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Cardiac outcomes in patients with acute coronary syndrome attributable to calcified nodule

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ABSTRACT

Background and aims: Calcified nodule (CN) is an eruptive calcified mass causing acute coronary syndrome (ACS). Since coronary calcification is associated with an elevated cardiac event's risk, ACS attributable to CN may exhibit worse clinical outcome following percutaneous coronary intervention (PCI).

Methods: We retrospectively analyzed 657 ACS patients receiving PCI with newer-generation drug-eluting stent (DES) implantation under intravascular ultrasound (IVUS) guidance. CN was defined as (1) protruding calcification with its irregular surface and (2) the presence of calcification at adjacent proximal and distal segments. The primary endpoint was a composite of major adverse cardiac event [MACE = cardiac death + ACS recurrence + target lesion revascularization (TLR)].

Results: CN was identified in 5.3% (=35/657) of the study subjects. CN patients were more likely to have coronary risk factors including hypertension ($p = 0.005$), chronic kidney disease ($p < 0.001$), maintenance hemodialysis ($p < 0.001$) and a history of PCI ($p < 0.001$). During the observational period (median = 1304 days), CN was associated with an increased risk of MACE (HR = 7.68, 95%CI = 4.61–12.80, $p < 0.001$), ACS recurrence (HR = 12.32, 95%CI = 6.05–25.11, $p < 0.001$) and TLR (HR = 10.48, 95%CI = 5.80–18.94, $p < 0.001$). These cardiac risks related to CN were consistently observed by Cox proportional hazards model (MACE: $p < 0.001$, ACS recurrence: $p < 0.001$, TLR: $p < 0.001$) and a propensity score–matched cohort analysis (MACE: $p = 0.002$, ACS recurrence: $p = 0.01$, TLR: $p = 0.005$). Of note, over 80% of TLR at the CN lesion was driven by its reappearance within the implanted DES.

Conclusions: ACS patients attributable to CN have an increased risk of ACS recurrence and TLR, mainly driven by the continuous growth and protrusion of the calcified mass.

1. Introduction

Calcified nodule (CN) is a distinct plaque phenotype, which is a pathogenesis of acute coronary syndrome (ACS). It is characterized by a protruding nodular calcification penetrating the lumen surface with the attached thrombus [1]. In addition, the distribution of nodular calcification at CN lesions is normally eccentric [2]. Given that the presence of lesion calcification with this unique distribution pattern could affect clinical outcomes after percutaneous coronary intervention (PCI), ACS subjects attributable to CN may exhibit worse cardiac outcomes following PCI [3].

Accumulating evidence has demonstrated a significant reduction of repeat revascularization after drug-eluting stent implantation (DES) in the setting of ACS [4]. However, the efficacy has been shown to diminish

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at lesions with calcification [5–7]. Whether cardiac outcomes attributable to CN differ from those in ACS patients using currently available DES remains to be determined. A recent study has validated IVUS-derived features, which correspond to CN of *ex vivo* coronary artery specimen [8]. Therefore, using IVUS imaging, the current study investigated cardiac outcomes following the newer-generation DES implantation in ACS patients with CN.

2. Patients and methods

2.1. Study population

We retrospectively analyzed 1615 ACS subjects receiving primary PCI at the National Cerebral and Cardiovascular Center in Osaka, Japan from February 2011 to February 2018 (Supplementary Fig. 1). ACS included ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) according to the third universal definition of myocardial infarction [9]. In addition, unstable angina pectoris (uAP), which did not show any elevation of cardiac enzyme, was included. Of 1615 patients, the following subjects were excluded: subjects with ACS caused by ISR (n = 94), those with culprit lesion within the bypass graft (n = 5), those who did not receive newer-generation DES (n = 669) and did not undergo IVUS imaging (n = 187) (Supplementary Fig. 1). The remaining 657 ACS subjects (661 culprit lesions) who received newer-generation DES implantation under the guidance of IVUS imaging were analyzed. This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center (M30-084-2).

2.2. IVUS analysis and definition of CN

IVUS imaging was performed before and after PCI as previously reported. Briefly, IVUS images (View IT®, Terumo, Tokyo, Japan or OptiCross™, Boston Scientific, Marlborough, MA, USA) within the culprit vessel were obtained with automated pull back (0.5 mm/s) after intracoronary administration of nitroglycerin (0.1–0.2 mg). All IVUS images were analyzed using a commercially available off-line software (QIvus®, Medis, Leiden, the Netherlands).

According to the published papers, CN was defined as the following IVUS features: (a) protruding calcification with its irregular surface and (b) the presence of calcification at adjacent proximal and distal segments (Supplementary Fig. 2 and Supplementary movie 1) [8]. Quantitative analysis was conducted at culprit lesions, which was defined as the lesion receiving newer-generation DES implantation. The slice with the smallest lumen and greatest amount of culprit lesion was selected as the minimum lumen area (MLA) site. Maximum calcium arc grade at culprit lesion was analyzed according to the following definition: grade 0 = no calcification, 1 = 1–90°, 2 = 91–180°, 3 = 181–270° and 4 = 271–360°. The proximal and distal reference segments with maximum lumen and least amount of plaque within 5 mm proximal or distal to the culprit lesion were identified. The maximum reference areas at these two segments were measured and averaged for analysis. Identification of CN and these quantitative analyses were conducted by 2 independent cardiologists (YK and KM) blinded to the clinical presentation. Intra-observer and inter-observer variabilities yielded acceptable concordance for CN ($\kappa = 0.99$ and 0.96, respectively).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2020.11.005

Minimal stent area (MSA) and stent eccentricity index were measured as well on IVUS imaging after newer-generation DES implantation. MSA was defined as the minimal cross-sectional lumen area of lesion on post stenting IVUS imaging [10]. Stent eccentricity index was also analyzed by the ratio between minimal and maximal stent diameter [11].

The current study further analyzed IVUS images in 43 subjects (45 lesions) who required re-PCI due to ISR at the implanted newer-generation DES. ISR was defined as a lesion with angiographic diameter stenosis >50% within stent or the 5-mm borders proximal or distal to the implanted stent. Qualitative analysis was conducted to evaluate the presence or absence of (a) neointimal hyperplasia alone and (b) reappearance of CN within the implanted stent (Supplementary Fig. 2 and Supplementary movie 2).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2020.11.005

2.3. PCI procedures and clinical follow-up

After identification of culprit lesion on coronary angiography, primary PCI was performed. All procedural decisions were made at the discretion of the individual PCI operator. Dual antiplatelet therapy was continued for at least 1 year after primary PCI. Study subjects were followed at our institute's outpatient office and/or local clinics. Testing for evaluation of myocardial ischemia following PCI was conducted at each physician's discretion.

2.4. Quantitative coronary angiography analysis

Quantitative coronary angiography (QCA) analysis was conducted at culprit lesion using an off-line commercially available software (QAngio® XA, Medis, Leiden, the Netherlands). QCA analysis included minimal lumen diameter, percent diameter stenosis, lesion length and reference vessel diameter.

2.5. Outcomes

The primary endpoint was the occurrence of major adverse cardiac events (MACE) which included cardiac-cause death, the recurrence of ACS, and target lesion revascularization (TLR) after primary PCI. The cause of ACS recurrence was determined as follows: (a) ISR at the implanted newer-generation DES, (b) the progression of non-culprit lesion and (c) other. TLR was defined as either repeat PCI or coronary artery bypass surgery due to ISR. The secondary endpoint was the occurrence of each component of MACE (cardiac-death, recurrence of ACS or TLR). These outcomes were determined through medical record review by two physicians (HS and YK).

2.6. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and compared using the t-test if data were normally distributed. Categorical variables were compared using the Fisher exact test or the Chi-square test as appropriate. The Kaplan-Meier method was used to estimate survival curves for primary and secondary outcomes, and the log-rank test was used to assess differences between patients with and without CN. The propensity score was estimated using logistic regression models, with MACE as the outcome and baseline clinical demographics as predictors. Patients with and without CN were matched by propensity score on a 1:1 basis using the nearest-neighbour matching method with a calliper <0.2 standard deviation with the psmatch2 procedure in the STATA program. All p values < 0.05 were considered statistically significant. All analyses were performed with SPSS (SPSS Japan, Tokyo, Japan) or STATA 13 (Stata Corp, College Station, TX).

3. Results

3.1. Clinical demographics of study subjects

CN was identified in 5.3% (35/657) of ACS patients and 5.2% (=35/661) of culprit lesions. ACS patients with CN were more likely to have coronary risk factors including hypertension ($p = 0.005$), chronic kidney disease ($p < 0.001$), maintenance hemodialysis ($p < 0.001$) and a history of PCI ($p < 0.001$) (Table 1). They were less likely to have a smoking

Table 1
Clinical demographics.

	CN (+) (n = 35)	CN (−) (n = 622)	*p* value
Age (years)	71 ± 10	70 ± 12	0.43
Female, n (%)	10 (29)	130 (21)	0.29
BMI (kg/m^2)	23.3 ± 2.4	23.4 ± 3.7	0.78
Hypertension, n (%)	32 (91)	444 (72)	0.005
Dyslipidemia, n (%)	25 (71)	439 (71)	0.93
Diabetes mellitus, n (%)	17 (49)	216 (35)	0.10
Smoking, n (%)	4 (11)	156 (25)	0.04
CKD (eGFR<60), n (%)	24 (69)	272 (44)	0.003
Multivessel disease, n (%)	22 (63)	309 (50)	0.13
Hemodialysis, n (%)	7 (20)	18 (3)	<0.001
A history of PCI, n (%)	17 (49)	126 (20)	<0.001
A history of CABG, n (%)	4 (11)	31 (5)	0.17
LVEF (%)	53 ± 16	52 ± 13	0.63
Calcium (mg/dl)	9.2 ± 0.6	9.0 ± 0.6	0.12
Phosphorus (mg/dl)	3.5 ± 0.8	3.3 ± 1.6	0.40
ALP (U/L)	238 ± 120	232 ± 88	0.70
LDL-C at admission (mmol/l)	2.6 ± 0.9	3.1 ± 0.9	0.003
LDL-C at 1year (mmol/l)	2.1 ± 0.7	2.0 ± 0.5	0.37
ACS presentation			
STEMI, n (%)	14 (40)	382 (61)	0.04
NSTEMI, n (%)	9 (26)	127 (20)	
UAP, n (%)	12 (34)	113 (18)	
Medications at discharge			
Aspirin, n (%)	33 (94)	571 (92)	0.58
$P2Y_{12}$ antagonist inhibitor, n (%)	32 (91)	573 (92)	0.88
ACEI/ARB, n (%)	24 (69)	460 (74)	0.48
Beta-blocker, n (%)	24 (69)	441 (71)	0.76
Statin, n (%)	29 (83)	592 (95)	0.01

ACEI = angiotensin converting enzyme inhibitor, ALP = alkaline phosphatase, ARB = angiotensin II receptor blocker, BMI = body mass index, CABG = coronary artery bypass graft, CN = calcified nodule, eGFR estimated glomerular filtration rate, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, STEMI=ST-elevation myocardial infarction, UAP = unstable angina pectoris.

habit ($p = 0.04$). CN subjects more frequently presented with uAP ($p = 0.04$). With regard to medication use at discharge, CN subjects were less likely to receive a statin at discharge (83 *vs.* 95%, $p = 0.01$), whereas there were no significant differences in the use of other medications (Table 1). A lower baseline low-density lipoprotein cholesterol (LDL-C) level was observed in CN subjects (2.6 ± 0.9 *vs.* 3.1 ± 0.9 mmol/l, $p = 0.003$), whereas its one-year level was similar between the two groups (2.1 ± 0.7 *vs.* 2.0 ± 0.5 mmol/l, $p = 0.37$) (Table 1).

3.2. Coronary angiographic and IVUS measures of culprit lesions

Table 2 shows angiographic and IVUS measures of 661 culprit lesions. Culprit lesions exhibiting CN were more frequently located within the left circumflex artery, especially at its proximal segment (Table 2). A larger minimum lumen diameter ($p = 0.04$) and a smaller percent diameter stenosis ($p = 0.03$) were observed at culprit lesions with CN. Predictably, CN lesions were associated with an increased calcium arc score ($p < 0.001$).

3.3. PCI procedural characteristics

PCI procedural characteristics, and QCA and IVUS measures after PCI are shown in Supplementary Table I. Prior to stent implantation, calcium modification devices were more frequently used at culprit lesions containing CN (rotablator: $p = 0.03$, scoring balloon: $p < 0.001$) (Table 3). After PCI, culprit lesions in both groups were favourably dilated, as reflected by QCA analysis (minimum lumen diameter: $p = 0.81$, percent diameter stenosis: $p = 0.44$). On IVUS imaging analysis,

Table 2
Coronary angiographic and IVUS measures of culprit lesions.

	CN (+) (n = 35)	CN (−) (n = 626)	*p* value
Location			
LMT, n (%)	0 (0)	20 (3)	<0.001
LAD, n (%)	6 (17)	252 (40)	
Proximal, n (%)	2 (6)	147 (24)	
LCX, n (%)	11 (31)	77 (12)	
Proximal, n (%)	9 (26)	29 (5)	
RCA, n (%)	18 (51)	277 (44)	
Proximal, n (%)	8 (23)	94 (15)	
Middle, n (%)	7 (20)	71 (11)	
Pre QCA data			
Reference diameter (mm)	3.0 ± 0.5	3.1 ± 0.5	0.51
MLD (mm)	0.5 ± 0.4	0.3 ± 0.5	0.04
%DS (%)	85.2 ± 13.6	90.4 ± 11.7	0.03
Lesion length (mm)	16.9 ± 10.1	18.7 ± 10.1	0.34
IVUS measures			
MLA (mm^2)	2.1 ± 0.6	1.8 ± 0.6	0.14
Reference area (mm^2)	14.3 ± 5.1	13.9 ± 4.6	0.57
Calcium arc score	2.8 ± 1.0	1.0 ± 1.1	<0.001

CN = calcified nodule, LAD = left anterior descending artery, LCX = left circumflex, LMT = left main trunk, RCA = right coronary artery, MLD = minimum lumen diameter, %DS = percent diameter stenosis, QCA = quantitative coronary angiography.

Table 3
Univariate and multivariate analysis of predictors for MACE.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.03	1.00–1.05	0.02	1.01	0.98–1.03	0.51
Female	1.18	0.70–2.00	0.53	1.36	0.75–2.47	0.31
DM	1.35	0.91–2.01	0.14	1.27	0.83–1.95	0.27
Smoker	1.18	0.72–1.94	0.50	2.07	1.12–3.83	0.02
eGFR	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001
HTN	1.26	0.74–2.12	0.92	0.78	0.47–1.39	0.40
Statin	0.15	0.01–0.27	<0.001	0.15	0.08–0.30	<0.001
STEMI	0.83	0.52–1.30	0.41	1.05	0.65.-1.70	0.85
MSA	0.84	0.75–0.95	0.005	0.84	0.74–0.96	0.01
Stent eccentricity index	0.02	0.01–0.30	0.004	0.14	0.01–3.38	0.23
CN	7.68	4.61–12.80	<0.001	4.57	2.51–8.62	<0.001

CI = confidential interval, CN = calcified nodule, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HR = hazard ratio, HTN = hypertension, MACE = major adverse cardiac event, MSA = minimal stent area, STEMI=ST-elevation myocardial infarction.

however, while the achieved MSA after PCI was similar between the two groups ($p = 0.31$), a lower stent eccentricity index was observed at culprit lesions with CN ($p < 0.001$).

3.4. Clinical outcomes in ACS subjects with CN

During the observational period [median = 1304 days (interquartile range = 846–1747 days)], all subjects experienced 75 composite outcomes, which included 22 cardiac-deaths, 34 ACS recurrence and 49 TLR (Supplementary Table II). ACS patients attributable to CN were associated with a greater likelihood of experiencing MACE (HR = 7.68, 95%CI = 4.61–12.80, $p < 0.001$), recurrence of ACS (HR = 12.32, 95% CI = 6.05–25.11, $p < 0.001$) and TLR (HR = 10.48, 95%CI = 5.80–18.94, $p < 0.001$), whereas the relationship of CN with cardiac-cause death did not meet statistically significance (HR = 2.76, 95%CI = 0.81–9.36, $p = 0.10$) (Table 3, Supplementary Table III–V and Fig. 1). Even after adjusting for covariates, CN-related ACS was still an

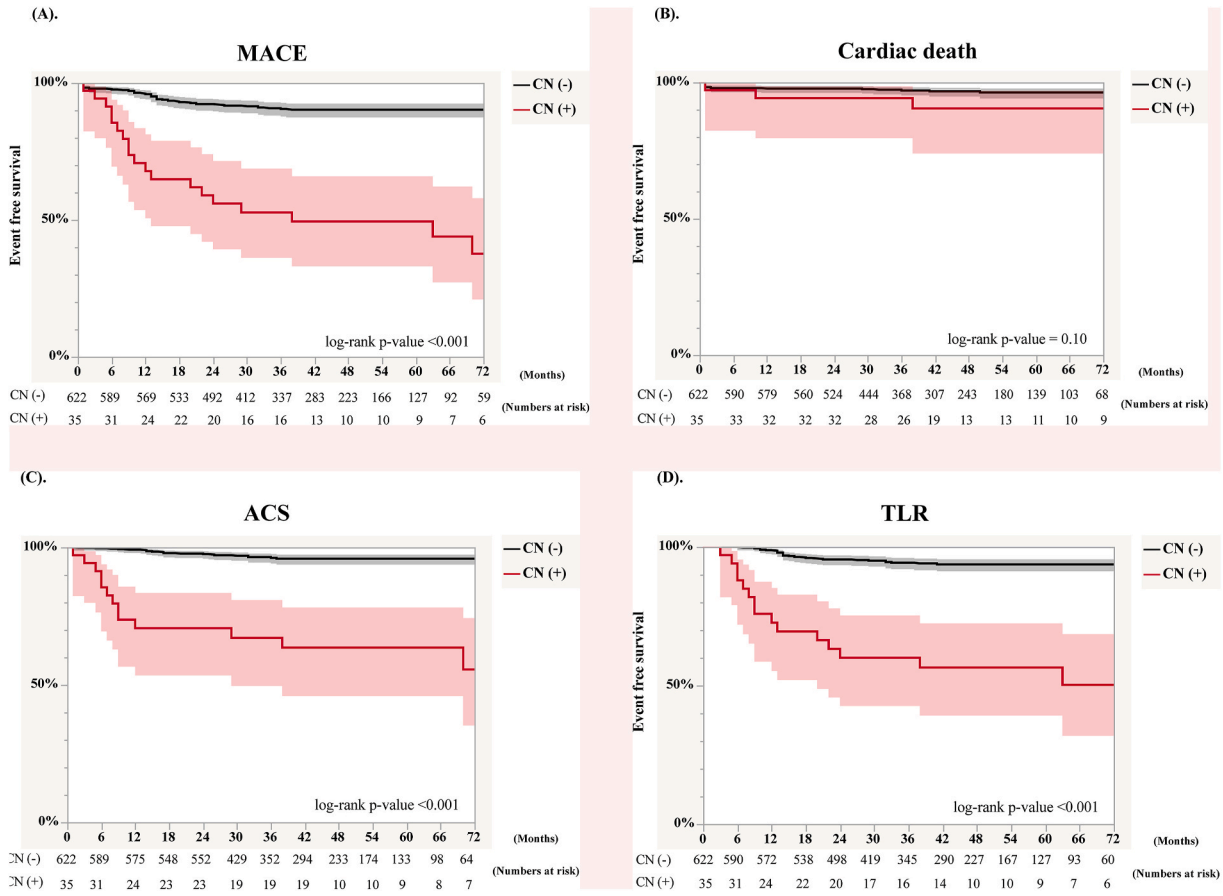

Fig. 1. Comparison of cardiac outcomes between patients with and without CN.
(A) MACE, (B) cardiac death, (C) ACS, (D) TLR. ACS = acute coronary syndrome, CN = calcified nodule, MACE = major adverse cardiac event, TLR = target lesion revascularization.

independent predictor of MACE ($p < 0.001$), recurrence of ACS ($p < 0.001$) and TLR ($p < 0.001$) (Table 3 and Supplementary Tables IV and V). This association was further analyzed using propensity score-matching analysis, which selected 34 patients in each group. In this model, clinical characteristics were well matched between the two groups (Supplementary Table VI). This propensity score-matched analysis demonstrated that ACS attributable to CN predicted MACE ($p = 0.002$), ACS recurrence ($p = 0.01$) and TLR ($p = 0.005$).

3.5. Characteristics of ACS recurrence and TLR in subjects with CN

The current study further investigated clinical characteristics of CN subjects with recurrent ACS and who required TLR, respectively. In all subjects (n = 657), recurrence of ACS occurred in 34 patients (Supplementary Table II). Of these, patients with CN were more likely to experience recurrence of ACS due to ISR at the implanted newer-generation DES ($p < 0.001$) (Supplementary Table II and Supplementary Figure 3A), whereas the frequency of ACS recurrence due to the progression of non-culprit lesion was not significantly elevated in CN-related ACS ($p = 0.32$) (Supplementary Table II and Supplementary Figure 3B).

In 45 patients (47 ISR lesions) requiring TLR with PCI, 45 ISR lesions in 43 subjects were evaluated by IVUS imaging prior to PCI. Compared to ISR at CN lesions, the frequency of neointimal hyperplasia at ISR was significantly higher in non-CN lesions ($p = 0.001$) (Fig. 2). Over 80% of ISR at CN lesion was driven by re-appearance of CN within the implanted newer-generation DES, whereas this feature was not observed at any ISR of non-CN lesions ($p = 0.001$) (Fig. 2).

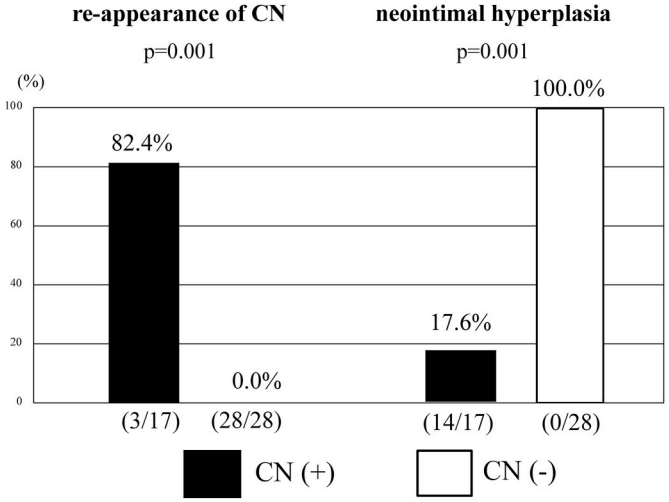

Fig. 2. Comparison of IVUS features at ISR between lesions with and without CN.
CN = calcified nodule, ISR = in-stent restenosis, IVUS = intravascular ultrasound.

4. Discussion

There is a paucity of clinical data about cardiac outcomes in subjects with ACS attributable to CN. In the current study, patients with CN had

an elevated risk of MACE, mainly driven by the recurrence of ACS and the need for TLR. Of note, the re-protrusion of CN into the lumen was a major cause for their unfavourable cardiac outcomes.

We observed a quite low event rate (4%) in ACS subjects without CN at culprit lesions. By contrast, over one third of patients with CN required ACS recurrence and TLR. Interestingly, around 78% of ISR at CN lesions was caused by the formation of a protruding mass with acoustic shadowing rather than neointimal hyperplasia. These findings suggest that CN still continues to protrude even after stent implantation. ISR at CN lesion has been characterized in one pathohistological study, which reported its mechanism as (a) protrusion of CN through the stent struts, and (b) calcification of thrombus or neointima within the implanted stent [12]. According to our observation on IVUS imaging, the former mechanism seems to more likely account for an increased TLR rate. Given that the efficacy of DES is mainly driven by halting neointimal hyperplasia [13], CN lesion may not respond well to newer-generation DES implantation.

During the observational period, ACS more frequently recurred in CN subjects mainly due to ISR. Histologically, rupture of in-stent neo-atherosclerosis with thrombus formation is considered as the main mechanism of ACS related ISR after newer-generation DES implantation [14]. In-stent neo-atherosclerosis is characterized by a large amount of lipid plaque with macrophage filtration, which could be observed as low attenuation plaque on IVUS imaging [14]. However, given the frequent appearance of a protruding mass with acoustic shadow within the stent at CN lesions, this morphological feature could be responsible for a distinctively increased risk of ACS recurrence, because the eruption could not be suppressed by stent placement, and likely cause turbulent flow to promote thrombus formation irrespective of in-stent neo-atherosclerosis.

In line with findings from recent studies, ACS patients with CN had concomitant CKD [15,16]. Since deterioration of kidney function causes abnormal metabolism of calcium and phosphorus, and the secretion of calcification-related proteins and inflammatory cytokines, these CKD-related properties may be an important substrate, which develops CN [17]. We observed that the proximal segment of left circumflex artery was more frequently involved in CN-related ACS. Mechanical stress due to coronary hinge motion through beating may be associated with the development of eruptive CN, and the proximal segment of left circumflex artery is more likely to receive this beating-related influence.

Several caveats should be noted. Firstly, CN was diagnosed according to its definition on IVUS but not OCT. Since a recent study using OCT reported its frequency as 4.2%, IVUS-based definition may over-diagnose CN [18]. Secondly, this study was a single-center retrospective observational study, and the number of CN patients was relatively small. Thirdly, the type of stent and adjunctive devices was selected according at the operator's discretion, which was susceptible to selection bias.

In conclusion, ACS attributable to CN was associated with worse cardiac outcomes, mainly driven by its recurrence and a higher TLR rate. IVUS imaging analysis revealed a continuous growth of CN into the lumen as a major contributor to its poor clinical course. Futures studies should focus on additional therapeutic approaches to modulate the dynamic nature of CN in ACS subjects.

CRediT authorship contribution statement

Hiroki Sugane: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. **Yu Kataoka:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision. **Fumiyuki Otsuka:** Writing - review & editing. **Yuriko Nakaoku:** Formal analysis, Writing - review & editing. **Kunihiro Nishimura:** Formal analysis, Writing - review & editing. **Hiroki Nakano:** Writing - review & editing. **Kota Murai:** Writing - review & editing. **Satoshi Honda:** Writing - review & editing. **Hayato Hosoda:** Writing - review & editing. **Hideo Matama:** Writing - review & editing. **Takahito Doi:** Writing - review & editing. **Takahiro Nakashima:** Writing - review & editing. **Masashi Fujino:** Writing - review & editing. **Kazuhiro Nakao:** Writing - review & editing. **Shuichi Yoneda:** Writing - review & editing. **Yoshio Tahara:** Writing - review & editing. **Yasuhide Asaumi:** Writing - review & editing. **Teruo Noguchi:** Writing - review & editing. **Kazuya Kawai:** Writing - review & editing. **Satoshi Yasuda:** Writing - review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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