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. Many studies have reported higher incidence and mortality in winter. Heat has also been associated with an increased risk of ACS. 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. ACS are the leading cause of mortality worldwide and are usually precipitated by coronary thrombosis, leading to a sudden reduction in blood flow. The 3 most common underlying mechanisms for ACS are...
PLAQUE Rupture, Plaque Erosion, and Calcified Nodule. 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).

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

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 de-identified, 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 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.
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 means±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.
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

### 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 | 0.486 |
| 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 m² | 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.
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
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%. 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%. 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%.

### Table 2. Optical Coherence Tomography Findings

| Lesion characteristics | Spring (n=284) | Summer (n=243) | Autumn (n=290) | Winter (n=296) | P Value |
|------------------------|---------------|----------------|----------------|---------------|---------|
| 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.

![Figure 4](image-url)  
*Comparison of temperature among 3 culprit lesion types.*  
The lowest maximum and minimum temperatures were observed among patients with plaque rupture.
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. Previous studies have also reported a higher incidence of ACS in winter. The higher prevalence of infections, particularly influenza and other respiratory tract infections, promote systemic inflammation that may enhance plaque destabilization during the winter season. 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. 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 |            |                |                |                |                |         |
| 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 |            |                |                |                |                | 0.698   |
| Plaque rupture    | 117 (51)     | 28 (50)        | 23 (46)        | 29 (51)        | 37 (57)        |         |
| 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).
healthy people had no seasonal difference in blood pressure.\textsuperscript{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.\textsuperscript{17} High blood

| Variable                  | Unadjusted | Adjusted |
|---------------------------|------------|----------|
|                           | OR         | 95% CI   | P Value | OR         | 95% CI   | P Value |
| Plaque rupture            |            |          |         |            |          |         |
| Age                       | 1.001      | 0.991–1.011 | 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* | 0.823 | 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      | 0.739–1.684 | 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 | 0.320–1.042 | 0.069 |
| Autumn                    | 0.876      | 0.523–1.467 | 0.614 | 0.635 | 0.259–1.123 | 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.
pressure is considered a main mechanical trigger of plaque rupture, although some investigators suggest that rupture is affected by high shear stress.\textsuperscript{18,19} Another potential mechanism is related to cholesterol crystallization from liquid to solid crystal,\textsuperscript{20} which can cause the sudden expansion of plaque volume and the elevation of intraplaque pressure, mechanically tearing the overlying fibrous caps.\textsuperscript{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.\textsuperscript{22,23}

In addition, the incidence and mortality of ACS is increased in winter.\textsuperscript{24} It is known that plaque rupture is more frequently found in STEMI than in non-ST-segment-elevation ACS.\textsuperscript{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.\textsuperscript{25} A previous study showed seasonal variation in the infarction size of myocardium, with larger sizes occurring in winter.\textsuperscript{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.\textsuperscript{8,27} High shear rates are known to activate platelets.\textsuperscript{28–30} In hot environments, hemoconcentration increases blood viscosity,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

Data S1

Tables S1–S4

Figures S1–S3

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SUPPLEMENTAL MATERIAL
Supplemental Methods

*OCT image analysis*

All OCT plaque morphologies were analyzed using previously validated criteria. 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. 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. Thrombus was defined as a mass > 250 μm attached to the luminal surface or floating within the lumen. 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).

*Definitions*

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or currently on antihypertensive drugs. 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. 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 m²) = 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-March/2017    |
| Iwate Medical University                     | 4               | March/2011-January/2014|
| Nippon Medical School                        | 3               | March 2011-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-January/2018** |
### Table S2. Comparison of PR vs. non-PR.

| Patients, n | PR | Non-PR | p-value | PR | Non-PR | PR | Non-PR | PR | Non-PR | PR | Non-PR | p Value |
|-------------|----|--------|---------|----|--------|----|--------|----|--------|----|--------|---------|
|             | All |        |         | Spring |        | Summer |        | Autumn |        | Winter |        |         |         |
|             | 1113| 284    | 243     | 290    | 296    |         |         |         |         |         |         |         |         |
| 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%) | 0.97 | 10 (7 %) | 11 (8 %) | 11 (10 %) | 10 (7 %) | 5 (3 %) | 8 (5 %) | 14 (8 %) | 10 (8 %) | 0.57 |
| Previous MI | 40 (7%) | 39 (7%) | 0.98 | 12 (8 %) | 10 (7 %) | 11 (10 %) | 10 (7 %) | 8 (6 %) | 10 (7 %) | 14 (8 %) | 14 (11%) | 0.77 |
| 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 | | | | | | | | | | | |
| ST elevation | 369 (66%) | 245 (44%) | | 94 (66%) | 66 (47%) | 66 (62%) | 52 (38%) | 90 (63%) | 69 (66%) | 119 (71%) | 58 (46%) | <0.001 |
| 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 |
| Parameter          | Value 1 | Value 2 | p-value |
|--------------------|---------|---------|---------|
| Hb (g/dl)          | 14.0 ± 1.8 | 14.0 ± 1.9 | 0.95    |
| T-cholesterol level (mg/dl) | 194.6 ± 41.9 | 190.0 ± 42.8 | **0.03** |
| LDL-C level (mg/dl) | 129.1 ± 42.2 | 120.2 ± 40.2 | **<0.001** |
| HDL-C level (mg/dl) | 45.7 ± 13.9 | 47.6 ± 13.9 | **0.03** |
| TG level (mg/dl)   | 119.5 ± 93.8 | 132.1 ± 101.0 | **0.04** |
| Hs-CRP level (mg/dl) | 0.83 ± 2.23 | 0.57 ± 1.31 | **0.03** |
| HbA1c (%)          | 6.2 ± 1.3 | 6.2 ± 1.2 | 0.56    |
| Creatinine (mg/dl) | 0.97 ± 0.82 | 1.11 ± 1.45 | 0.06    |
| eGFR (mL/min per 1.73 m²) | 104 ± 171 | 99 ± 151 | 0.59    |
| Peak CK (IU)       | 2201 ± 2435 | 1455 ± 1998 | **<0.001** |
| Peak CKMB (IU)     | 222 ± 258 | 150 ± 198 | **<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      | P-Value |
|------------------|----------|----------|-----------|----------|----------|----------|----------|---------|
| Patients, n      | 1113     | 841      | 82        | 100      | 62       | 15       | 13       |         |
| 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 |          |          |          |          |          |          |          |
|---------------------------|------------|----------|----------|----------|----------|----------|----------|----------|
|                           |            | OR       | 95% CI   | P-value  | OR       | 95% CI   | P-value  |          |
| Plaque rupture            |            |          |          |          |          |          |          |          |
| Age                       | 1.001      | 0.991-1.011 | 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   |          |          |
| Country     | USA   | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         | Plaque erosion | CI         |
|-------------|-------|------------|----------------|------------|----------------|------------|----------------|------------|----------------|------------|----------------|------------|----------------|------------|----------------|------------|----------------|------------|----------------|------------|
| 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
Number of cases in each year

Cases, n

Figure S3