual PCI operators. Differences in the diagnostic accuracy between IVUS and OCT/OFDI may not be negligible. Third, the present study was limited to patients with CN. In the absence of a control group without CNs, we cannot say definitively that the findings are specific to CNs; instead, they may be common to calcified coronary lesions, regardless of the presence of CNs.

Conclusions

Hemodialysis, diabetes, RCA location, and not using RA were strong predictors of poor outcomes after PCI for CNs. To reduce the rate of TLR, it may be better to use RA whenever possible. Because the use of a DES did not affect the TLR rate, stent-less PCI with RA and DCB may be a feasible option for treating CNs.

Sources of Funding

This study did not receive any specific funding.

Disclosures

The authors declare no conflicts of interest.

IRB Information

This study was approved by the ethics committee of Saiseikai Fukuoka General Hospital (2021-8-3).

References

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000; **20:** 1262–1275.
2. Khalifa AKM, Kubo T, Ino Y, Terada K, Emori H, Higashioka D, et al. Optical coherence tomography comparison of percutaneous coronary intervention among plaque rupture, erosion, and calcified nodule in acute myocardial infarction. *Circ J* 2020; **84:** 911–916.
3. Xu Y, Mintz GS, Tam A, McPherson JA, Iñiguez A, Fajadet J, et al. Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: A 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). *Circulation* 2012; **126:** 537–545.
4. Lee T, Mintz GS, Matsumura M, Zhang W, Cao Y, Usui E, et al. Prevalence, predictors, and clinical presentation of a calcified nodule as assessed by optical coherence tomography. *JACC Cardiovasc Imaging* 2017; **10:** 883–891.
5. Sato Y, Finn AV, Virmani R. Calcified nodule: A rare but important cause of acute coronary syndrome with worse clinical outcomes. *Atherosclerosis* 2021; **318:** 40–42.
6. Iwai S, Watanabe M, Okamura A, Kyodo A, Nogi K, Kamon D, et al. Prognostic impact of calcified plaque morphology after drug eluting stent implantation: An optical coherence tomography study. *Circ J* 2021; **85:** 2019–2028.
7. Kobayashi N, Takano M, Tsurumi M, Shibata Y, Nishigoori S, Uchiyama S, et al. Features and outcomes of patients with calcified nodules at culprit lesions of acute coronary syndrome: An optical coherence tomography study. *Cardiology* 2018; **139:** 90–100.
8. Morofuji T, Kuramitsu S, Shinozaki T, Jinnouchi H, Sonoda S, Domei T, et al. Clinical impact of calcified nodule in patients with heavily calcified lesions requiring rotational atherectomy. *Catheter Cardiovasc Interv* 2021; **97:** 10–19.
9. Jeger RV, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): An open-label randomised non-inferiority trial. *Lancet* 2018; **392:** 849–856.
10. Nagai T, Mizobuchi M, Funatsu A, Kobayashi T, Nakamura S. Acute and mid-term outcomes of drug-coated balloon following rotational atherectomy. *Cardiovasc Interv Ther* 2020; **35:** 242–249.
11. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, et al. Patterns of calcification in coronary artery disease: A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation* 1995; **91:** 1959–1965.
12. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012; **59:** 1058–1072.
13. Lee JB, Mintz GS, Lisauskas JB, Biro SG, Pu J, Sum ST, et al. Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. *Am J Cardiol* 2011; **108:** 1547–1551.
14. Otake H, Shite J, Ako J, Shinke T, Tanino Y, Ogasawara D, et al. Local determinants of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography. *JACC Cardiovasc Interv* 2009; **2:** 459–466.
15. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; **48:** 452–458.
16. Yamamoto K, Natsuaki M, Serikawa T, Okabe M, Yamamoto Y. Nodular calcification in saphenous vein graft successfully treated by percutaneous coronary intervention. *Case Rep Cardiol* 2018; **2018:** 5138705.
17. Isodono K, Fujii K, Fujimoto T, Kasahara T, Ariyoshi M, Irie D, et al. The frequency and clinical characteristics of in-stent restenosis due to calcified nodule development after coronary stent implantation. *Int J Cardiovasc Imaging* 2021; **37:** 15–23.
18. Yahagi K, Kolodgie FD, Otsuka F, Finn AV, Davis HR, Joner M, et al. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. *Nat Rev Cardiol* 2016; **13:** 79–98.
19. Torii S, Sato Y, Otsuka F, Kolodgie FD, Jinnouchi H, Sakamoto A, et al. Eruptive calcified nodules as a potential mechanism of acute coronary thrombosis and sudden death. *J Am Coll Cardiol* 2021; **77:** 1599–1611.
20. Honda Y, Fitzgerald PJ. Stent expansion as a mechanical parameter to predict late stent patency: Back to the basics. *JACC Cardiovasc Interv* 2009; **2:** 1276–1278.