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ORIGINAL RESEARCH

Seasonal Variations in the Pathogenesis of Acute Coronary Syndromes

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BACKGROUND: Seasonal variations in acute coronary syndromes (ACS) have been reported, with incidence and mortality peaking in the winter. However, the underlying pathophysiology for these variations remain speculative.

METHODS AND RESULTS: Patients with ACS who underwent optical coherence tomography were recruited from 6 countries. The prevalence of the 3 most common pathologies (plaque rupture, plaque erosion, and calcified plaque) were compared between the 4 seasons. In 1113 patients with ACS (885 male; mean age, 65.8±11.6 years), the rates of plaque rupture, plaque erosion, and calcified plaque were 50%, 39%, and 11% in spring; 44%, 43%, and 13% in summer; 49%, 39%, and 12% in autumn; and 57%, 30%, and 13% in winter (P=0.039). After adjusting for age, sex, and other coronary risk factors, winter was significantly associated with increased risk of plaque rupture (odds ratio [OR], 1.652; 95% CI, 1.157–2.359; P=0.006) and decreased risk of plaque erosion (OR, 0.623; 95% CI, 0.429–0.905; P=0.013), compared with summer as a reference. Among patients with rupture, the prevalence of hypertension was significantly higher in winter (P=0.010), whereas no significant difference was observed in the other 2 groups.

CONCLUSIONS: Seasonal variations in the incidence of ACS reflect differences in the underlying pathobiology. The proportion of plaque rupture is highest in winter, whereas that of plaque erosion is highest in summer. A different approach may be needed for the prevention and treatment of ACS depending on the season of its occurrence.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03479723.

Key Words: optical coherence tomography ■ plaque erosion ■ plaque rupture ■ season

Although the exact trigger of acute coronary syndromes (ACS) may not always be readily apparent, seasonal variations in their incidence have been known for decades.[1] Many studies have reported higher incidence and mortality in winter.[2,3] Heat also has been associated with an increased risk of ACS.[4] These seasonal variations may result from the complex interactions between environmental factors and susceptibility to coronary thrombus formation in each individual patient. There are many environmental factors that affect the risk of ACS such as low atmospheric air pressure, high wind velocity, and shorter sunshine duration; nevertheless, the most evident association for the risk of ACS was observed for air temperature.[5]

ACS are the leading cause of mortality worldwide and are usually precipitated by coronary thrombosis, leading to a sudden reduction in blood flow.[6] The 3 most common underlying mechanisms for ACS are

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CLINICAL PERSPECTIVE

What Is New?

- The underlying mechanism of acute coronary syndromes varies with the time of year.
- The proportion of plaque rupture is highest in winter.
- The proportion of plaque erosion is highest in summer.

What Are the Clinical Implications?

- A different approach may be needed for the prevention and treatment of acute coronary syndromes depending on the season of its occurrence.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndromes
OCT	optical coherence tomography
OR	odds ratio
STEMI	ST-segment–elevation myocardial infarction

plaque rupture, plaque erosion, and calcified nodule.[7] Recently, optical coherence tomography (OCT), which is an intracoronary imaging modality with high resolution, has enabled detailed characterization of coronary plaques including the diagnosis of these 3 pathologies.[8] In this study, we sought to compare the pathobiology of the culprit lesions assessed by OCT between the 4 seasons.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The study population was selected from the multicenter international registry "Identification of Predictors for Coronary Plaque Erosion in Patients With Acute Coronary Syndrome Study" (http://www.clinicaltrials.gov; NCT03479723). Patients presenting with ACS who underwent OCT imaging of the culprit lesion were eligible. Among 1699 patients, 586 patients were excluded and 1113 cases were included in the final analysis (Figure S1). Although the study cohort consists of patients from 6 countries, the majority of patients (75.6%) were from Japan (Table S1). The study period at each institution and the number of cases per year are shown in Figures S2 and S3. The diagnosis of ACS, which included ST-segment–elevation myocardial infarction (STEMI) and non-ST-segment–elevation ACS, was made according to the current American Heart Association/American College of Cardiology guidelines.[9,10] STEMI was defined as continuous chest pain that lasted >30 minutes, arrival at the hospital within 12 hours from the onset of symptoms, ST-segment elevation >0.1 mV in ≥2 contiguous leads or new left bundle branch block on the 12-lead ECG, and elevated cardiac markers (creatine kinase myocardial band or troponin T/I). Non–ST-segment–elevation ACS included non–ST-segment–elevation myocardial infarction (NSTEMI) and unstable angina pectoris. NSTEMI was defined as ischemic symptoms in the absence of ST-segment elevation on ECG with elevated cardiac markers. Unstable angina pectoris was defined as having newly developed or accelerating chest symptoms on exertion or rest angina within 2 weeks. The culprit lesion was determined based on angiographic findings, ECG changes, and/or left ventricular wall motion abnormalities. Demographic and OCT findings of the culprit lesions were evaluated. All images were deidentified, digitally stored, and sent to Massachusetts General Hospital (Boston, MA). The protocol was approved by the institutional review board at each site, and written informed consent was obtained from all patients before enrollment.

OCT Image Acquisition and Analysis

OCT examination was performed in consecutive ACS patients undergoing catheterization using either a frequency-domain (C7/C8 OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN) or time-domain (M2/M3 Cardiology Imaging Systems, Light Lab Imaging Inc., Westford, MA) OCT system. All OCT images were submitted to the Cardiology Laboratory for Integrative Physiology and Imaging at Massachusetts General Hospital and analyzed by 2 independent investigators who were blinded to clinical, angiographic, and laboratory data using an offline review workstation (St. Jude Medical). Any discordance was resolved by consensus with a third reviewer. The method of OCT analysis has previously been described in detail[8] and is summarized in Data S1. Underlying plaques were categorized into 3 groups using the previously established criteria: plaque rupture, plaque erosion, or calcified plaque (Figure 1). The intraobserver κ coefficients for plaque rupture, plaque erosion, and calcified plaque were 0.902, 0.922, and 0.934, respectively. The interobserver κ coefficients for plaque rupture, plaque erosion, and calcified plaque were 0.878, 0.895, and 0.935, respectively.

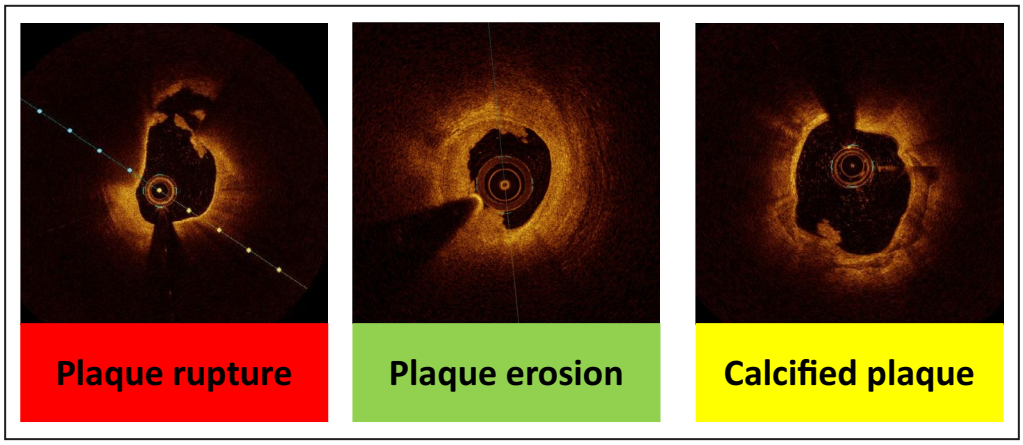

Figure 1. Optical coherence tomography images of 3 plaque pathologies.
Plaque rupture was defined by the presence of fibrous cap discontinuity with a communication between the lumen and the inner core of a plaque or with a cavity formation within the plaque. Plaque erosion was defined as a culprit plaque with an intact fibrous cap with or without attached thrombus. Calcified plaque was defined by the presence of superficial substantive calcium at the culprit site without evidence of ruptured lipid plaque.

Definition

For the purposes of this study, the date of OCT procedure was used to define the season. The seasons were defined as follows: spring, March to May; summer, June to August; autumn, September to November; winter, December to February. Climate records for each case were obtained from the closest meteorological stations at each country's official sources (http://www.jma.go.jp/jma/, https://www.ecad.eu/, https://data.kma.go.kr/cmmn/main.do, https://www.weather.gov.hk/contente.htm, https://www.ncdc.noaa.gov/). We evaluated the maximum and minimum temperature in Celsius recorded during the day of OCT procedure. The definitions of coronary risk factors, including hypertension, hyperlipidemia, diabetes mellitus, and chronic kidney disease are summarized in Data S1.

Statistical Analysis

Categorical variables are presented as frequencies, and these were compared using the chi-square test. Continuous variables were expressed as mean±SD, and these were compared using the Student *t* test or 1-way analysis of variance as appropriate. Logistic regression models were used to estimate odds ratio and 95% CIs for plaque rupture, plaque erosion, and calcified plaque. These modeling analyses were performed between the 4 groups based on season using summer as the reference. After adjusting for age, sex, and other coronary risk factors (hypertension, dyslipidemia, low-density lipoprotein cholesterol levels, diabetes mellitus, smoking history, and chronic kidney disease), these variables were tested for their independent association in both univariable and multivariable logistic regression models. All differences were evaluated at a significance level of 0.05. All statistical analyses were performed using the SPSS 23.0 software (International Business Machines Corporation, Armonk, NY).

RESULTS

Patient Characteristics

We enrolled a total of 1113 patients: 284 patients (25%) in spring, 243 patients (22%) in summer, 290 patients (26%) in autumn, and 296 patients (27%) in winter. The clinical characteristics of the 1113 patients are summarized in Table 1. There were no differences in the baseline characteristics between the 4 seasons, except for the higher prevalence of hypertension (P=0.002) and lower temperature in winter (P<0.001).

OCT Findings

Among 1113 patients, plaque rupture was diagnosed in 561 patients (50%), plaque erosion in 417 patients (38%), and calcified plaque in 135 patients (12%) (Figure 2). Figure 3 shows the distribution of the 3 most common pathologies of ACS depending on the season. The rates of plaque rupture, plaque erosion, and calcified plaque were 50%, 39%, and 11% in spring; 44%, 43%, and 13% in summer; 49%, 39%, and 12% in autumn; and 57%, 30%, and 13% in winter (P=0.039). The proportion of plaque rupture was highest in winter, but lowest in summer. In contrast, the proportion of plaque erosion was highest in summer, but lowest in winter.

Table 1. Baseline Characteristics

Characteristic	Spring (n=284)	Summer (n=243)	Autumn (n=290)	Winter (n=296)	*P* Value
Age, y	66.3±11.9	65.5±11.2	65.4±11.6	65.8±11.6	0.773
Sex, male	228 (80)	193 (79)	233 (80)	231 (78)	0.892
Hypertension	192 (68)	143 (59)	184 (63)	218 (74)	0.002*
Dyslipidemia	206 (73)	164 (67)	207 (71)	219 (74)	0.397
Diabetes mellitus	92 (32)	89 (37)	77 (27)	101 (34)	0.075
CKD	45 (16)	41 (17)	57 (20)	60 (20)	0.457
Smoking history	166 (59)	154 (63)	179 (62)	187 (63)	0.609
Current	107 (38)	100 (41)	121 (42)	119 (40)	0.865
Past	59 (21)	54 (22)	58 (20)	68 (23)	
Previous MI	21 (7)	21 (9)	13 (4)	24 (8)	0.223
Previous PCI	22 (8)	21 (9)	18 (6)	28 (9)	0.515
Clinical presentation					0.106
ST-segment–elevation MI	160 (56)	118 (49)	159 (55)	177 (60)	
Non–ST-segment–elevation MI	98 (35)	87 (36)	99 (34)	91 (31)	
Unstable angina pectoris	26 (9)	38 (15)	32 (11)	28 (9)	
Medication on admission					
Statin	54 (19)	54 (22)	54 (19)	56 (19)	0.265
ACE-I/ARB	72 (25)	57 (23)	67 (23)	84 (28)	0.063
Beta blockers	40 (14)	24 (10)	34 (12)	33 (11)	0.195
Calcium channel blocker	65 (23)	52 (21)	59 (20)	75 (25)	0.067
Aspirin	44 (15)	40 (16)	52 (18)	42 (14)	0.409
Laboratory data					
Hb, g/dL	13.9±2.0	14.0±2.0	14.0±1.8	14.1±1.7	0.501
T-cholesterol level, mg/dL	188.8±41.2	191.9±41.3	190.4±45.7	196.3±41.0	0.196
LDL-C level, mg/dL	123.7±41.4	124.7±39.6	122.6±43.3	127.9±41.1	0.456
HDL-C level, mg/dL	46.1±13.7	45.7±12.4	47.1±14.9	47.6±13.7	0.369
TG level, mg/dL	127.3±104.1	126.8±96.6	123.5±98.9	125.0±90.9	0.970
Hs-CRP level, mg/dL	0.78±2.09	0.64±1.81	0.70±1.85	0.71±1.63	0.904
HbA1c, %	6.2±1.3	6.3±1.3	6.1±1.3	6.2±1.1	0.485
Creatinine, mg/dL	1.02±1.22	0.96±0.92	1.04±1.09	1.12±1.43	0.490
eGFR, mL/min per 1.73 m^2	93.2±36.2	117.4±283.1	99.1±130.3	98.3±118.4	0.359
Peak CK, IU	1877±2350	1851±2301	1882±2299	1761±2130	0.922
Peak CKMB, IU	188.2±222.7	192.4±240.1	192.2±251.7	179.1±220.5	0.901
Temperature					
Maximum, °C	17.7±6.3	29.1±4.2	21.6±6.5	10.3±5.1	<0.001*
Minimum, °C	8.0±6.3	20.8±3.8	13.2±6.8	1.3±4.9	<0.001*

Values are number (percentage) or mean±SD. ACE-I indicates angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CK, creatine kinase; CKD, chronic kidney disease; CKMB, creatine kinase MB; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; T-cholesterol, total cholesterol; and TG, triglyceride.

*indicate statistically significant.

OCT findings are summarized in Table 2. The incidence of plaque rupture was highest in winter, but lowest in summer. In contrast, the incidence of plaque erosion was lowest in winter. Except for the higher prevalence of macrophage density in the winter, qualitative and quantitative assessments of plaque features did not differ among the 4 seasons. Both the maximum and minimum temperature were significantly lower in the plaque rupture group than in the other groups (maximum temperature, 18.5±8.7°C in plaque rupture, 20.0±8.4°C in plaque erosion, and 19.8±9.5°C in calcified plaque, *P*=0.02; minimum temperature, 9.6±9.0°C in plaque rupture, 11.3±8.9°C in plaque

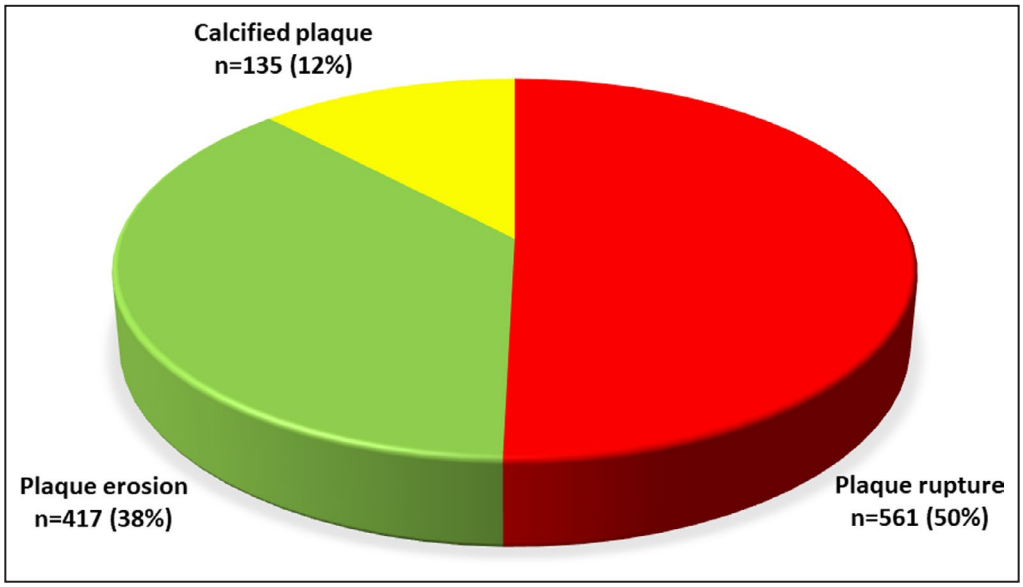

Figure 2. Overall proportion of plaque rupture, plaque erosion, and calcified plaque.
Plaque rupture was diagnosed in 561 patients (50%), plaque erosion in 417 patients (38%), and calcified plaque in 135 patients (12%).

erosion, and 10.8±9.2°C in calcified plaque, *P*=0.012) (Figure 4). Figure 5 shows that the prevalence of hypertension was significantly higher in winter only in the plaque rupture group. Table 3 shows the proportion of pathogenesis between men and women. There were no significant differences in seasonal variations between the sexes. Table 4 shows that winter was significantly associated with an increased risk of plaque rupture and decreased risk of plaque erosion compared with summer as a reference; season was not associated with calcified plaque.

DISCUSSION

The present study demonstrates an association between the type of plaque disruption and season in ACS patients. We found that the highest proportion

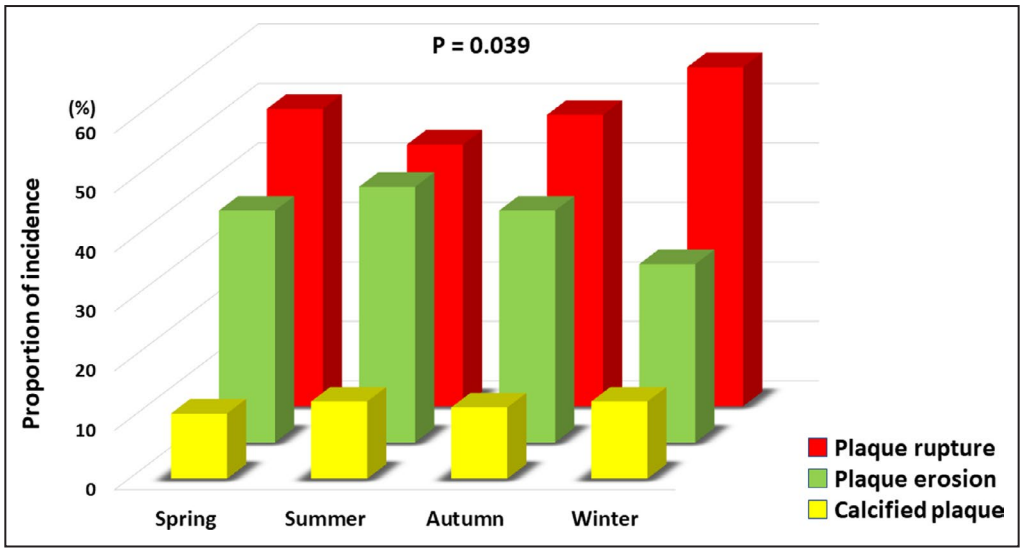

Figure 3. Proportion of plaque rupture, plaque erosion, and calcified plaque in each season.
The proportion of culprit lesion characteristics were significantly different between the 4 seasons (*P*=0.039). The highest proportion of plaque rupture was in winter and the lowest in summer. In contrast, the highest proportion of plaque erosion was in summer and the lowest in winter.

Table 2. Optical Coherence Tomography Findings

	Spring (n=284)	Summer (n=243)	Autumn (n=290)	Winter (n=296)	*P* Value
Lesion characteristics					
Plaque rupture	143 (50)	106 (44)	143 (49)	169 (57)	0.039*
Plaque erosion	111 (39)	105 (43)	113 (39)	88 (30)	
Calcified plaque	30 (11)	32 (13)	34 (12)	39 (13)	
Qualitative assessment					
Lipid rich plaque	179 (63)	147 (60)	174 (60)	194 (66)	0.498
TCFA	97 (34)	74 (30)	89 (31)	115 (39)	0.118
Macrophage	191 (67)	155 (64)	175 (60)	210 (71)	0.046*
Cholesterol crystal	67 (24)	48 (20)	51 (18)	55 (19)	0.292
Calcification	119 (42)	94 (39)	133 (46)	147 (50)	0.057
Thrombus	235 (83)	200 (82)	234 (81)	239 (81)	0.934
White	125 (53)	94 (47)	109 (47)	103 (43)	0.428
Red	64 (27)	50 (25)	64 (27)	64 (27)	
Mix	46 (20)	56 (28)	61 (26)	72 (30)	
Quantitative assessment					
Minimum fibrous cap thickness, μm	87.0±55.4	92.0±51.3	83.5±44.5	86.0±92.5	0.689
Max lipid arc, °	301.9±65.9	300.2±65.9	304.5±72.4	309.5±64.0	0.593

Values are presented as number (percentage) or mean±SD. TCFA indicates thin cap fibroatheroma.
*indicate statistically significant.

of plaque rupture was in winter, whereas the highest proportion of plaque erosion was in summer.

Underlying Mechanisms of ACS

Pathology studies have shown that plaque rupture was responsible for sudden cardiac death in 55% to 60% of patients, plaque erosion in 33% to 44%, and calcified nodule in 4% to 7%.[7,8,11] Subsequent in vivo studies using OCT showed that plaque rupture was the underlying mechanism in 44% to 71% of patients with ACS, plaque erosion 24% to 41%, and calcified plaque in about 8%.[11] Consistent with previously published reports, our study showed that plaque rupture was diagnosed in 50% of patients, plaque erosion in 38%, and calcified plaque in 12%.

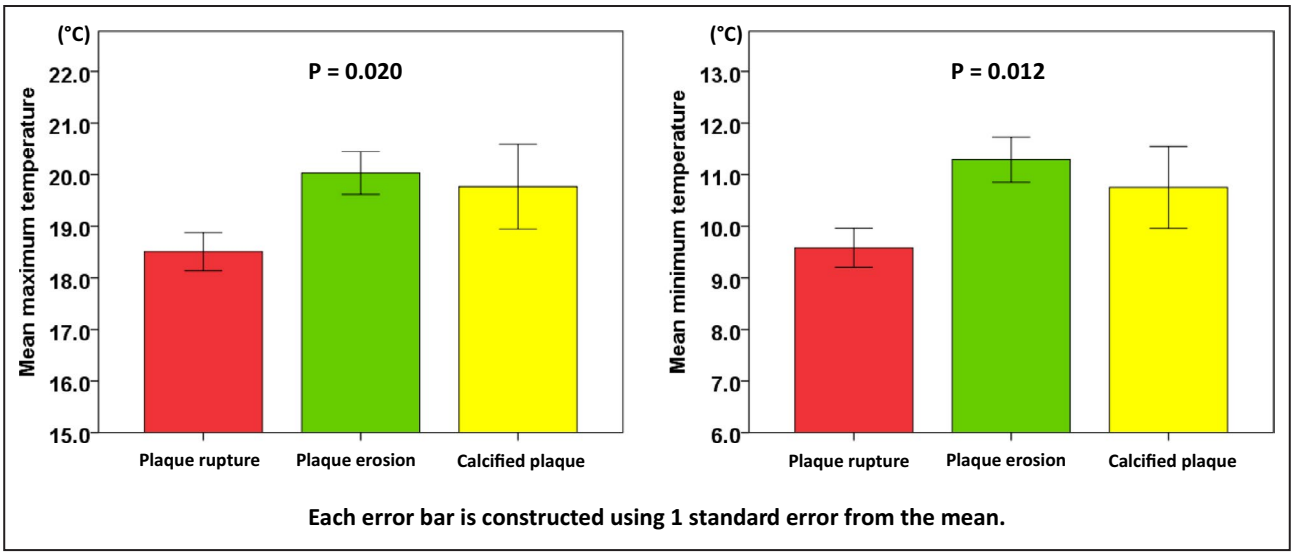

Figure 4. Comparison of temperature among 3 culprit lesion types.
The lowest maximum and minimum temperatures were observed among patients with plaque rupture.

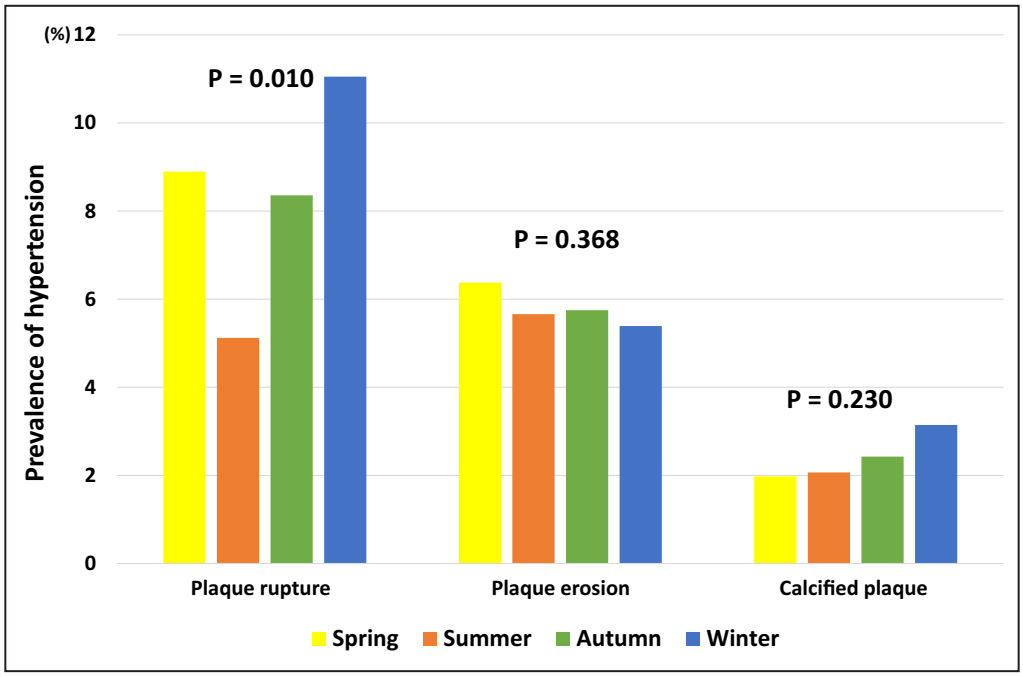

Figure 5. Prevalence of hypertension in each season among 3 culprit types.
The prevalence of hypertension was highest in winter only in patients with plaque rupture, whereas the prevalence of hypertension was similar in other seasons among patients with plaque erosion or calcified plaque.

Season and Plaque Rupture

Our study shows that the highest proportion of plaque rupture is observed in winter and that the mean temperatures at the time of the ACS are the lowest in patients with plaque rupture.

During plaque rupture, a disruption of the fibrous cap exposes the thrombogenic contents of the necrotic core including tissue factor to circulating cellular and noncellular blood elements, resulting in coronary thrombosis.[12] Previous studies have also reported a higher incidence of ACS in winter.[2,3] The higher prevalence of infections, particularly influenza and other respiratory tract infections, promote systemic inflammation that may enhance plaque destabilization during the winter season.[13,14] In this study, the highest incidence of ACS was in winter, and the prevalence of macrophage density at the culprit lesion was significantly higher in winter than in the other seasons.

The stimulation of cold receptors in the skin leads to a rise in catecholamine levels and subsequent increased blood pressure.[15] In addition, a previous report showed that the blood pressure of patients with hypertension has seasonal variation with higher pressures in the winter than in the summer, although

Table 3. Proportion of Pathogenesis Between Men and Women

	All (n=1113)	Spring (n=284)	Summer (n=243)	Autumn (n=290)	Winter (n=296)	*P* Value
Men, n=885						0.999
Lesion characteristics		228	193	233	231	
Plaque rupture	444 (50)	115 (50)	83 (43)	114 (49)	132 (57)	0.115
Plaque erosion	334 (38)	88 (39)	84 (44)	92 (39)	70 (30)	
Calcified plaque	107 (12)	25 (11)	26 (13)	27 (12)	29 (13)	
Women, n=228						
Lesion characteristics		56	50	57	65	
Plaque rupture	117 (51)	28 (50)	23 (46)	29 (51)	37 (57)	0.698
Plaque erosion	83 (37)	23 (41)	21 (42)	21 (37)	18 (28)	
Calcified plaque	28 (12)	5 (9)	6 (12)	7 (12)	10 (15)	

Values are presented as number (percentage).

Table 4. Logistic Regression Analyses for Each Pathogenesis

Variable	Unadjusted			Adjusted		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Plaque rupture						
Age	1.001	0.991–1011	0.843	1.002	0.991–1.014	0.718
Sex (male)	0.955	0.714–1.278	0.758	1.025	0.741–1.418	0.882
Hypertension	1.008	0.787–1.293	0.947	0.929	0.710–1.215	0.590
Dyslipidemia	1.107	0.854–1.437	0.443	0.914	0.686–1.218	0.541
LDL-C	1.005	1.002–1.008	<0.001*	1.006	1.003–1.009	<0.001*
Diabetes mellitus	1.123	0.873–1.444	0.366	1.121	0.859–1.462	0.400
CKD	1.175	0.866–1.594	0.300	1.351	0.967–1.887	0.078
Smoking	0.902	0.708–1.149	0.404	0.857	0.652–1.128	0.271
Season classification						
Summer (reference)						
Spring	1.311	0.929–1.849	0.123	1.357	0.949–1.942	0.095
Autumn	1.257	0.893–1.771	0.190	1.296	0.907–1.852	0.155
Winter	1.720	1.221–2.422	0.002*	1.652	1.157–2.359	0.006*
Plaque erosion						
Age	0.981	0.970–0.991	<0.001*	0.985	0.973–0.996	0.010*
Sex (male)	1.059	0.783–1.432	0.710	0.956	0.681–1.341	0.793
Hypertension	0.735	0.570–0.948	0.018*	0.877	0.666–1.155	0.349
Dyslipidemia	0.857	0.656–1.120	0.259	0.877	0.651–1.181	0.386
LDL-C	0.999	0.996–1.002	0.451	0.998	0.994–1.001	0.161
Diabetes mellitus	0.718	0.551–0.936	0.014*	0.794	0.600–1.051	0.107
CKD	0.469	0.331–0.663	<0.001*	0.481	0.328–0.705	<0.001*
Smoking	1.177	0.915–1.513	0.204	1.087	0.816–1.447	0.568
Season classification						
Summer (reference)						
Spring	0.843	0.595–1.194	0.337	0.885	0.614–1.278	0.515
Autumn	0.839	0.593–1.187	0.321	0.902	0.626–1.299	0.579
Winter	0.556	0.390–0.794	0.001*	0.623	0.429–0.905	0.013*
Calcified plaque						
Age	1.045	1.027–1.063	<0.001*	1.037	1.016–1.058	<0.001*
Sex (male)	0.982	0.630–1.532	0.937	1.058	0.637–1.756	0.828
Hypertension	2.111	1.365–3.265	0.001*	1.834	1.120–3.005	0.016*
Dyslipidemia	1.109	0.739–1.664	0.618	1.634	1.030–2.592	0.037*
LDL-C	0.989	0.984–0.994	<0.001*	0.989	0.984–0.995	<0.001*
Diabetes mellitus	1.524	1.054–2.205	0.025*	1.248	0.830–1.878	0.287
CKD	2.595	1.746–3.857	<0.001*	1.733	1.105–2.719	0.017*
Smoking	0.893	0.619–1.289	0.545	1.170	0.757–1.807	0.480
Season classification						
Summer (reference)						
Spring	0.779	0.458–1.324	0.356	0.586	0.329–1.042	0.069
Autumn	0.876	0.523–1.467	0.614	0.635	0.359–1.123	0.119
Winter	1.001	0.606–1.653	0.998	0.810	0.474–1.387	0.443

CKD indicates chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; and OR, odds ratio.
*indicate statistically significant.

healthy people had no seasonal difference in blood pressure.[16] In our series, the prevalence of hypertension was significantly higher in winter only in the plaque rupture group. Previous pathology studies showed that hypertension tended to be more common in plaque rupture than in erosion.[17] High blood

pressure is considered a main mechanical trigger of plaque rupture, although some investigators suggest that rupture is affected by high shear stress.[18,19] Another potential mechanism is related to cholesterol crystallization from liquid to solid crystal,[20] which can cause the sudden expansion of plaque volume and the elevation of intraplaque pressure, mechanically tearing the overlying fibrous caps.[21] Cholesterol solidification may lead to unequal stiffness in the plaque, and its mechanical strain may precipitate plaque rupture as well as microcalcification in the culprit plaque of ACS.[22,23]

In addition, the incidence and mortality of ACS is increased in winter.[24] It is known that plaque rupture is more frequently found in STEMI than in non-ST-segment–elevation ACS.[8] The prevalence of STEMI tended to be higher than NSTEMI in winter, and the increase in the incidence of ACS in winter was limited to patients presenting with STEMI.[25] A previous study showed seasonal variation in the infarction size of myocardium, with larger sizes occurring in winter.[26] Although peak creatine kinase was similar among the seasons in our series, it was significantly higher in plaque rupture than nonplaque rupture (Table S2).

Season and Plaque Erosion or Calcified Plaque

Our data show that the highest proportion of plaque erosion was in summer and that the mean temperatures at the time of the ACS were the highest in patients with plaque erosion. In contrast to plaque rupture, fibrous cap disruption with exposure of necrotic core does not occur in plaque erosion and the underlying mechanism of thrombus formation remains less well understood. Local flow perturbation and changes in endothelial shear stress and blood viscosity may lead to the upregulation of Tol-like receptor 2, resulting in endothelial damage and neutrophil extracellular trap formation and thrombosis. Previous pathology and clinical studies showed that a fibrin-rich red thrombus was frequently found in plaque rupture, whereas platelet-rich white thrombus was the predominant type of thrombus formed in plaque erosion.[8,27] High shear rates are known to activate platelets.[28–30] In hot environments, hemoconcentration increases blood viscosity,[31] which may contribute to an increase in local endothelial shear stress.

Our data show that the proportion of calcified plaque was similar between the 4 seasons. In the multivariate logistic regression analysis, season was not associated with calcified plaque. Pathology and OCT studies have reported that the proportion of calcified nodule or calcified plaque were small in sudden cardiac death or in ACS patients.[7,11,32] Therefore, our data should be interpreted with caution.

Study Limitations

This study has several limitations. First, we included only patients who had an OCT procedure and the decision to perform OCT was left at the discretion of each operator. Therefore, the true denominator is unknown. In addition, the study periods are different among the participating countries and sites (Table S1 and Figure S2), and age, sex, and coronary risk factors were different among the participating countries (Table S3). However, the seasonal pattern of incidence and the proportion of pathogenesis in this cohort are consistent with previous findings.[2,11] We also performed multivariate analysis for estimating potential likely interaction by country. After adjusting for age, sex, coronary risk factors, and country, season remained significantly associated with plaque rupture and erosion in multivariate regression analysis, and countries were not significantly associated with pathogenesis (Table S4). Because the number of participants at some of the institutions was too small (Table S1), we could not evaluate a potential likely interaction by participating sites within the participating country. Therefore, inherent selection bias and the bias between geographic sites cannot be excluded. Second, although data were collected from 6 countries that included sites in Europe and the United States, the majority of cases were from Japan (75.6%). Third, the temperature was defined on the day of OCT procedure, as it is difficult to know the exact onset of ACS. Although it is possible that the temperature in the several days before the procedure or the amplitude of temperature difference might be higher or lower, the difference would have been relatively small. Fourth, although there are many other environmental factors (low atmospheric air pressure, high wind velocity, shorter sunshine duration, air pollution, etc) that may affect the risk of ACS, this study focused on air temperature because the most evident association for the risk of ACS has been observed for air temperature.[5]

CONCLUSIONS

This study demonstrated that the underlying mechanism of ACS varies with season of the year. The proportion of plaque rupture is the highest in the winter, and the proportion of plaque erosion is the highest in the summer. A season-based approach may be needed for better prevention of ACS.

ARTICLE INFORMATION

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Supplementary Materials

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

OCT image analysis

All OCT plaque morphologies were analyzed using previously validated criteria.[33] Fibrous cap thickness (FCT) was measured at its thinnest part three times and the average value was calculated. Lipid was defined as a signal poor region with a poorly defined or diffuse border, and the degree of lipid arc was measured on the cross-sectional image. Lipid rich plaque was defined as a plaque with a maximal lipid arc > 90 degree. Thin-cap fibroatheroma was defined as a lipid rich plaque with the FCT ≤ 65 μm on the cross-sectional image.[34] Macrophage infiltration was defined as signal-rich, distinct or confluent punctuated regions that exceeded the intensity of background speckle noise. Cholesterol crystals were defined as thin linear regions of high light intensity without signal attenuation. Calcification was defined as a signal-poor or heterogeneous region with a sharply delineated border.[33] Thrombus was defined as a mass > 250 μm attached to the luminal surface or floating within the lumen.[35] Thrombus was classified into three types: 1) red thrombus (identified by high backscattering with high signal attenuation); 2) white thrombus (identified by homogeneous backscattering with low signal attenuation); and 3) mixed thrombus (identified by features observed in both red and white thrombi).[36,37]

Definitions

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or currently on antihypertensive drugs.[38] Hyperlipidemia was defined as currently on cholesterol lowering therapy, previously known hyperlipidemia, or serum low-density

lipoprotein cholesterol (LDL-C) ≥140 mg/dL. Diabetes mellitus was defined as a fasting plasma glucose level ≥ 126 mg/dL, two hour plasma glucose level ≥ 200 mg/dL by oral glucose tolerance test, classic symptoms with random plasma glucose level ≥ 200 mg/dL, hemoglobin A1c (HbA1c) level ≥ 6.5%, or receiving insulin or oral hypoglycemic agents.[39] Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m2 for ≧3 months. The eGFR on admission was calculated using the Modification of Diet in Renal Disease equation: eGFR (mL/min per 1.73 m^2) = 175 × (serum creatinine [mg/dL])$^{-1.154}$×(age)$^{-0.203}$ × 0.742 (if female) × 1.210 (if black).

Table S1. Study period and number of cases in each participating site.

Participating sites	Number of cases	Study Period
Japan	**841**	**October/2008-June/2017**
Tsuchiura Kyodo General Hospital	264	October/2008-January/2014
Nara Medical University	229	September/2010-December/2016
Chiba Hokusoh Hospital	127	October/2015-April/2017
Hirosaki University	121	January/2013-July/2014
Kameda Medical Center	52	February/2016-June/2017
Kitasato University School of Medicine	41	May/2014-March2017
Iwate Medical University	4	March/2011-January/2014
Nippon Medical School	3	March2011-July/2011
Hong Kong	**82**	**July/2015-December/2016**
Chinese University of Hong Kong	82	July/2015-December/2016
Italy	**100**	**March/2010- October/2017**
Catholic University	100	March/2010- October/2017
Belgium	**62**	**June/2009-January/2018**
University Hospitals Leuven	62	June/2009-January/2018
Korea	**15**	**December/2010-July/2013**
Asan Medical Center	11	June/2011-July/2013
Ajou University Medical Center	3	December/2010-April/2011
Yonsei University	1	March./2011
USA	**13**	**October/2011-May/2014**
Massachusetts General Hospital	7	May/2011-April/2013
University of Pittsburgh	3	January/2013-May/2014
University of Vermont	2	October/2011-August/2013
Mayo Clinic	1	May/2012
Total	1113	October/2008-January2018

Table S2. Comparison of PR vs. non-PR.

	All			Spring		Summer		Autumn		Winter		
	1113			284		243		290		296		
	PR	Non-PR	p-value	PR	Non-PR	PR	Non-PR	PR	Non-PR	PR	Non-PR	p Value
Patients, n	**561**	**552**		**143**	**141**	**106**	**137**	**143**	**147**	**169**	**127**	
Age (years)	65.9 ± 11.6	65.8 ± 11.5	0.84	67.2 ± 11.9	65.4 ± 11.8	64.8 ± 11.4	66.1 ± 11.0	65.7 ± 11.4	65.1 ± 11.6	65.6 ± 11.8	66.6 ± 11.4	0.74
Sex, male	444 (79 %)	441 (80 %)	0.76	115 (80 %)	113 (80 %)	83 (78 %)	110 (80 %)	114 (80 %)	119 (81 %)	132 (78 %)	99 (78 %)	0.10
Hypertension	372 (66 %)	365 (66 %)	0.95	99 (69 %)	93 (66 %)	57 (54 %)	86 (63 %)	93 (65 %)	91 (62 %)	123 (73 %)	95 (75 %)	**0.02**
Dyslipidemia	407 (73 %)	389 (70 %)	0.44	107 (75 %)	99 (70 %)	72 (68 %)	92 (67 %)	105 (73 %)	102 (69 %)	123 (73 %)	96 (76 %)	0.71
Diabetes mellitus	188 (34 %)	171 (31 %)	0.37	52 (36 %)	40 (28 %)	43 (41 %)	46 (34 %)	39 (27 %)	38 (26 %)	54 (32 %)	47 (37 %)	0.13
CKD	109 (19%)	91 (16%)	0.30	27 (19 %)	18 (13 %)	18 (17 %)	23 (17 %)	27 (19 %)	30 (20 %)	37 (22 %)	23 (18 %)	0.64
Smoking history	339 (60%)	347 (63%)	0.40	82 (57 %)	84 (60 %)	69 (65 %)	85 (62 %)	88 (61 %)	91 (62 %)	100 (59 %)	87 (68 %)	0.67
Current	242 (43%)	205 (37%)	**0.002**	55 (38 %)	52 (37 %)	52 (49 %)	48 (35 %)	62 (43 %)	59 (40 %)	73 (43 %)	46 (36 %)	0.09
Past	97 (17%)	142 (26%)		27 (19 %)	32 (23 %)	17 (16 %)	37 (27 %)	26 (18 %)	32 (22 %)	27 (16 %)	41 (32 %)	
Previous MI	40 (7%)	39 (7%)	0.97	10 (7 %)	11 (8 %)	11 (10 %)	10 (7 %)	5 (3 %)	8 (5 %)	14 (8 %)	10 (8 %)	0.57
Previous PCI	45 (8%)	44 (8%)	0.98	12 (8 %)	10 (7 %)	11 (10 %)	10 (7 %)	8 (6 %)	10 (7 %)	14 (8 %)	14 (11 %)	0.77
Clinical presentation			**<0.001**									**<0.001**
ST elevation	369 (66 %)	245 (44 %)		94 (66 %)	66 (47 %)	66 (62 %)	52 (38 %)	90 (63 %)	69 (66 %)	119 (71 %)	58 (46 %)	
Non ST elevation	153 (27 %)	222 (40 %)		40 (28 %)	58 (41 %)	29 (28 %)	58 (42 %)	43 (30 %)	56 (27 %)	41 (24 %)	50 (39 %)	
Unstable angina	39 (7 %)	85 (16 %)		9 (6 %)	17 (12 %)	11 (10 %)	27 (20 %)	10 (7 %)	22 (7%)	9 (5 %)	19 (15 %)	
Medication												
Statin	102 (18 %)	116 (21 %)	0.32	25 (17 %)	29 (21 %)	19 (18 %)	35 (26 %)	27 (19 %)	27 (18 %)	31 (18 %)	25 (20 %)	0.56
ACE-I/ARB	127 (23 %)	153 (28 %)	0.11	37 (26 %)	35 (25 %)	16 (15 %)	41 (30 %)	33 (23 %)	34 (23 %)	41 (24 %)	43 (34 %)	0.06
Beta blockers	54 (10 %)	77 (14 %)	0.05	18 (13 %)	22 (16 %)	7 (7 %)	17 (12 %)	14 (10 %)	20 (14 %)	15 (9 %)	18 (14 %)	0.33
Calcium channel blocker	121 (22 %)	130 (24 %)	0.08	37 (26 %)	28 (20 %)	20 (19 %)	32 (23 %)	27 (19 %)	32 (22 %)	37 (22 %)	38 (30 %)	0·08
Aspirin	78 (14 %)	100 (18 %)	0.11	19 (13 %)	25 (18 %)	15 (14 %)	25 (18 %)	21 (15 %)	31 (21 %)	23 (14 %)	19 (15 %)	0.55

Laboratory data												
Hb (g/dl)	14.0 ± 1.8	14.0 ± 1.9	0.95	13.6 ± 2.0	14.1 ± 1.9	14.0 ± 1.9	13.9 ± 2.0	14.1 ± 1.6	13.9 ± 1.9	14.3 ± 1.7	14.0 ± 1.6	0.21
T-cholesterol level (mg/dl)	194.6 ± 41.9	190.0 ± 42.8	**0.03**	191.3 ± 43.1	186.3 ± 39.1	195.4 ± 38.7	188.9 ± 43.3	192.3 ± 42.7	188.5 ± 48.7	199.0 ± 42.3	192.6 ± 39.0	0.26
LDL-C level (mg/dl)	129.1 ± 42.2	120.2 ± 40.2	**<0.001**	128.1 ± 43.4	119.0 ± 38.7	130.9 ± 39.4	119.8 ± 39.3	125.0 ± 41.0	120.0 ± 45.5	132.3 ± 43.9	122.0 ± 36.5	**0.03**
HDL-C level (mg/dl)	45.7 ± 13.9	47.6 ± 13.9	**0.03**	45.1 ± 12.2	47.1 ± 15.1	44.7 ± 11.0	46.5 ± 13.5	47.0 ± 16.6	47.2 ± 12.9	45.9 ± 14.2	49.9 ± 12.7	0.12
TG level (mg/dl)	119.5 ± 93.8	132.1 ± 101.0	**0.04**	124.9 ± 106.2	129.8 ± 102.3	122.4 ± 91.3	130.5 ± 101.0	113.4 ± 100.5	133.9 ± 96.6	118.2 ± 77.7	134.1 ± 105.6	0.57
Hs-CRP level (mg/dl)	0.83 ± 2.23	0.57 ± 1.31	**0.03**	0.96 ± 2.63	0.58 ± 1.28	0.78 ± 2.28	0.53 ± 1.30	0.87 ± 2.31	0.52 ± 1.21	0.74 ± 1.75	0.67 ± 1.46	0.52
HbA1c (%)	6.2 ± 1.3	6.2 ± 1.2	0.56	6.3 ± 1.4	6.2 ± 1.2	6.4 ± 1.2	6.3 ± 1.3	6.3 ± 1.5	6.0 ± 1.0	6.0 ± 0.9	6.3 ± 1.3	0.15
Creatinine (mg/dl)	0.97 ± 0.82	1.11 ± 1.45	0.06	0.97 ± 0.78	1.07 ± 1.55	0.89 ± 0.49	1.01 ± 1.16	0.93 ± 0.58	1.15 ± 1.41	1.06 ± 1.13	1.19 ± 1.75	0.44
eGFR (mL/min per 1.73 m^2)	104 ± 171	99 ± 151	0.59	91 ± 34	95 ± 39	121 ± 297	114 ± 272	102 ± 140	96 ± 120	105 ± 154	89 ± 32	0.76
Peak CK (IU)	2201 ± 2435	1455 ± 1998	**<0.001**	2241 ± 2651	1456 ± 1868	2172 ± 2339	1591 ± 2246	2256 ± 2451	1500 ± 2074	2139 ± 2304	1264 ± 1766	**<0.001**
Peak CKMB (IU)	222 ± 258	150 ± 198	**<0.001**	212 ± 250	153 ± 182	230 ± 255	163 ± 225	230 ± 279	156 ± 218	220 ± 521	128 ± 161	**0.001**

Values are numbers (%) or means ± SD.

ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CK = creatine kinase; CKD; chronic kidney disease; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; Hs-CRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; PR = plaque rupture; T-cholesterol = total cholesterol; TG = triglyceride

Table S3. Baseline characteristics in each country.

	All	Japan	Hong Kong	Italy	Belgium	Korea	USA	
Patients, n	**1113**	**841**	**82**	**100**	**62**	**15**	**13**	**P-Value**
Age (years)	65.8 ± 11.6	66.9 ± 11.5	60.8 ± 10.8	64.6 ± 11.9	62.9 ± 10.3	62.2 ± 11.3	57.5 ± 12.0	**< 0.001**
Sex, male	885 (80%)	668 (79 %)	69 (84 %)	76 (76 %)	55 (89 %)	9 (60 %)	8 (62 %)	**0.049**
Hypertension	737 (66%)	588 (70 %)	30 (37 %)	65 (65 %)	38 (61 %)	8 (53 %)	8 (62 %)	**< 0.001**
Dyslipidemia	796 (72%)	605 (72 %)	38 (46 %)	82 (82 %)	52 (84 %)	11 (73 %)	8 (62 %)	**< 0.001**
Diabetes mellitus	359 (32%)	303 (36 %)	21 (26 %)	20 (20 %)	9 (15 %)	3 (20 %)	3 (23 %)	**< 0.001**
Smoking history	686 (61%)	527 (63%)	48 (58%)	56 (56%)	39 (63%)	7 (47%)	9 (69%)	0.574
Current	447 (40%)	335 (40 %)	33 (40 %)	56 (56 %)	13 (21 %)	4 (27 %)	6 (46 %)	**< 0.001**
Past	239 (21%)	192 (23%)	15 (18%)	0 (0%)	26 (42%)	3 (20%)	3 (23%)	
CKD	203 (18%)	150 (18%)	35 (43%)	0 (0%)	9 (15%)	4 (27%)	5 (38%)	**< 0.001**

Values are numbers (%) or means ± SD

CKD; chronic kidney disease

Table S4. Logistic regression analyses for plaque rupture and erosion.

Variable	*Unadjusted*			*Adjusted*		
	OR	***95% CI***	***P-value***	***OR***	***95% CI***	***P-value***
Plaque rupture						
Age	1.001	0.991-1011	0.843	1.002	0.990-1.014	0.757
Sex (male)	0.955	0.714-1.278	0.758	1.016	0.731-1.411	0.926
Hypertension	1.008	0.787-1.293	0.947	0.955	0.727-1.254	0.740
Dyslipidemia	1.107	0.854-1.437	0.443	1.000	0.744-1.345	0.998
LDL-C	1.005	1.002-1.008	**< 0.001**	1.005	1.002-1.009	**0.002**
Diabetes mellitus	1.123	0.873-1.444	0.366	1.083	0.828-1.418	0.559
CKD	1.175	0.866-1.594	0.300	1.280	0.905-1.810	0.162
Smoking	0.902	0.708-1.149	0.404	0.850	0.645-1.120	0.248
Season classification						
Summer (Reference)						
Spring	1.311	0.929-1.849	0.123	1.363	0.951-1.954	0.092
Autumn	1.257	0.893-1.771	0.190	1.278	0.891-1.833	0.182
Winter	1.720	1.221-2.422	**0.002**	1.645	1.150-2.354	**0.006**
Country						
Japan (Reference)						
Hong Kong	1.025	0.651-1.616	0.914	1.448	0.841-2.494	0.182
Italy	0.615	0.404-0.938	0.024	0.783	0.498-1.231	0.290
Belgium	0.362	0.206-0.637	**< 0.001**	0.561	0.299-1.053	0.072
Korea	0.590	0.208-1.674	0.322	0.494	0.146-1.666	0.255

USA	0.759	0.253-2.278	0.623	0.804	0.235-2.752	0.728
Plaque erosion						
Age	0.981	0.970-0.991	**< 0.001**	0.984	0.972-0.997	0.013
Sex (male)	1.059	0.783-1.432	0.710	0.964	0.684-1.358	0.832
Hypertension	0.735	0.570-0.948	**0.018**	0.857	0.647-1.134	0.279
Dyslipidemia	0.857	0.656-1.120	0.259	0.831	0.611-1.130	0.238
LDL-C	0.999	0.996-1.002	0.451	0.998	0.995-1.001	0.247
Diabetes mellitus	0.718	0.551-0.936	**0.014**	0.807	0.607-1.072	0.139
CKD	0.469	0.331-0.663	**< 0.001**	0.485	0.327-0.720	**< 0.001**
Smoking	1.177	0.915-1.513	0.204	1.090	0.818-1.454	0.556
Season classification						
Summer (Reference)						
Spring	0.843	0.595-1.194	0.337	0.894	0.618-1.292	0.551
Autumn	0.839	0.593-1.187	0.321	0.918	0.634-1.327	0.648
Winter	0.556	0.390-0.794	0.001	0.628	0.432-0.914	**0.015**
Country						
Japan (Reference)						
Hong Kong	1.085	0.679-1.732	0.733	0.746	0.421-1.322	0.315
Italy	1.292	0.848-1.970	0.233	0.937	0.591-1.485	0.782
Belgium	1.568	0.934-2.634	0.089	1.469	0.795-2.716	0.220
Korea	2.040	0.732-5.680	0.173	2.542	0.784-8.244	0.120
USA	1.115	0.362-3.440	0.849	0.920	0.247-3.424	0.901

CI = confidence interval; CKD = chronic kidney disease; LDL-C= low-density lipoprotein cholesterol; OR = odds ratio

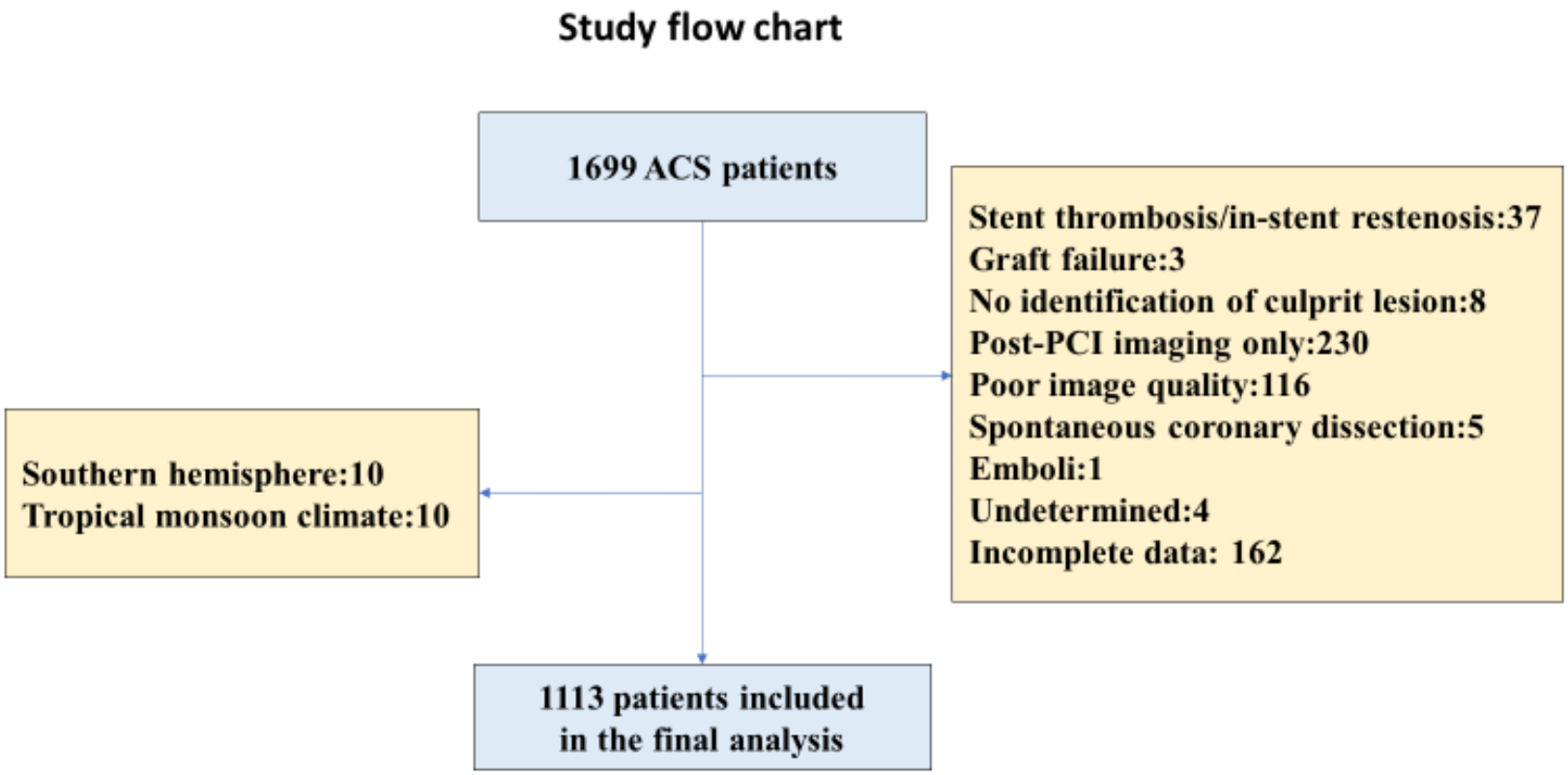
Study flow chart
1699 ACS patients
Stent thrombosis/in-stent restenosis:37
Graft failure:3
No identification of culprit lesion:8
Post-PCI imaging only:230
Poor image quality:116
Spontaneous coronary dissection:5
Emboli:1
Undetermined:4
Incomplete data: 162
Southern hemisphere:10
Tropical monsoon climate:10
1113 patients included
in the final analysis

Figure S1

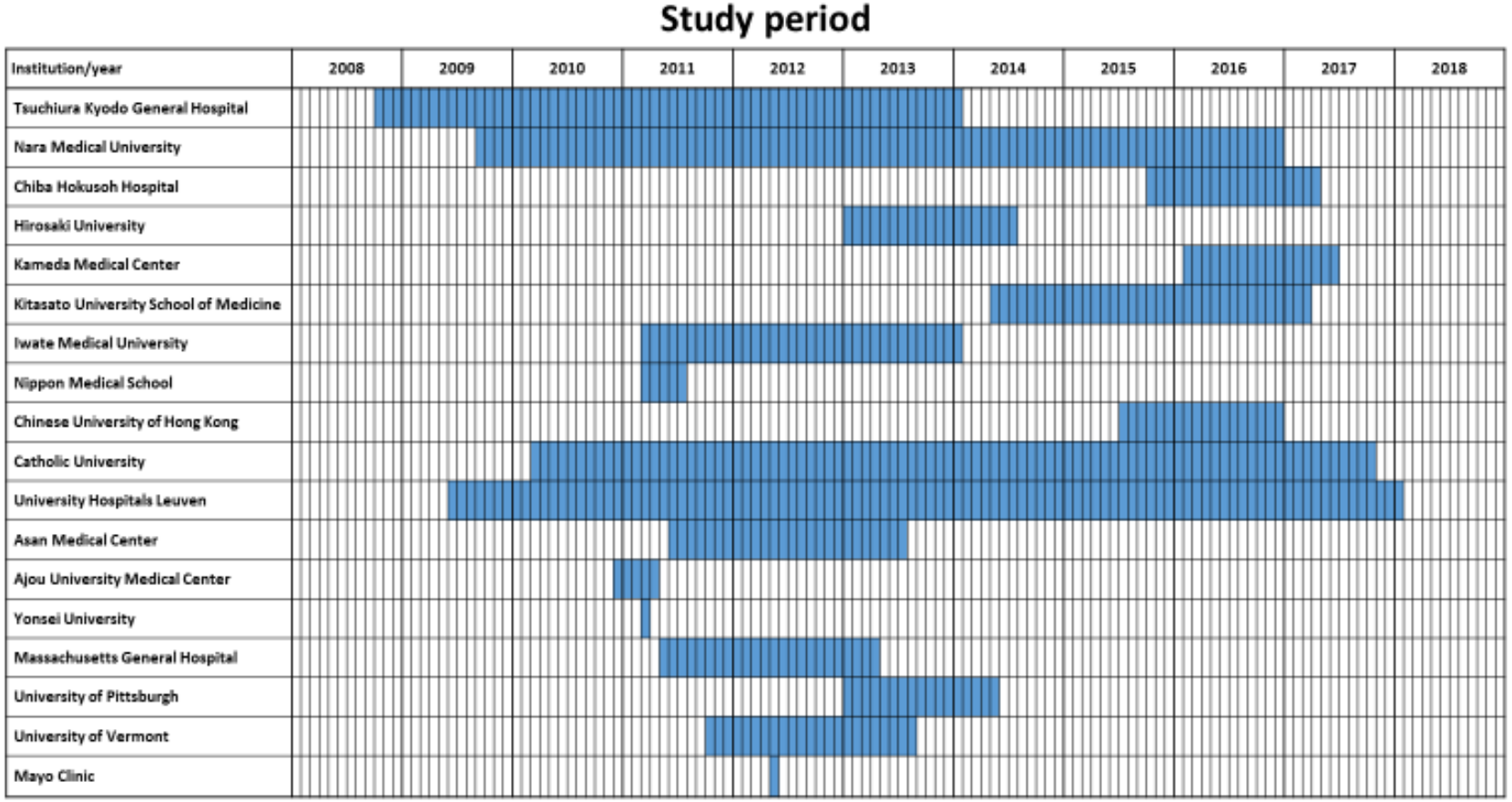
Study period
Institution/year
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Tsuchiura Kyodo General Hospital
Nara Medical University
Chiba Hokusoh Hospital
Hirosaki University
Kameda Medical Center
Kitasato University School of Medicine
Iwate Medical University
Nippon Medical School
Chinese University of Hong Kong
Catholic University
University Hospitals Leuven
Asan Medical Center
Ajou University Medical Center
Yonsei University
Massachusetts General Hospital
University of Pittsburgh
University of Vermont
Mayo Clinic

Figure S2

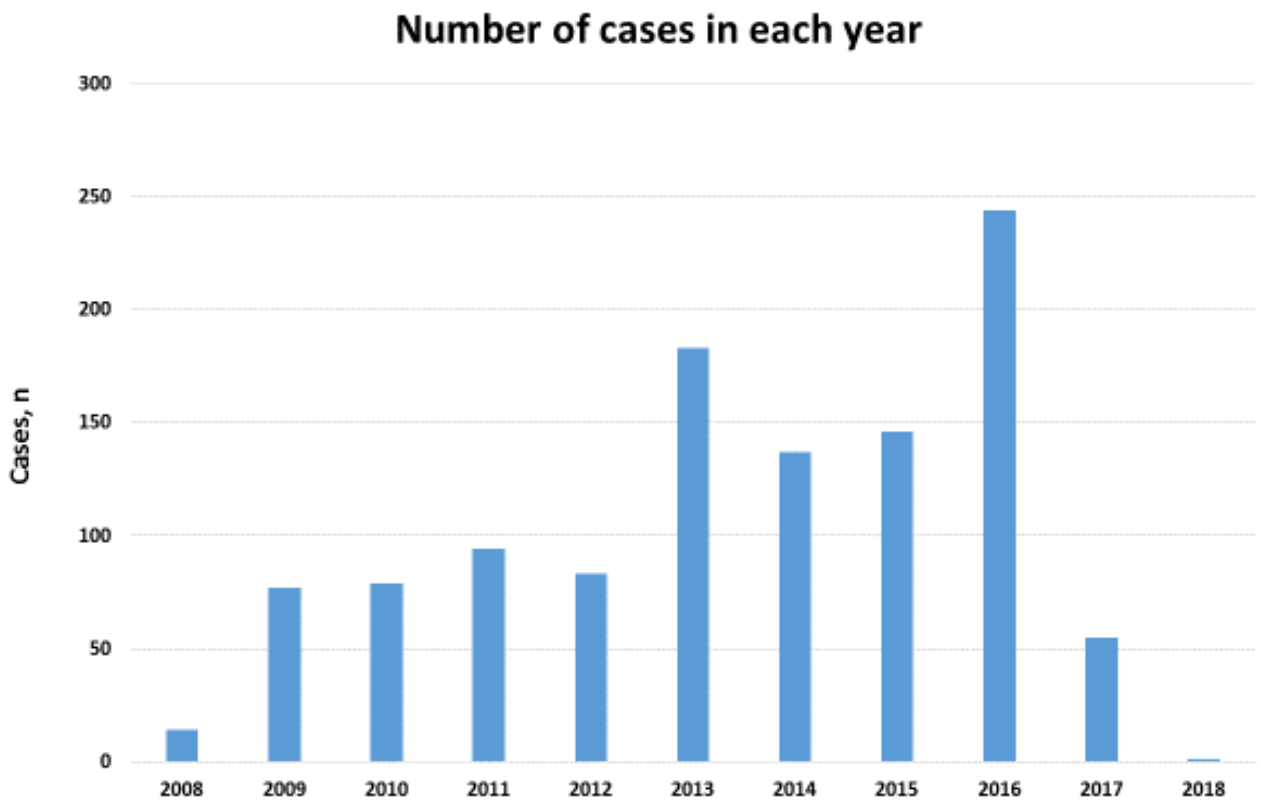
Number of cases in each year
Cases, n
300
250
200
150
100
50
0
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

Figure S3