Impact of the Temporal Distribution of Coronary Artery Disease Progression on Subsequent Consequences in Patients with Acute Coronary Syndrome

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Summary
The late consequences of acute coronary syndrome (ACS) have been underestimated. We hypothesized that the temporal distribution of the clinically silent coronary artery disease progression (CP) is associated with the subsequent consequences of ACS.

We studied 243 patients (202 men, 64 ± 10 years) with ACS undergoing percutaneous coronary intervention (PCI) during initial hospitalization. All patients underwent serial coronary angiograms (CAGs) immediately before PCI and at 7 ± 3 and 60 ± 10 months after presentation. CP was defined as an increase ≥ 15% in stenosis severity of the lesion between 2 serial CAGs. The impact of CP between each 2 serial CAGs on subsequent major adverse cardiovascular and cerebrovascular events (MACCEs) after the final CAG was examined using multivariate Cox and propensity-matched analyses.

During the median follow-up duration after the final CAG of 67 months, 76 MACCEs (31.3%) were observed. Multivariate Cox proportional hazards analysis revealed that CP between the first and second CAGs (hazard ratio [HR], 2.28; 95% confidence interval [CI], 1.32-3.94; P = 0.003) and CP between the second and final CAGs (HR, 1.96; 95% CI, 1.20-3.21; P = 0.008) were independently associated with a higher rate of MACCEs beyond the final CAG. Consistent results were obtained in the propensity score-matched analyses.

CP in both the early (0-7 months) and late phases (7-60 months) were independently associated with subsequent clinical events. This may indicate the prognostic significance of persistent widespread coronary disease activity following presentation in patients with ACS undergoing PCI.

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Key words: Coronary angiography, Follow-up study

Recent reports have revealed that the late consequences of acute coronary syndrome (ACS) may have been underestimated.1-3 In ACS patients, the late events are recognized to be substantially greater than those seen in the early phase. Meanwhile, regardless of whether clinically silent or associated with acute coronary events, coronary artery disease progression (CP) detected on serial coronary angiograms (CAGs) has been shown to be a powerful predictor of cardiovascular events in patients with stable angina pectoris14 and ACS.15 However, in these previous reports, the intervals between serial CAGs were mostly limited to months, with a maximum of up to 2 years.16 In addition, the relationship between the temporal distribution of clinically silent CP and subsequent consequences in ACS patients has not been elucidated. Therefore, in the past, routine follow-up CAGs were performed at 7 and 60 months after index presentation in ACS patients undergoing percutaneous coronary intervention (PCI) at our institution.

Thus, the purpose of the present study was to evaluate the impact of CP in the early (0-7 months) and late (7-60 months) phases on subsequent clinical events in ACS patients who underwent PCI, and survived 5 years without recurrence.

Methods

Study population: A total of 243 patients (mean age, 64 ± 10 years; 202 men, 41 women) with ACS were studied. All patients were admitted to our institution and fulfilled the following criteria: (1) successful PCI (residual narrowing < 20%) of the culprit lesion (de novo lesion) during the initial hospitalization; (2) serial CAGs immediately before PCI, at 7 ± 3 months, and 60 ± 10 months after index presentation; and (3) fully assessable angiographic data of the 3 serial CAGs. As shown in the time-
line of the present study (Figure 1), clinical information beyond the final CAG was obtained to evaluate the impact of CP between each two serial CAGs on subsequent clinical outcomes.

ACS consists of ST-segment elevation ACS (STEACS) and non-ST-segment elevation ACS (NSTEACS). STEACS was defined as the presence of angina symptoms (>20 minutes) associated with electrocardiographic ST-segment elevation of at least 0.1 mV in two limb leads or at least 0.2 mV in two contiguous precordial leads, and an increase in biochemical markers of cardiac necrosis (creatine kinase-myocardial band, creatine phosphokinase, or troponin T). NSTEACS included non-ST-segment elevation myocardial infarction and unstable angina pectoris. Non-ST-segment elevation myocardial infarction was defined as ischemic symptoms in the absence of ST elevation on the electrocardiogram (ECG) with elevated biochemical markers of cardiac necrosis. Unstable angina pectoris was defined as new-onset severe angina, accelerated angina, or angina at rest without a significant increase in cardiac-specific troponin T values. New-onset angina was defined as that occurring <2 months from the date of initial symptoms. Accelerated angina was defined as angina in which symptoms were more frequent, more severe, longer, or precipitated by distinctly less exertion than previous occurrences with the patient in a stable condition.

Patients with any of the following characteristics were excluded: (1) history of ACS, (2) history of coronary artery bypass grafting, (3) bundle branch block on initial ECG, (4) inability to detect clinically significant stenosis on initial CAG, or (5) recurrence of ACS within 5 years after index presentation.

Within 5 years after index presentation, 15 patients died within 7 months of presentation of ACS (all cardiac causes), and 11 patients died at 7-60 months while scheduled for repeat follow-up CAG. A second CAG was refused by 2 patients, and 9 patients refused a final CAG. Meanwhile, 10 patients in the early phase and 19 patients in the late phase were admitted for recurrent ACS. These patients were not included in the present study.

This study was approved by the institutional review board of Kanagawa Cardiovascular and Respiratory Center. Due to the retrospective nature of the present study,
the review board waived the need for written informed patient consent for participation in the present study. **CAG analysis:** Serial CAGs were performed immediately before PCI and at 7 ± 3 and 60 ± 10 months after presentation. Images of the coronary tree were obtained in routine standardized projections with an INTEGRIS BH3000 system (Philips Healthcare, Best, The Netherlands).

The images were recorded as appropriate and reproduced at the time of follow-up CAGs. After direct intracoronary injection of 2.5 mg isosorbide dinitrate into the left and right coronary arteries to exclude the effects of coronary spasm, diagnostic and follow-up CAG images were obtained. Quantitative CAG (QAngioXA 7.1; Medis Medical Imaging Systems, Leiden, The Netherlands) was used to analyze the images of the coronary tree. Pairs of first, second, and final CAGs obtained in the same projection were quantitatively and qualitatively assessed by two experienced cardiologists blinded to all other clinical data. The stem of a Judkins coronary catheter was used for calibration to determine absolute measurements in millimeters. For each segment, measurements were carried out on end-diastolic frames in which the severity of the stenoses appeared maximal. A stenosis > 50% was considered clinically significant. Stenoses < 30% on all CAGs were not included in the quantitative measurement of stenosis severity and qualitative assessment of stenosis morphology. Stenosis was classified as complex (eccentric, with overhanging edges, irregular borders, and/or showing ulceration or thrombus) or smooth (concentric or eccentric lesions with smooth edges, in the absence of complex features).5,6 The culprit lesion was defined as a lesion with the most severe narrowing or that with complex morphology, intracoronary thrombus, or both. Lesions within 20 mm of the culprit lesion were excluded. We evaluated the CP of non-culprit lesions that had not been treated by PCI. Similar to previous studies, CP was defined as an increase in the stenosis severity of the non-culprit lesion by > 15% between two serial CAGs, or the progression of any lesion to total occlusion on the second angiography. Between the first and second CAGs, 53 of the 243 patients (21.8%) had CP: 51 patients had > 15% reduction in the lumen diameter and 2 had progression of a lesion to total occlusion on the second angiography. Between the first and second CAGs, 83 of the 243 patients (34.2%) had CP: 80 patients had > 15% reduction in the lumen diameter and 3 had progression of a lesion to total occlusion on final angiography.

**Biochemical markers:** Blood samples for the measurement of serum creatinine, lipid profiles, hemoglobin A1c, and white blood cell count were taken on initial admission and at follow-up CAGs. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation for creatinine, as modified by the Japanese Society of Nephrology11: eGFR (mL/minute/1.73 m²) = 194 × (serum creatinine)^−1.094 × (age)^−0.203 (× 0.739 if female). In addition, a quantitative assay for cardiac-specific troponin T (Roche Diagnostic, Tokyo, Japan; detection limit, 0.1 ng/mL) was performed on initial admission. A troponin T level ≥ 0.1 ng/mL was defined as positive.

**Follow-up:** Clinical information beyond 5 years after index presentation was obtained from hospital records and via telephone interviews of patients. Major adverse cardiovascular and cerebrovascular events (MACCEs) included death, non-fatal myocardial infarction, unstable angina requiring revascularization, cerebral infarction, and hospitalization due to heart failure. When a patient experienced more than one event, the first event was included in the analysis. When at least two events occurred simultaneously, the events were selected in the order of death > non-fatal myocardial infarction > cerebral infarction > unstable angina > heart failure.

**Statistical analysis:** The data were statistically analyzed using SPSS statistics version 24 (IBM, Armonk, NY) and Medcalc 11.1 (Medcalc, Gent, Belgium). Continuous values are expressed as means ± standard deviation. Categorical data are presented as frequencies and percentages. Normality was evaluated by the Shapiro-Wilk test. Normally distributed values were compared by an unpaired t-test, and non-normally distributed values were compared by the Mann-Whitney U test. Categorical data were compared by the chi-squared test or Fisher's exact test. Univariate associations with MACCEs were determined by Cox proportional hazards regression including CP between each two serial CAGs, and the baseline patient characteristics are shown in Table I and Table II. Event-free survival stratified by CP between each two serial CAGs was estimated with the Kaplan-Meier survival methods. Clinical and angiographic variables showing values of $P < 0.1$ in univariate models were incorporated into multivariate Cox proportional hazards analyses. Since the patient characteristics related to the presence or absence of CP between each two serial CAGs may confound subsequent clinical outcomes, we performed a propensity score-matched analysis. The following variables were used to estimate the propensity score according to CP in the early and late phases: eGFR < 60 (mL/minute/1.73 m²), multivessel disease, multiple complex lesions at index presentation, and statin use at the second CAG for patients with or without CP in the early phase; eGFR < 60 (mL/minute/1.73 m²), diabetes mellitus, NSTEACS at index presentation, and statin use at the final CAG for patients with or without CP in the late phase. These variables were selected based on previous studies addressing this issue from a similar clinical perspective.9,10,12-14 Patients with CP were 1:1 matched to patients without CP based on their propensity score using a caliper of 0.1 of the standard deviation of the logit of the propensity score. For all analyses, $P$ values < 0.05 were considered to indicate statistical significance.

**Results**

A total of 243 culprit lesions and 534 non-culprit lesions (mean, 2.20 per patient) were analyzed. Among the 534 non-culprit lesions, 191 complex lesions were identified. The rate of multiple complex lesions50 (at least 2 complex lesions including the culprit lesions) was 46.1%. Between the first and second CAGs, 53 of the 243 patients (21.8%) had CP: 51 patients had > 15% reduction in the lumen diameter and 2 had progression of a lesion to total occlusion on the second angiography. Between the second and final CAGs, 83 of the 243 patients (34.2%) had CP: 80 patients had > 15% reduction in the lumen diameter and 3 had progression of a lesion to total occlusion on final angiography.
Patient characteristics: The baseline and follow-up data of the clinical characteristics and angiographic findings according to the presence or absence of CP between each two serial CAGs are summarized in Table I and Table II. Patients with CP between the first and second CAGs were older than those without. At acute presentation, in the second CAG and final CAG, the eGFR was significantly lower in patients with CP in the early phase than in those without. Medication and angiographic follow-up periods did not differ according to CP in the early phase. There was a higher prevalence of multivessel disease (79% versus 55%, \( P = 0.002 \)) and multiple complex lesions (76% versus 38%, \( P < 0.001 \)) in patients with CP in the early phase.
Diabetes mellitus (40% versus 25%, \( P = 0.017 \)) and NSTEACS (72% versus 52%, \( P = 0.002 \)) was found more frequently in patients with CP between the second and final CAGs than those without. The presence of CP in the late phase was significantly associated with lower eGFR at the final CAG. With the exception of triglycerides at acute presentation and high-density lipoprotein cholesterol at the final CAG, lipid profiles did not differ between patients with and without CP in the late phase. Patients with and without CP in the late phase were similar with respect to medications and angiographic follow-up periods. Multiple complex lesions were more often found in patients with CP in the late phase than those without.

**Subsequent consequences:** During the median follow-up duration beyond the final CAG of 67 months, 76 patients (31.3%) experienced cardiovascular events: 14 deaths, 7 myocardial infarctions, 22 unstable anginas, 27 heart failures, and 6 cerebral infarctions. Kaplan-Meier curves demonstrated that the best prognosis was seen in patients without CP in the early or late phase, with no interactions found between CP in the early and late phases and MACCEs beyond the final CAG (Figure 2). The detailed incidence of adverse events stratified by CP between the two serial CAGs during the follow-up period is shown in Figure 3, with the lowest rates of unstable angina and heart failure in patients without CP in the early or late phases.

**Predictors of MACCEs beyond 5 years after index presentation of ACS:** As shown in Table III, multiple Cox proportional hazards analysis revealed that independent and significant predictors for MACCEs beyond the final CAG were CP between the first and second CAGs [hazard ratio (HR), 2.28; 95% confidence interval (CI), 1.32-3.94; \( P = 0.003 \)], CP between the second and final CAGs (HR, 1.96; 95% CI, 1.20-3.21; \( P = 0.008 \)), age > 65 (HR, 1.71; 95% CI, 1.03-2.82; \( P = 0.036 \)), positive troponin T (HR, 1.94; 95% CI, 1.17-3.21; \( P = 0.010 \)), and NSTEACS (HR, 1.81; 95% CI, 1.07-3.06; \( P = 0.028 \)).

**Propensity score-matched analysis:** Propensity score matching resulted in 49 pairs of patients with or without CP in the early phase and 78 pairs of those with or without CP in the late phase. Figure 4A and B show the changes in standardized differences in covariates of patients with or without CP between each two serial CAGs after 1:1 propensity score matching. None of the covariates had a post-matching standardized difference > 0.2, which indicates an acceptable balance. CP in both the early (\( P = 0.009 \) by Log-Rank test) and late phases (\( P = 0.011 \) by Log-Rank test) was significantly associated with a higher incidence of MACCEs beyond the final CAG in the propensity score-matched cohort (Figure 4C and D).

**Discussion**

The major findings of this study were that CP in both the early (0-7 months) and late (7-60 months) phases during 5 years after presentation with ACS were independently associated with subsequent clinical events. This indicates that sustained disease activity across the coronary artery tree during 5 years after the presentation has long-term prognostic significance in patients with ACS undergoing PCI.

**CP during the 5 years after index presentation of ACS and subsequent events:** In the present study, disease progression during a mean interval of 7 months between the first and second CAGs was detected in 21.8% of patients presenting with ACS, which is consistent with previous reports that showed that the incidence of stenosis progression in non-culprit lesions was 28% and 23% on repeat angiography at 7 and 11 months, respectively.\(^{12,14}\) Although several reports have assessed the effect of CP on clinical outcomes, the intervals between serial CAGs were mainly limited to months,\(^{5,7}\) up to a maximum of 2 years.\(^{6}\) On the other hand, with the exception of our previous report,\(^{10}\) CP in the late phase has not been investigated. A strong point of the current study was that we evaluated the impact of the temporal distribution of CP on subsequent clinical outcomes by analyzing both CP in the early and late phases during 5 years after index presentation of ACS. As a result, silent CP in both the early and late phases was shown to indicate an ongoing risk of subsequent clinical events in patients with ACS surviving 5 years without recurrences.

**Clinical implications:** Recently, several reports on 10-
Figure 2. Event-free survival curves beyond 5 years after index presentation of acute coronary syndrome, stratified by coronary artery disease progression between each two serial coronary angiographies. CP indicates coronary artery disease progression.

Figure 3. Detailed incidence of major adverse cardiovascular and cerebrovascular events stratified by coronary artery disease progression between each two serial coronary angiographies. CP indicates coronary artery disease progression; CAG, coronary angiography; MACCEs, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; UAP, unstable angina pectoris; HF, heart failure; and CI, cerebrovascular infarction.
Table III. Cox Proportional Hazards Analysis for Major Cardiovascular and Cerebrovascular Events Beyond Final Coronary Angiography

|                               | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                               | HR (95% CI)         | P value               | HR (95% CI)         | P value               |
| CP between the first and second CAGs | 2.73 (1.71-4.38)    | <0.001                | 2.28 (1.32-3.94)    | 0.003*                |
| CP between the second and final CAGs | 2.53 (1.61-3.99)    | <0.001                | 1.96 (1.20-3.21)    | 0.008*                |
| Multiple complex lesions       | 2.06 (1.30-3.27)    | 0.002                 | 1.22 (0.73-2.05)    | 0.45                  |
| Age > 65 (years)               | 1.99 (1.24-3.19)    | 0.004                 | 1.71 (1.03-2.82)    | 0.036*                |
| eGFR < 60 (mL/minute/1.73m²)   | 1.77 (1.09-2.88)    | 0.022                 | 0.87 (0.50-1.51)    | 0.62                  |
| Positive troponin T            | 2.09 (1.32-3.29)    | 0.001                 | 1.94 (1.17-3.21)    | 0.010*                |
| NSTEACS                        | 1.50 (0.93-2.41)    | 0.09                  | 1.81 (1.07-3.06)    | 0.028*                |

A multivariate Cox proportional hazards analysis was used to identify the predictors of MACCEs beyond the final CAG among the variables associated (P < 0.1) with this outcome on univariate analysis including CP between two serial CAGs and baseline patient characteristics shown in Table I and Table II. *Statistically significant values (P < 0.05) in multivariate analysis. MACCE indicates major cardiovascular and cerebrovascular event; CAG, coronary angiography; HR, hazard ratio; CI, confidence interval; CP, coronary artery disease progression; eGFR, estimated glomerular filtration rate; and NSTEACS, non-ST-segment elevation acute coronary syndrome.

Figure 4. The standardized differences and event-free survival curves after propensity-matched analyses. A: Covariable balance before (blue triangles) and after (red circles) matching in patients with or with CP in the early phase. B: Covariable balance before (blue triangles) and after (red circles) matching in patients with or with CP in the late phase. C: Kaplan-Meier event-free survival curves for major adverse cardiac and cerebrovascular events in propensity score-matched pairs of patients with or without CP in the early phase. D: Kaplan-Meier event-free survival curves for major adverse cardiac and cerebrovascular events in propensity score-matched pairs of patients with or without CP in the late phase. CP indicates coronary artery disease progression; eGFR, estimated glomerular filtration rate; CAG, coronary angiography; and NSTEACS, non-ST-segment elevation acute coronary syndrome.
year follow-up outcomes of ACS have been published.\(^{16-18}\) However, little information is available about predictors of adverse events beyond 5 years after index presentation of ACS. In the present study, age > 65 and positive troponin T at acute presentation were significant predictors of MACCEs beyond the final CAG. Additionally, NSTEACS was also significantly associated with MACCEs beyond the final CAG. This finding is in line with previous reports showing ST-segment category at acute presentation and time-dependent outcomes of ACS patients.\(^{1-3}\) Meanwhile, the presence of multiple complex lesions, which indicates instability of the coronary tree, differed according to the presence or absence of CP in the early and late phases but was not a significant predictor of MACCEs beyond the final CAG. These results confirm and extend previous studies showing the impact of patient characteristics on the clinical outcomes of ACS patients.\(^{13,15,19,20}\)

**The appropriateness of follow-up CAG:** The appropriateness of routine follow-up CAG remains controversial, with a range of reports yielding contradictory findings. Although some reports point to an association between asymptomatic restenosis at routine follow-up CAG and long-term mortality,\(^{21}\) others have failed to identify a meaningful association.\(^{22}\) Based on the consistent findings indicating the prognostic significance of CP, more attention should be paid to non-culprit lesions during follow-up CAG in ACS patients who have undergone previous PCI.\(^{23}\) At present, it is unclear how to apply these results to the treatment strategy for improvement of outcomes in ACS patients. Routine procedural interventions for progressed lesions at follow-up CAGs would be highly ineffective because lesions with an increase in stenosis severity by 15% at follow-up CAG do not always progress, leading to the induction of ischemia in perfusion territory. However, to this day, the effectiveness and durability of long-term therapies in ACS patients have yet to be conclusively determined. Basically, routine follow-up CAGs for all patients undergoing PCI would be questionable from the perspective of medical economics. To discuss the appropriateness of follow-up CAGs in greater depth, further studies are required to assess the prognostic effect of more aggressive pharmacotherapy for patients with clinically silent CP between serial CAGs, especially in high-risk patients such as those with ACS. Meanwhile, scrutinizing plaque characteristics of progressed lesions with dedicated imaging modalities might contribute to further risk stratification for ACS patients with CP in follow-up CAGs.

**Limitations:** Several limitations to this study should be acknowledged. First, this was a small retrospective study that included only ACS patients who underwent PCI during the initial hospitalization and planned CAGs. A significant number of patients who refused follow-up CAGs were not included in the present study, which may have introduced a bias. Second, data regarding cardiac function, such as the left ventricular ejection fraction, were not obtained. Third, the choice of a cut-off point to define progression is necessarily arbitrary. The choice of 15% in the present study was based on widely accepted criteria.\(^{9,10}\)

**Conclusions**

CP in both the early (0-7 months) and late (7-60 months) phases during 5 years after index presentation of ACS were independently associated with subsequent clinical events. This may indicate the prognostic significance of persistent widespread coronary disease activity following presentation in patients with ACS undergoing PCI.

**Disclosures**

**Conflicts of interest:** The authors declare that they have no conflict of interest.

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