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Incidence, factors, and clinical significance of cholesterol crystals in coronary plaque: An optical coherence tomography study

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HIGHLIGHTS

- The incidence of cholesterol crystals in culprit lesions requiring PCI was 29%.
- Lower EPA/AA was associated with the presence of cholesterol crystals.
- The presence of cholesterol crystals was associated with worse clinical outcomes.

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ABSTRACT

Background and aims: Intraplaque cholesterol crystal (CC) is recognized as a component of vulnerable plaques. However, the clinical characteristics of patients with CC and the impact of CC on clinical events remain unknown.

Methods: A total of 340 consecutive patients who underwent optical coherence tomography (OCT) imaging of culprit lesions were included in the study. CC was defined as a thin linear structure with high reflectivity and low signal attenuation on OCT images. The incidence of major adverse cardiovascular events (MACE) at 1-year was compared between patients with CC (CC group) and those without CC (non-CC group). MACE included cardiac death, non-fatal myocardial infarction, target vessel revascularization (TVR), and non-TVR (NTVR).

Results: CC was observed in 29% (n = 98) of the patients. There was no significant difference in baseline clinical characteristics between the CC and non-CC groups, other than in eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio (0.39 ± 0.29 *vs.* 0.47 ± 0.33, $p = 0.047$) and hemoglobin A1c (HbA1c) levels (6.51 ± 0.97 *vs.* 6.25 ± 0.87%, $p = 0.016$). The incidence of MACE and NTVR at 1-year was significantly higher in the CC group than in the non-CC group (15.3 *vs.* 7.9%, P = 0.038; 8.1 *vs.* 2.5%, $p = 0.017$). The presence of CC was significantly associated with a higher rate of 1-year MACE (odds ratio 4.78, confidential interval 2.02–10.10, $p < 0.001$).

Conclusions: Patients with CC in the culprit lesion had higher HbA1c and lower EPA/AA than patients without CC. The 1-year clinical outcomes in patients with CC in the culprit lesion were worse than in those without CC.

1. Introduction

Previous pathological studies and intracoronary imaging studies have clarified the impact of various plaque characteristics and components on the onset of acute coronary syndrome (ACS) and clinical outcomes. The presence of lipid-rich plaque (LRP) and thin-cap fibroatheroma (TCFA) has been demonstrated to predispose patients to plaque rupture and subsequent clinical events [1,2]. Intraplaque microstructures including macrophage accumulation [3], spotty calcification, and microchannels [4] are also reported to have important roles in the development of coronary plaque and degradation of the overlying fibrous cap. Cholesterol crystal (CC) is also an intraplaque microstructure that may accelerate plaque progression through the activation of local and systemic inflammation, and may perforate the fibrous cap owing to its sharp-tipped shape and/or through destabilization of local physical stress [5]. CCs are observed as thin, linear, sharp-bordered regions with high intensity on optical coherence tomography (OCT) images [6]. Recent OCT studies reported that CC is

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frequently observed in patients with ACS, particularly in cases of ST-segment elevation myocardial infarction (STEMI) caused by plaque rupture [7]. Thus, CC may have an important role for the development of LRP and the onset of subsequent clinical events. However, the generating factors, clinical characteristics, and impact on clinical course had not been fully evaluated thus far. The aims of this study were (1) to evaluate the incidence of CC in culprit lesions detected with OCT, (2) to explore the factors for the presence of CC, and (3) to assess the impact of CC on clinical outcomes.

2. Patients and methods

2.1. Study population

Among 928 culprit lesions in 928 patients (204 patients with ACS and 724 patients with stable angina or asymptomatic myocardial ischemia) who underwent percutaneous coronary intervention (PCI) between February 2013 and November 2016 at Kitasato University Hospital (Sagamihara, Japan), a total of 382 culprit lesions in 382 patients imaged using OCT were identified. A total of 340 *de novo* lesions in 340 patients were enrolled in the present study after excluding cases of restenosis (n = 29) and poor OCT images of culprit lesions (n = 13) (Supplementary Fig. 1). All devices during PCI as well as the imaging modality (OCT/intra vascular ultra sound [IVUS]) and stent type were selected according to the physician's discretion (Supplementary methods). Complete 1-year follow-up data were available for 306 patients (90.0%). All patients provided written informed consent for the procedure, and this study was conducted in compliance with the Declaration of Helsinki and approved by the institutional ethical committee.

2.2. Definition

The culprit lesion was defined as a lesion treated by PCI. If multiple lesions were treated in one PCI session, a lesion with more severe ischemia demonstrated by scintigram or physiological findings was retrospectively defined as the culprit lesion and included in the analysis. In patients with stable angina or asymptomatic myocardial ischemia, the presence of ischemia was determined by scintigram, physiology (e.g. fractional flow reserve) or the combination of typical angina and angiographical severe stenosis. Patients with multivessel disease was defined as those who had more than one diseased vessel. Diseased vessel was defined on the basis of a history of stenting or the presence of angiographical stenosis (≥75% diameter stenosis) irrespective of the presence of ischemia.

2.3. OCT image acquisition and analysis

OCT images of culprit vessels were acquired before stent implantation after intracoronary administration of 100–200 μg nitroglycerin, by using frequency-domain OCT (ILUMIEN OCT Intravascular Imaging Systems; Abbott, Santa Clara, CA, USA). If antegrade coronary flow was insufficient to enable OCT imaging, thrombectomy was performed at the operator's discretion. All images were analyzed using offline proprietary software at the cardiovascular laboratory in Kitasato University School of Medicine. The images were qualitatively and quantitatively analyzed at 0.2-mm intervals. Plaque morphologies were evaluated using previously validated criteria [6] (Supplementary methods). CCs were defined as thin, linear regions of high intensity within the target lesion (see Fig. 1). Analysis was conducted by 2 independent investigators who were blinded to the patients' clinical information. When there was discordance between the investigators, a consensus reading was obtained from a 3rd independent investigator. The intraobserver and interobserver reproducibility values of the CC identification were good (intraclass correlation coefficients were 0.929 and 0.897, respectively).

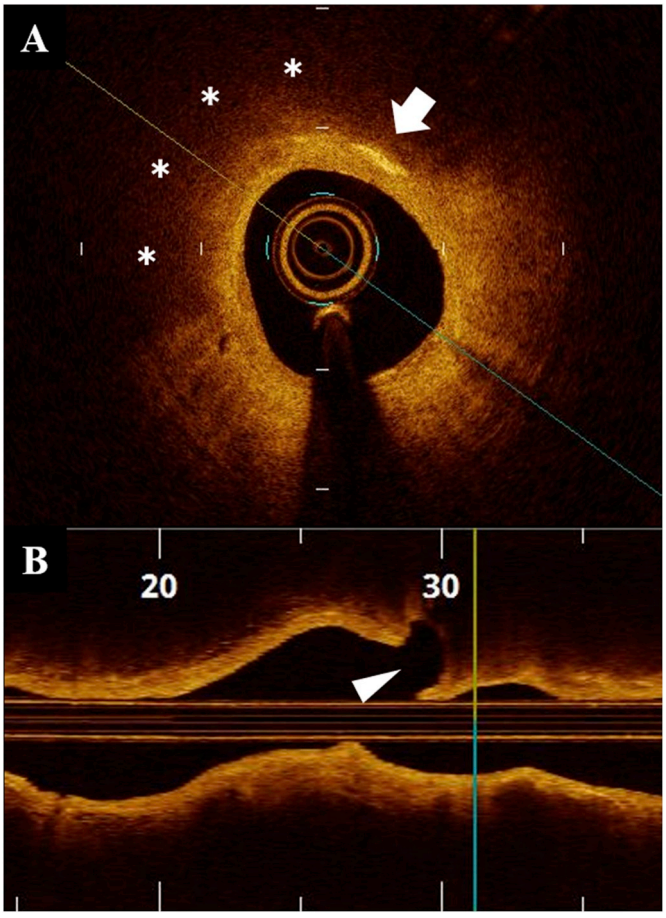


Fig. 1. Representative optical coherence tomography (OCT) image of cholesterol crystal.
(A) Cross-sectional OCT image showing a cholesterol crystal (arrow) as a thin, linear region of high intensity within the culprit lesion. Asterisks represent lipid accumulation. (B) Longitudinal reconstructed OCT image of the culprit lesion. A ruptured cavity (arrowhead) is observed at the distal portion of the cross-section (yellow/blue bar) with cholesterol crystal.

2.4. Study endpoint

The primary outcome measures were major adverse cardiac events (MACE), defined as a composite of cardiac death, acute myocardial infarction defined as STEMI and NSTEMI by the American College of Cardiology/American Heart Association guidelines [8], and ischemia-driven revascularization. Peri-procedural myocardial infarction was not included in the primay outcome measures (Supplementary methods). Ischemia-driven revascularization was defined as an unplanned repeat PCI or bypass surgery of the lesions with either AMI, unstable angina, stable angina, or documented silent ischemia. On the basis of angiographic findings, revascularization was further categorized as target lesion (previous PCI site) revascularization (TLR), target vessel (previous PCI vessel) revascularization (TVR), and non-TVR (NTVR) (previously untreated segment in any 1 of 3 coronary arteries), whichever occurred first in the patient. More than 1 event recorded in the same patient at the same time point was considered 1 composite cardiac event in statistical analysis. The primary outcome measures were compared between patients with and without CC in both an unadjusted cohort and an adjusted cohort with propensity score-matching analysis.

2.5. Statistical analysis

Continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test for comparisons among independent groups, according

Table 1
Baseline clinical characteristics.

Variables	CC n = 98	Non-CC n = 242	*p* value
Age, year	70.0 ± 8.9	68.2 ± 10.2	0.118
Male, n (%)	87 (89)	215 (89)	0.986
BMI, kg/m^2	23.6 ± 3.2	24.1 ± 3.6	0.192
Clinical presentation			
Stable angina/ACS, n (%)	87/11 (89/11)	207/35 (86/14)	0.429
Culprit vessel, n (%)			0.990
LAD	55 (56)	134 (55)	
LCX	21 (21)	53 (22)	
RCA	20 (20)	54 (22)	
LMT	2 (2)	5 (2)	
Risk factors, n (%)			
Hypertension	90 (92)	211 (87)	0.223
Dyslipidemia	87 (89)	202 (83)	0.215
Diabetes mellitus	29 (30)	58 (24)	0.282
Current smoker	8 (8)	19 (8)	0.923
Family history of IHD	21 (21)	32 (13)	0.059
CKD (eGFR < 60)	23 (23)	76 (31)	0.145
Multivessel disease, n (%)	70 (71)	169 (70)	0.770
Echo LVEF, %	55.6 ± 10.5	57.7 ± 10.2	0.090
Medication, n (%)			
ARB/ACEI	87 (89)	211 (87)	0.687
Beta-blocker	28 (29)	78 (32)	0.509
CCB	17 (17)	58 (24)	0.182
Statin	90 (92)	215 (89)	0.411
Aspirin	89 (91)	225 (93)	0.498
Thienopyridine	84 (86)	212 (88)	0.638
Ethyl icosapentate	4 (4)	18 (7)	0.255
Laboratory findings			
HbA1c, %	6.51 ± 0.97	6.25 ± 0.87	0.016
LDL-C, mg/dl	97.4 ± 26.8	94.1 ± 29.5	0.335
HDL-C, mg/dl	51.1 ± 13.4	52.3 ± 14.5	0.344
eGFR, ml/min/1.73 m^2	60.8 ± 17.1	56.7 ± 22.0	0.100
BNP, pg/dl	101.0 (162.3–69.9)	97.1 (61.9–150.6)	0.376
EPA, mg/dl	65.7 ± 42.4	77.7 ± 50.6	0.051
AA, mg/dl	187.9 ± 61.3	178.3 ± 50.3	0.164
EPA/AA	0.39 ± 0.29	0.47 ± 0.33	0.047

AA, arachidonic acid; ACE-I, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CC, cholesterol crystal; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; IHD, ischemic heart disease; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LMT, left main trunk artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery.

to the data distribution. Categorical variables were reported as counts (%) and compared using Fisher's exact test or the chi-square test, according to the data distribution. The mean ± standard deviation was reported for normally distributed data. The composite cardiac event-free data during the entire 1-year follow-up were presented as Kaplan-Meier estimates. Logistic regression models with multiple predictor variables of OCT plaque morphologies were used to determine independent predictors for 1-year MACE. Propensity score-matching analysis was further performed to control selection bias for the incidence of MACE, using the nearest neighbor one-to-one pair matching based on clinical factors which might affect the incidence of MACE (Supplementary methods). Statistical significance was defined as a p value of < 0.05. Statistical analyses were performed using JMP version 9.0 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Clinical characteristics

CC was detected in 98 of 340 lesions (29%). The baseline clinical characteristics are shown in Table 1 and Supplementary Table 1. The percentage of ACS was comparable between the CC group (11%) and the non-CC group (14%). The prevalence of conventional risk factors for atherosclerosis was similar between the 2 groups. The hemoglobin A1c (HbA1c) level was significantly higher in the CC group than in the non-CC group (6.51 ± 0.97 *vs.* 6.25 ± 0.87%, $p = 0.016$), although the low-density lipoprotein cholesterol (LDL-C) value was comparable between the 2 groups. The eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio was significantly lower in the CC group than in the non-CC group (0.39 ± 0.29 *vs.* 0.47 ± 0.33, $p = 0.047$). The incidence of peri-procedural myocardial infarction was comparable between the 2 groups (7 *vs.* 8%, $p = 0.729$).

Table 2
OCT findings of culprit lesion morphologies.

Variables	CC n = 98	Non-CC n = 242	*p* value
Qualitative assessment			
Lipid-rich plaque, n (%)	46 (47)	50 (21)	< 0.001
TCFA, n (%)	24 (24)	13 (5)	< 0.001
Macrophage, n (%)	49 (50)	44 (18)	< 0.001
Micro channel, n (%)	53 (54)	51 (21)	< 0.001
Calcification, n (%)	69 (70)	203 (84)	0.005
Spotty calcification, n (%)	80 (82)	213 (88)	0.122
Thrombus, n (%)	4 (4)	2 (1)	0.039
Quantitative assessment			
Max lipid arc, °	279.2 ± 69.0	220.4 ± 53.7	< 0.001
Thinnest FCT, μm	75.1 ± 41.4	87.0 ± 51.8	0.329
Reference vessel area, mm^2	7.85 ± 3.49	7.83 ± 3.32	0.967
Reference vessel diameter, mm	3.02 ± 0.74	3.06 ± 0.64	0.535
Minimal lumen area, mm^2	1.46 ± 0.82	1.58 ± 1.05	0.326
Minimal lumen diameter, mm	1.32 ± 0.35	1.35 ± 0.41	0.552
Percent area stenosis, %	76.1 ± 10.4	75.0 ± 13.2	0.458
Percent diameter stenosis, %	54.2 ± 14.9	55.4 ± 13.3	0.498
Lesion length, mm	29.3 ± 13.2	25.6 ± 12.9	0.017
Characteristics of CC			
Number of CC	1 (1–1)		
Multiple CC, n (%)	22 (22)	-	-
Maximum area, mm^2	0.03 ± 0.14	-	-
Maximum volume, mm^3	0.01 ± 0.01	-	-
Distance from lumen surface, mm	0.17 ± 0.10	-	-

FCT, fibrous cap thickness; TCFA, thin-cap fibroatheroma.

3.2. Lesion characteristics on OCT

The results of OCT analyses of culprit plaques are shown in Table 2. The incidence of lipid plaque was significantly higher in the CC group than in the non-CC group (47 *vs.* 21%, $p < 0.001$). Other vulnerable plaque characteristics, including the presence of TCFA, macrophage, microchannel, and thrombus, were more frequently observed in the CC group than in the non-CC group. The maximum lipid arc and lesion length were significantly larger in the CC group than in the non-CC group.

3.3. Clinical and OCT factors for CC

A receiver operating characteristic curve was constructed to assess the ability of clinical and OCT parameters to detect CC (Supplementary Fig. 2). The area under curve for detecting CC was 0.58, 0.56, 0.59, and 0.71 for EPA/AA ($p = 0.047$), HbA1c ($p = 0.034$), lesion length ($p = 0.016$), and maximum lipid arc ($p = 0.002$), respectively. The best cutoff was 0.21, 7.30, 32.4, and 257, respectively.

3.4. Clinical events at 1 year in patients with CC

The incidence of clinical events at 1-year is shown in Fig. 2, Supplementary Table 2, and Supplementary Fig. 3. The overall rate of MACE at 1-year was 10%. The incidence of MACE was significantly higher in the CC group than in the non-CC group in both an unadjusted cohort (15.3 *vs.* 7.9%, $p = 0.038$) and an adjusted cohort (13.7 *vs.*

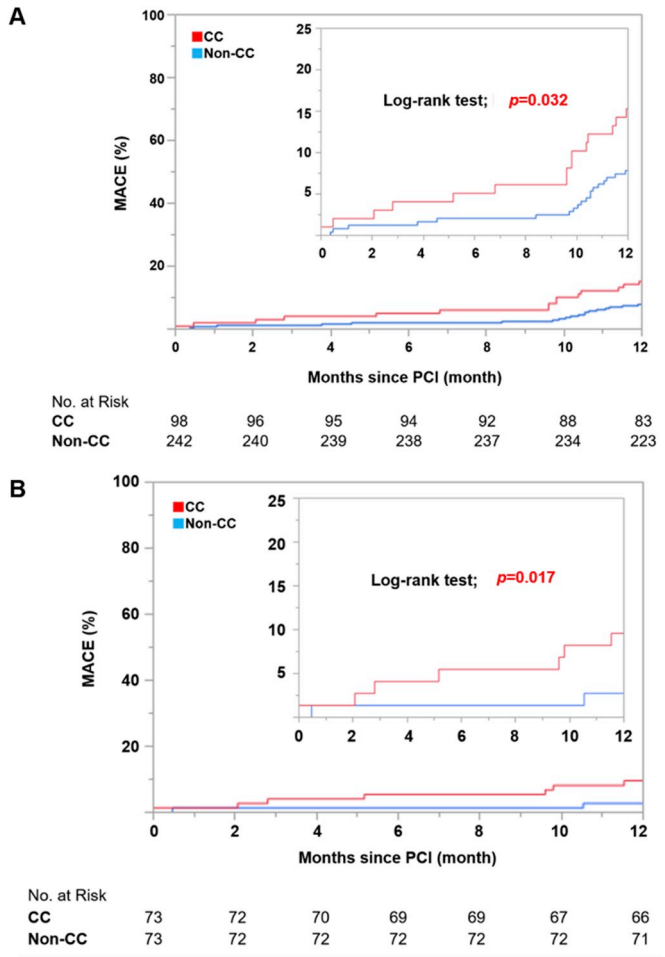


Fig. 2. Incidence of MACE according to the presence of cholesterol crystal. (A) Unadjusted cohort; (B) adjusted cohort. CC: cholesterol crystal, MACE: major adverse cardiac events.

2.7%, $p = 0.016$). The incidence of NTVR was also significantly higher in the CC group than in the non-CC group in an unadjusted cohort (8.1 *vs.* 2.5%, $p = 0.017$), although the difference was statistically marginal in an adjusted cohort (8.2 *vs.* 1.4, $p = 0.052$). The incidence of MACE according to the presence of plaque components including CC is shown in Fig. 3. A significant hazard ratio (HR) was observed in the presence of CC for the incidence of MACE. The combination of CC and TCFA had a greater HR than that of TCFA. The baseline clinical characteristics in the adjusted cohort is shown in Supplementary Table 3.

3.5. OCT predictors for MACE at 1-year

Multivariate models with micro structures in culprit plaque showed that the presence of CC was not independently associated with the incidence of 1-year MACE and NTVR although the presence of TCFA was demonstrated as an independent factor (Supplementary Table 4). The univariate model including baseline clinical characteristics for the incidence of 1-year MACE is shown in Supplementary Table 5. The univariate model including culprit plaque morphologies for the incidence of 1-year MACE is shown in Supplementary Table 6. Comparisons of baseline clinical characteristics and culprit plaque morphologies between cases with and without MACE are shown in Supplementary Tables 7 and 8

4. Discussion

The main findings of this study were as follows: (1) the incidence of CC in culprit lesions requiring PCI was 29%; (2) lower EPA/AA and higher HbA1c values were associated with the presence of CC; (3) the presence of CC was associated with a higher prevalence of vulnerable characteristics in coronary plaques; and (4) patients with CC in the culprit lesion had worse 1-year clinical outcomes than those without CC.

4.1. Incidence and factors of CC in previous studies

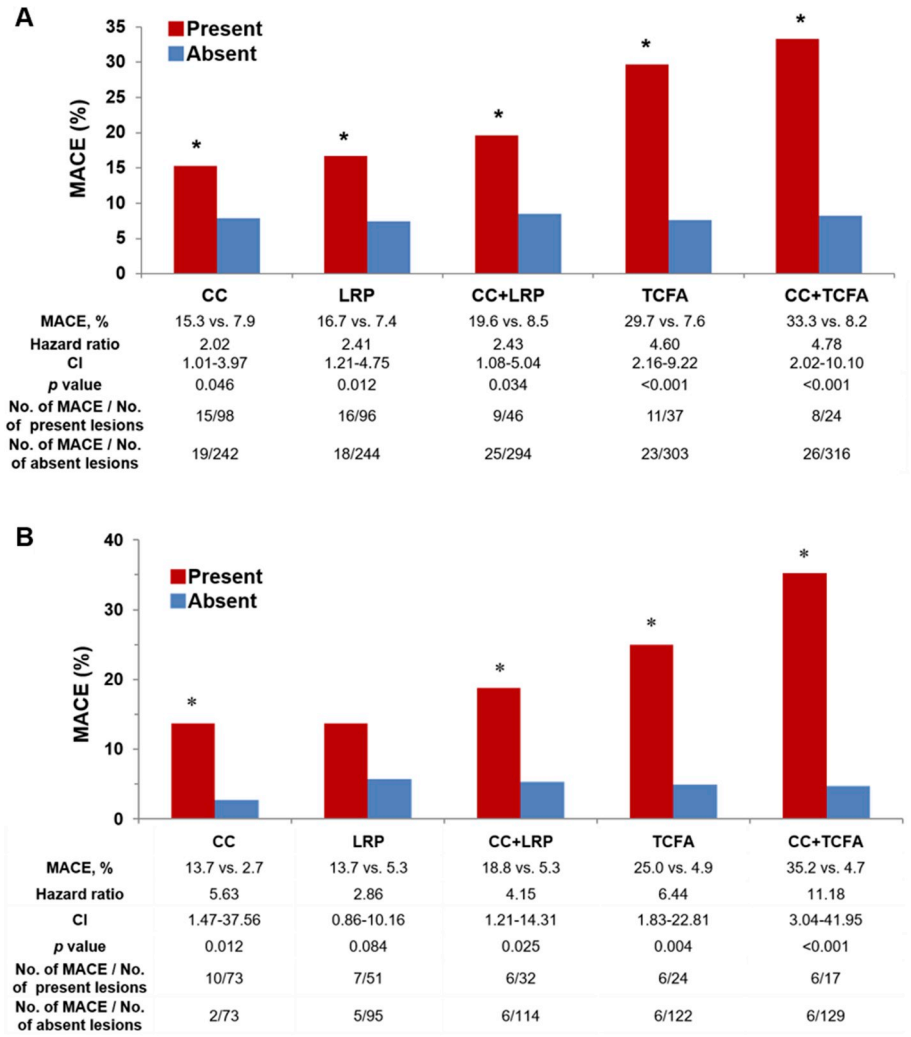
Several previous clinical studies using OCT have reported the incidence of CC. Xing et al. [1] and Hou et al. [9] reported an incidence of 17–24% in non-culprit plaques. In culprit plaques in patients with ACS, the incidence was reported to be 35–40% [7,10]. Tian et al. reported that the incidence was 40% in lesions with significant stenosis and TCFA [11]. Thus, the incidence of CC seems to be in line with worse clinical presentation and focal plaque vulnerability [12], as shown by the present study. A few studies have reported the incidence of CC according to baseline clinical characteristics. Kato et al. reported that the incidence of CC in non-culprit plaques was significantly higher in patients with chronic kidney disease (CKD) (23%) than in those without CKD (11%, $p = 0.048$) [13]. Kataoka et al. demonstrated a higher incidence of CC in non-culprit plaques in male patients than in female patients [10]. On the other hand, the incidence of CC was not different between patients with and without diabetes [14], or among patients with different smoking status [15]. In these reports, the authors did not only focus on the incidence of CC but also compared the incidence of plaque components including CC among groups. Thus, the precise impact of those clinical factors on the incidence of CC had not been determined from those previous studies.

4.2. Pathogenesis of CC

Cholesterol crystallization was considered the result of accumulation of free cholesterol in macrophages and disruption in cholesterol homeostasis through the imbalance of esterification and de-esterification. Overloaded esterified cholesterol and crystals are released from dying foam cells into the extracellular space and then identified as CC in coronary plaque [16]. In the present study, we found a significant association of lower EPA/AA with the presence of CC, although LDL-C or high-density lipoprotein cholesterol values did not show an association. EPA is an n-3 polyunsaturated fatty acid (PUFA) derived from fish or fish oil, and is known as a suppressor of atherosclerosis through the reduction of inflammatory cytokines and macrophage activities [17,18]. Previous studies demonstrated that EPA increases the mRNA expression of acyl-coenzyme A cholesterol acyltransferase 1 (ACAT1) by binding with peroxisome proliferator activated receptor alpha [19,20]. Thus, a lower EPA level is considered to accelerate CC formation in addition to inducing atherosclerosis progression through the inactivation of ACAT1, which converts free cholesterol into the esterified state. On the contrary, AA is an n-6 PUFA and known to contribute to the progression of atherosclerosis through the production of inflammatory cytokines and activation of macrophage function. The combined evaluation of serum EPA and AA was reported as an indicator of risk stratification of atherosclerotic disease, and a lower EPA/AA was considered a “residual risk” and associated with a higher incidence of cardiovascular events [21,22]. In addition, a higher frequency of vulnerable coronary plaques in patients with lower EPA/AA was demonstrated in studies using OCT [23,24]. Taking these findings together, lower EPA/AA is considered to activate CC generation in atherosclerotic plaques and to further deteriorate the plaque integrity, leading to clinical events.

4.3. CC and clinical event

In the present study, a higher incidence of MACE at 1-year was observed in patients with CC in the culprit lesion than in those without CC. In particular, the incidence of NTVR was significantly higher in patients with CC than in those without CC. This indicates the potential of the



	CC	LRP	CC+LRP	TCFA	CC+TCFA
MACE, %	15.3 vs. 7.9	16.7 vs. 7.4	19.6 vs. 8.5	29.7 vs. 7.6	33.3 vs. 8.2
Hazard ratio	2.02	2.41	2.43	4.60	4.78
CI	1.01-3.97	1.21-4.75	1.08-5.04	2.16-9.22	2.02-10.10
p value	0.046	0.012	0.034	<0.001	<0.001
No. of MACE / No. of present lesions	15/98	16/96	9/46	11/37	8/24
No. of MACE / No. of absent lesions	19/242	18/244	25/294	23/303	26/316

	CC	LRP	CC+LRP	TCFA	CC+TCFA
MACE, %	13.7 vs. 2.7	13.7 vs. 5.3	18.8 vs. 5.3	25.0 vs. 4.9	35.2 vs. 4.7
Hazard ratio	5.63	2.86	4.15	6.44	11.18
CI	1.47-37.56	0.86-10.16	1.21-14.31	1.83-22.81	3.04-41.95
p value	0.012	0.084	0.025	0.004	<0.001
No. of MACE / No. of present lesions	10/73	7/51	6/32	6/24	6/17
No. of MACE / No. of absent lesions	2/73	5/95	6/114	6/122	6/129

Fig. 3. Incidence of MACE according to the presence of plaque components.
Unadjusted cohort; (B) adjusted cohort. CI: confidence interval, CC: cholesterol crystal, LRP: lipid-rich plaque, MACE: major adverse cardiac events, TCFA: thin-cap fibroatheroma.

presence of CC within the culprit lesion as a maker of future clinical events related to non-culprit vessels. In fact, the presence of CC had a similar HR to LRP, which is a known indicator of future cardiovascular events [1]. In addition, the combination of CC and LRP or TCFA had a higher HR than either CC, LRP, or TCFA for the incidence of MACE. Although the exact causal relationship between the presence of CC in the culprit lesion and the clinical event in the non-culprit lesion is still unclear, the simultaneous presence or the development of vulnerable plaques in non-culprit vessels might cause future clinical events. A previous study demonstrated that culprit plaques with CC had more vulnerable features, including a larger lipid arc, macrophages, and microchannel, than plaques without CC [7], which is consistent with our results. In addition, multiple studies demonstrated that the vulnerability of non-culprit plaque is in line with the vulnerability of culprit plaque in the same patients [25,26]. Thus, patients with CC in the culprit plaque may have a higher chance of having a vulnerable plaque in a non-culprit vessel than patients without CC in the culprit plaque.

4.4. CC as a marker for risk stratification

Risk stratification for secondary events according to the presence of CC in the culprit lesion may be more practical in daily clinical practice than using LRP or TCFA. This is because CC is easy to detect owing to its simple appearance on OCT images, whereas the identification of LRP or TCFA needs quantitative assessment in addition to expertise in OCT image interpretation. Thus far, the association between the morphological change of CC and pharmacological therapy or laboratory findings including cholesterol profile or EPA/AA had not been investigated. Thus, it may be a target of a future study to further clarify the clinical significance of CC on OCT images.

4.5. Limitations

Several limitations need to be mentioned. First, this is a retrospective and observational study conducted at a single center with a limited number of patients. Second, the present study exclusively included patients treated by PCI. The impact of CC on clinical events in patients with bypass grafting or pharmacological therapy remains undetermined. Third, the use of OCT during PCI was determined by physician's discretion. This may cause selection bias. Fourth, a small number of patients with ACS were enrolled in the present study, which may cause selection bias. Further studies with a larger number of patients with ACS may yield different results. Fifth, the non-culprit vessel was not observed using OCT because this is a retrospective study of OCT images obtained at the time of PCI for culprit lesions. Evaluation of CC in non-culprit plaques may clarify the further impact on future events. Finally, this was a pure OCT study without analysis of IVUS findings. The interrelationship between the presence of CC and IVUS findings

including plaque volume or remodeling index may be a future research target.

4.6. Conclusions

The incidence of CC in the culprit lesion requiring PCI was 29%. Patients with CC had higher HbA1c and lower EPA/AA values than patients without CC. The 1-year clinical outcomes in patients with CC were worse than in those without CC. Further studies are needed to clarify the independent association between the presence of CC and clinical outcomes.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

KF: Collecting data, analysis, manuscript writing, YM: Corresponding author, conceiving the project, manuscript writing, KI, AK, AK, YM, TS, RK, TN, TH, NS: Collecting data, KM, TS, TT: Critical revision of the manuscript, JA: Final approval of manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.02.009.

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