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ORIGINAL RESEARCH

Analysis of Coronary Arterial Aneurysm Regression in Patients With Kawasaki Disease by Aneurysm Severity: Factors Associated With Regression

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BACKGROUND: Coronary arterial aneurysms (CAAs) associated with Kawasaki disease (KD) significantly affect prognosis. However, the clinical course of CAAs and factors associated with CAA regression have not been well analyzed.

METHODS AND RESULTS: The cohort of the Z-Score 2nd Project Stage study, a multicenter, retrospective, cohort study involving 44 institutions in Japan including 1006 patients with KD, was examined. CAAs were classified by the *z* score of their internal diameter in the acute phase: small ($z<5$), medium ($5\leq z<10$), and large ($z\geq 10$). The lower limit of small CAA was based on the Japanese Ministry of Health, Labour and Welfare criteria. In the right coronary artery, the CAA regression rates 10 years after diagnosis were 95.5% for small, 83.2% for medium, and 36.3% for large. In the proximal left anterior descending artery, the regression rates 10 years after diagnosis were 95.3% for small, 80.1% for medium, and 28.8% for large. Cox regression analysis showed that diagnosis under the age of 1 year and onset of KD in 2010 to 2012 for the right coronary artery and the left anterior descending artery, and female for the right coronary artery were significantly associated with a high regression rate, whereas large CAAs for the right coronary artery and the left anterior descending artery were significantly associated with a low regression rate.

CONCLUSIONS: The current study, the largest Japanese study of its kind, found that small aneurysm, recent onset, and diagnosis under the age of 1 year predict regression, and that even giant aneurysms could regress. These data may contribute to long-term management of coronary aneurysms.

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Key Words: coronary aneurysm ■ Kawasaki disease ■ regression

Kawasaki disease (KD) is an acute medium vessel vasculitis of unknown cause and is the most common acquired cardiovascular disease in children in developed countries.[1,2] The development of a coronary arterial aneurysm (CAA) is the most important sequela affecting the prognosis in KD, with a reported incidence of 20% to 25% before immunoglobulin use.[3,4] After the preventive action of high-dose immunoglobulin against CAA was reported, many adjunctive therapies including prednisolone, methylprednisolone, infliximab, and

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For Sources of Funding and Disclosures, see page 11.

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CLINICAL PERSPECTIVE

What Is New?

- In this, the largest Japanese study with the longest follow-up of coronary arterial aneurysm (CAA), the severity of CAA classified by the *z* score of coronary arterial internal diameter in the acute phase was significantly associated with the CAA regression rate.
- Small CAAs, CAAs in patients younger than 1 year of age at diagnosis, CAAs in patients with onset of Kawasaki disease in the most recent period, and CAAs of the right coronary artery in female patients were factors associated with regression during long-term follow-up.

What Are the Clinical Implications?

- The present data may contribute to the investigation of the regression mechanisms and more appropriate long-term management of CAA according to its severity.
- Prospective studies to validate these data are warranted.

Nonstandard Abbreviations and Acronyms

CAA	coronary arterial aneurysm
KD	Kawasaki disease
LMP	luminal myofibroblastic proliferation

cyclosporine have been used in the treatment of KD.[5,6] Patients with CAAs, especially giant ones, are exposed to the risk of coronary arterial stenosis, obstruction, and thrombosis, which may result in angina pectoris or myocardial infarction. To prevent such cardiac events, patients with CAAs are usually managed with oral antiplatelet agents and/or warfarin.[5,6] On the other hand, CAAs often show regression to normal internal diameters. The incidence of regression was reported to be 55% to 65% before immunoglobulin use, and a recent report shows that 75% of CAAs regressed within 2 years of disease onset.[4,7]

The pathological process of CAA formation and regression is thought to include the following mechanisms. Acute necrotizing arteritis in the acute phase of KD destroys the normal structure of the coronary arteries, making them vulnerable. The weakened coronary arteries dilate as a result of the internal pressure of the blood vessels, resulting in the formation of CAAs. Luminal myofibroblastic proliferation (LMP) involving smooth muscle cell–derived myofibroblasts contributes to the normalization of coronary artery lumen morphology.[6,8] Although the vasodilatory and vasoconstrictive properties are not normal,[9] this process has been called regression. Despite the clinical implication for this endothelial disfunction being unclear, it should be included as a potential complication of CAA.

Recently, we reported that the classification of CAAs by the *z* score of the internal diameter was related to the risk of cardiac events.[10] However, there is limited knowledge of the clinical course of regression and the factors associated with regression when stratified by CAA size. In this study, the clinical course of CAA regression and the factors associated with regression were examined using the *z* score classification of the coronary arterial internal diameter.

METHODS

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

Study Design

A retrospective, cohort study of patients enrolled in the Z-Score Project 2nd Stage study from July 2012 to December 2015 was performed.[8] The design of the Z-Score Project 2nd Stage study was previously described in detail.[10] Briefly, consecutive patients with KD younger than 19 years who underwent coronary angiography between January 1992 and December 2011 in 44 participating institutions in Japan were included. Coronary angiography included cardiac catheterization, coronary multidetector computed tomography, and magnetic resonance coronary angiography. Patients were excluded if the internal diameter of the coronary artery in the acute phase had not been measured by echocardiography or if severe disorders that may affect coronary artery lesions or prognosis other than KD were present. Patients were diagnosed and treated based on the guidelines for medical treatment of acute KD of the Japanese Society of Cardiology and the Japanese Society of Pediatric Cardiology and Cardiac Surgery.[5] This study was conducted in compliance with the Declaration of Helsinki and the ethical guidelines issued by the Ministry of Health, Labour, and Welfare, Japan, and was approved by the ethics review board at Tokyo Metropolitan Children's Medical Center (approval number H23-105). This study was registered with the University Hospital Medical Information Network clinical trial registry (UMIN000010606). Because this was a retrospective, observational study, the need to obtain informed consent was waived.

Data Collection

The following data were obtained from the database of the Z-Score Project 2nd Stage study: demographic

data, medical interventions, coronary arterial internal diameter, and cardiac outcomes from the time of the first diagnosis to the last visit. Demographic data included sex, age at KD diagnosis, weight and height at the time of KD diagnosis, date of disease onset, and the data of the last visit. Medical interventions included intravenous immunoglobulin (IVIG), prednisolone or methylprednisolone, ulinastatin, infliximab, cyclosporine, or plasma exchange during acute-phase anti-inflammatory treatment, antiplatelet drugs in the acute or chronic phase, and warfarin treatment during the chronic phase. Maximum coronary arterial internal diameter of the right coronary artery (RCA) and that of the proximal left anterior descending artery (LAD) in the acute phase were determined by echocardiography.

Definition and Classification

In this study, CAA was defined in accordance with the report of the Japanese Ministry of Health and Welfare.[11] Namely, a CAA was defined as an actual internal diameter of ≥3 mm in a child younger than 5 years or ≥4 mm in a child 5 years or older, the internal diameter of the segment being at least 1.5 times greater than that of an adjacent segment, or the luminal contour being clearly irregular. The *z* score of coronary arterial internal diameter was calculated using the previously reported *z* score curve.[12] The CAA severity was classified by the *z* score of the internal diameter of the echocardiographic findings in the acute phase as follows: small, *z* score <5; medium, *z* score 5 to 10 and an actual internal diameter <8 mm; and large, *z* score ≥10, or an actual internal diameter of ≥8 mm.[6,13] Patients whose *z* score was unavailable and whose CAA internal diameter was <8 mm were defined as unclassifiable. A patient who required additional therapy following the initial treatment was defined as being resistant to the initial treatment. Regression was defined by repeat echocardiography or coronary angiography performed at least 30 days after the onset of KD showing that the internal diameter of a previously known CAA reduced spontaneously to the point where it could no longer qualify as a CAA by the Japanese Ministry of Health and Welfare criteria applicable to the patient. The regression rate was defined as the number of patients with regressed CAAs divided by the number of total patients with CAAs.

Statistical Analysis

Demographic data are described according to the CAA severity classification. Continuous variables are reported as medians and interquartile ranges (IQRs). Categorical variables are reported as frequencies and proportions. The regression rate was analyzed using the Kaplan–Meier method and log-rank test. The factors associated with regression were determined using Cox regression analysis with robust variance adjustment. All 5 variables that were considered to be important to consider from previous studies, namely CAA severity classified by the *z* score of the internal diameter, sex, age at diagnosis, initial treatment and response, and decade at onset, were tested independently. Subsequently, all variables were entered into the model together, regardless of whether they were significant. A 2-sided $P<0.05$ was considered significant. All statistical analyses were performed using SPSS version 23.0 (IBM).

RESULTS

Demographic and Clinical Data

During the study period, 1006 patients with KD were enrolled in the Z-Score Project 2nd Stage study. Of them, the data for 754 and 615 patients with CAAs in the RCA and LAD, respectively, were reviewed in this study. The median age at diagnosis of KD was 1.8 years (IQR, 0.64–3.81 years).

Table 1 shows the demographic data of patients with CAAs classified by CAA severity. In the RCA, the CAAs were small, medium, and large in 15.8%, 49.5%, and 34.6%, respectively. In the LAD, the CAAs were small, medium, and large in 18.5%, 62.7%, and 18.8%, respectively. Male patients accounted for 71.2% and 70.4% of patients with CAAs in the RCA and LAD, respectively. Patients younger than 1 year of age at diagnosis accounted for 35.4% of patients with CAAs in the RCA and 32.2% of patients with CAAs in the LAD.

Treatments

For the initial treatment, IVIG was not administered to 74 (9.9%) and 62 (10.2%) patients with CAAs in the RCA and LAD, respectively (Table 1). In patients with CAAs in the RCA, 259 (34.6%) responded to initial IVIG treatment, and 416 (55.5%) did not. In patients with CAAs in the LAD, 196 (32.1%) responded to initial IVIG treatment, and 352 (57.7%) did not. Steroids, including prednisolone and methylprednisolone, were administered to 42 (4.2%) and 209 (20.8%) patients as an initial treatment and as additional therapy, respectively. Other treatments in the acute phase were: ulinastatin in 95 (12.6%) and 75 (12.2%) patients, infliximab in 21 (2.8%) and 22 (3.6%) patients, cyclosporine A in 16 (2.1%) and 16 (2.6%) patients, and plasma exchange in 15 (2.0%) and 14 (2.3%) patients with CAAs in the RCA and LAD, respectively. In the chronic phase (defined as 91 days after onset), aspirin and warfarin were administered to 669 (88.7%) and 225 (29.8%) patients with CAAs in the RCA, and 545 (88.8%) and 200 (32.6%) patients with CAAs in the LAD, respectively. Multiple antiplatelet reagents were administered to 337 (44.7%) and 278 (45.3%) patients with CAAs in the RCA and LAD, respectively.

Table 1. Demographic Data of Patients With CAA

	No. (%)				
	Total*	Small	Medium	Large	Unclassifiable
RCA					
No. of patients	754	101	316	221	116
Male	537 (71.2)	76 (75.2)	241 (76.3)	135 (61.1)	85 (73.3)
Age at diagnosis <1 y	265 (35.4)	15 (14.9)	112 (35.4)	92 (42.0)	46 (41.1)
Age at diagnosis ≥1 to <5 y	368 (49.2)	63 (62.4)	160 (50.6)	90 (41.1)	55 (49.1)
Age at diagnosis ≥5 y	115 (15.4)	23 (22.8)	44 (13.9)	37 (16.9)	11 (9.8)
Initial IVIG-resistant	416 (55.5)	49 (48.5)	174 (55.4)	144 (65.5)	49 (43.0)
Initial IVIG-responsive	259 (34.6)	43 (42.6)	109 (34.7)	59 (26.8)	48 (42.1)
Initial IVIG-none	74 (9.9)	9 (8.9)	31 (9.9)	17 (7.7)	17 (14.9)
Regression	513 (68.0)	92 (91.1)	253 (80.1)	77 (34.8)	91 (78.4)
Date at diagnosis 1981–1999	246 (32.9)	33 (32.7)	94 (29.7)	71 (32.4)	48 (42.9)
Date at diagnosis 2000–2009	438 (58.6)	57 (56.4)	190 (60.1)	127 (58.0)	64 (57.1)
Date at diagnosis 2010–2012	64 (8.6)	11 (10.9)	32 (10.1)	21 (9.6)	0 (0.0)
LAD					
No. of patients	615	96	326	98	95
Male	433 (70.4)	81 (84.4)	224 (68.7)	63 (64.3)	65 (68.4)
Age at diagnosis <1 y	198 (32.2)	24 (25.0)	123 (37.7)	21 (21.4)	30 (31.9)
Age at diagnosis ≥1 to <5 y	317 (51.6)	59 (61.5)	158 (48.5)	50 (51.0)	50 (53.2)
Age at diagnosis ≥5 y	99 (16.1)	13 (13.5)	45 (13.8)	27 (27.6)	14 (14.9)
Initial IVIG-resistant	352 (57.7)	54 (56.8)	188 (57.8)	69 (70.4)	41 (44.6)
Initial IVIG-responsive	196 (32.1)	32 (33.7)	105 (32.3)	22 (22.5)	37 (40.2)
Initial IVIG-none	62 (10.2)	9 (9.5)	32 (9.9)	7 (7.1)	14 (15.2)
Regression	436 (70.9)	90 (93.8)	252 (77.3)	26 (26.5)	68 (71.6)
Date at diagnosis 1981–1999	193 (31.4)	26 (27.1)	102 (31.3)	25 (25.5)	40 (42.6)
Date at diagnosis 2000–2009	356 (58.0)	60 (62.5)	179 (54.9)	63 (64.3)	54 (57.4)
Date at diagnosis 2010–2012	65 (10.6)	10 (10.4)	45 (13.8)	10 (10.2)	0 (0.0)

IVIG indicates intravenous immunoglobulin; LAD, left anterior descending artery; and RCA, right coronary artery.
*Patients whose *z* score was unavailable and whose coronary arterial aneurysm (CAA) internal diameter was <8 mm were defined as unclassifiable.

Overall Regression Rate

The overall regression rate during the study period was 68.0% in the RCA and 70.9% in the LAD (Table 2). The overall regression rates of CAAs by patients' attributes during the study period are also shown in Table 2.

Time-Dependent Changes of Regression Rates

Regression was observed in 49.1% in the RCA and in 51.0% in the LAD within 2 years. In the RCA, the regression rates of CAAs 5 and 10 years after diagnosis were 86.8% and 95.5% for small, 75.5% and 83.2% for medium, and 29.6% and 36.3% for large, respectively. In the LAD, the regression rates 5 and 10 years after diagnosis were 87.6% and 95.3% for small, 69.9% and 80.1% for medium, and 20.8% and 28.8% for large, respectively (Figure 1A and 1B).

Figure 2 shows the Kaplan–Meier curves of the regression rate classified by CAA severity in male and female patients. In the RCA, the 10-year regression rate was 96.2%, 79.9%, and 27.3% in male patients and 92.5%, 93.2%, and 50.2% in female patients with small, medium, and large CAAs, respectively. In the LAD, the 10-year regression rate was 94.3%, 81.1%, and 22.5% in male patients and 100.0%, 78.5%, and 39.7% in female patients with small, medium, and large CAAs, respectively.

When CAAs were classified by age at onset, the CAA regression rate was higher in younger patients than in older patients in both the RCA and the LAD (Figure 3A and 3B). Furthermore, when classified by decade at onset, the CAA regression rate was higher in the more recent period than in the earlier period in both the RCA and the LAD (Figure 3C and 3D).

When patients were divided into 3 groups according to initial treatment and response, patients who were resistant to initial IVIG, patients who responded to initial IVIG, and patients who had no IVIG, there was no significant difference in the regression rate among the 3 groups in both the RCA and the LAD (Figure 4). When patients were divided into two groups treated

Table 2. Overall Number of Aneurysms Showing Regression and the Regression Rate of CAAs During the Study Period

	No. (%)				
	Total*	Small	Medium	Large	Unclassifiable
RCA					
No. of patients	754	101	316	221	116
Regression	513 (68.0)	92 (91.1)	253 (80.1)	77 (34.8)	91 (78.4)
Regression rate by attribute					
Male	355 (66.1)	69 (90.8)	185 (76.8)	33 (24.4)	68 (80.0)
Female	158 (72.8)	23 (92.0)	68 (90.7)	44 (51.2)	23 (74.2)
Age at diagnosis <1 y	201 (75.8)	14 (93.3)	99 (88.4)	49 (53.3)	39 (84.8)
Age at diagnosis ≥1 y to <5 y	250 (67.9)	59 (93.7)	129 (80.6)	20 (22.2)	42 (76.4)
Age at diagnosis ≥5 y	58 (50.4)	19 (82.6)	25 (56.8)	7 (18.9)	7 (63.6)
Initial IVIG-resistant	264 (63.5)	45 (91.8)	136 (78.2)	47 (32.6)	36 (73.5)
Initial IVIG-responsive	190 (73.4)	39 (90.7)	91 (83.5)	21 (35.6)	39 (81.3)
Initial IVIG-none	55 (74.3)	8 (88.9)	24 (77.4)	9 (52.9)	14 (82.4)
Date at diagnosis 1981–1999	173 (70.3)	30 (90.9)	79 (84.0)	25 (35.2)	39 (81.3)
Date at diagnosis 2000–2009	293 (66.9)	52 (91.2)	150 (78.9)	42 (33.1)	49 (76.6)
Date at diagnosis 2010–2012	43 (67.2)	10 (90.9)	24 (75.0)	9 (42.9)	—
LAD					
No. of patients	615	96	326	98	95
Regression	436 (70.9)	90 (93.8)	252 (77.3)	26 (26.5)	68 (71.6)
Regression rate by attribute					
Male	304 (70.2)	75 (92.6)	171 (76.3)	12 (19.0)	46 (70.8)
Female	132 (72.5)	15 (100.0)	81 (79.4)	14 (40.0)	22 (73.3)
Age at diagnosis <1 y	173 (87.4)	24 (100.0)	109 (88.6)	13 (61.9)	27 (90.0)
Age at diagnosis ≥1 to <5 y	220 (69.4)	55 (93.2)	123 (77.8)	10 (20.0)	32 (64.0)
Age at diagnosis ≥5 y	43 (43.4)	11 (84.6)	20 (44.4)	3 (11.1)	9 (64.3)
Initial IVIG-resistant	242 (68.8)	51 (94.4)	142 (75.5)	16 (23.2)	33 (80.5)
Initial IVIG-responsive	142 (72.4)	30 (93.8)	84 (80.0)	7 (31.8)	21 (56.8)
Initial IVIG-none	48 (77.4)	8 (88.9)	25 (78.1)	3 (42.9)	12 (85.7)
Date at diagnosis 1981–1999	140 (72.5)	24 (92.3)	80 (78.4)	9 (36.0)	27 (67.5)
Date at diagnosis 2000–2009	251 (70.5)	57 (95.0)	136 (76.0)	17 (27.0)	41 (75.9)
Date at diagnosis 2010–2012	45 (69.2)	9 (90.0)	36 (80.0)	0 (0.0)	—

IVIG indicates intravenous immunoglobulin; LAD, left anterior descending; and RCA, right coronary artery.
*Patients whose *z* score was unavailable and whose coronary arterial aneurysm (CAA) internal diameter was <8 mm were defined as unclassifiable.

with or without steroids in the acute phase, there was no significant difference in the regression rate between the two groups (data not shown).

Factors Associated With Regression

Finally, the factors associated with CAA regression were analyzed using Cox regression analysis. Table 3 shows the unadjusted and adjusted risk estimates for CAA regression. In the unadjusted analysis, CAA regression in the RCA and LAD was associated with small CAA and CAA with onset of KD in the most recent period, CAA regression in the RCA was associated with female sex, and CAA regression in the LAD was associated with age younger than 1 year at diagnosis. In the adjusted analysis, CAA regression was associated with small CAA, age younger than 1 year at diagnosis, and onset of KD in the most recent period in the RCA and LAD, and female sex in the RCA.

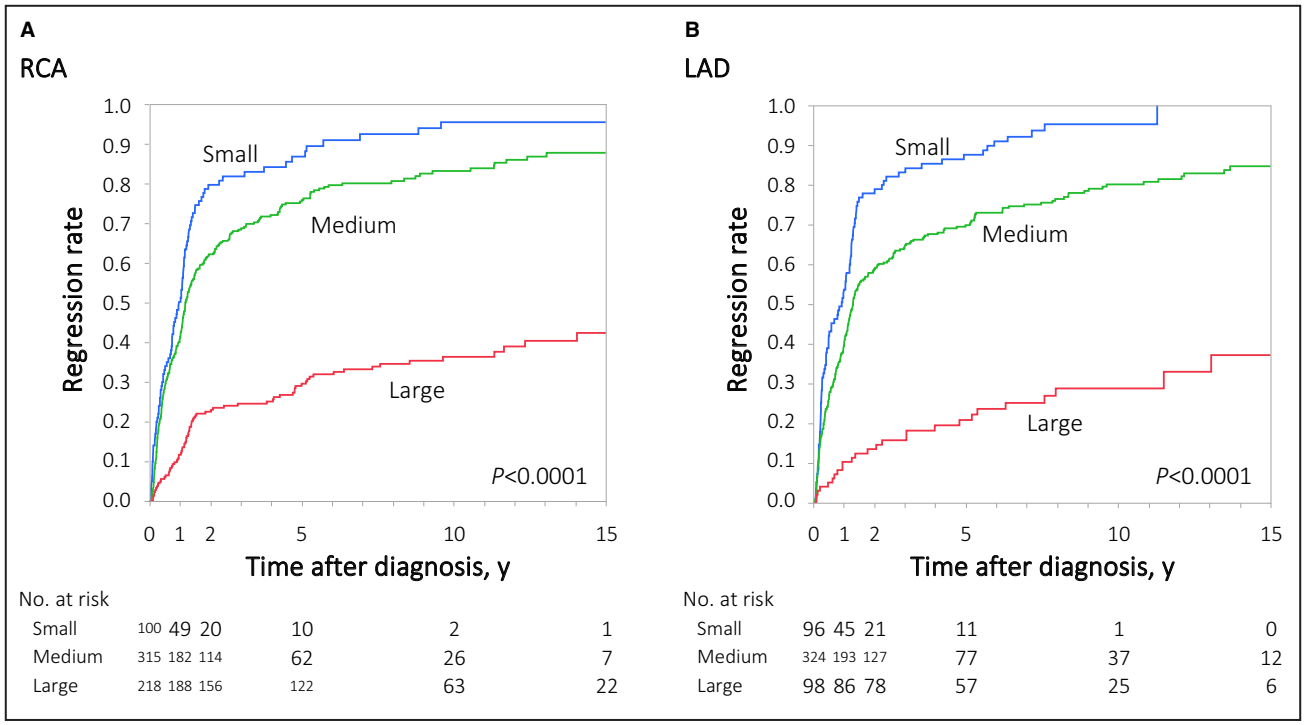

Figure 1. Kaplan–Meier curves for the coronary arterial aneurysm (CAA) regression rate by severity of CAA.
Regression rate classified by CAA severity in the right coronary artery (RCA) **(A)** and the left anterior descending (LAD) **(B)**.

DISCUSSION

In this trial, the largest Japanese study with the longest follow-up of CAA, the time-dependent change of CAA regression classified by the *z* score of coronary arterial internal diameter and the factors associated with CAA regression were analyzed. It was found that the time-dependent change of CAA regression was associated with the severity of CAA classified by the *z* score of coronary arterial internal diameter in the acute phase, and even large aneurysms could undergo regression. Furthermore, small CAA, CAA in patients younger than 1 year of age at diagnosis, CAA in patients with onset of KD in the most recent period, and CAA of the RCA in female patients were the factors associated with regression during long-term follow-up.

The overall regression rate during this study period was 68.0% in the RCA and 70.9% in the LAD. A previous Japanese study before immunoglobulin use showed that ≈55% of patients with CAAs showed regression.[4] The present study showed that the onset of KD in the most recent period was the factor associated with regression. Although it is possible that the change in regression rates over time is attributable to advances in acute treatment, it cannot be attributed solely to changes in the acute-phase treatments. Further investigation is needed to explore the cause for a better understanding of the mechanism of regression. On the other hand, a recent study from a US cohort showed that regression was observed in 75% of CAAs.[7] Their cohort showed a higher rate of CAAs with *z* scores of <5 and a higher percentage of patients treated after 2010 compared with the present cohort, which may result in a higher regression rate compared with that of the present study. In the present study, the timing of regression was in line with the previous reports and was often observed within 2 years.[4,7]

Although a previous Japanese study reported that giant aneurysms, defined as coronary arterial internal diameter ≥4 times that of normal or >8 mm, showed no regression,[4] the present study showed that even large aneurysms, defined as having a *z* score of ≥10 or an actual internal diameter of ≥8 mm, showed regression. Because the patients in this previous Japanese study were treated between 1973 and 1983, a pre-IVIG era, the improvement in the regression rate of the large aneurysms may be mainly attributable to the improvement of acute-phase treatment. The finding that even some large CAAs could undergo regression is consistent with the recent US report.[7] In addition, the present data newly showed that regression of large CAAs was observed even after >2 years. Because regression of a large aneurysm does not guarantee that no future cardiovascular events will occur, long-term observation after regression is warranted.

In the present cohort, CAAs in patients younger than 1 year at diagnosis were associated with a higher incidence of regression compared with the other age groups. Patient age is associated with the clinical course of CAAs in KD. Younger age is associated with a higher incidence

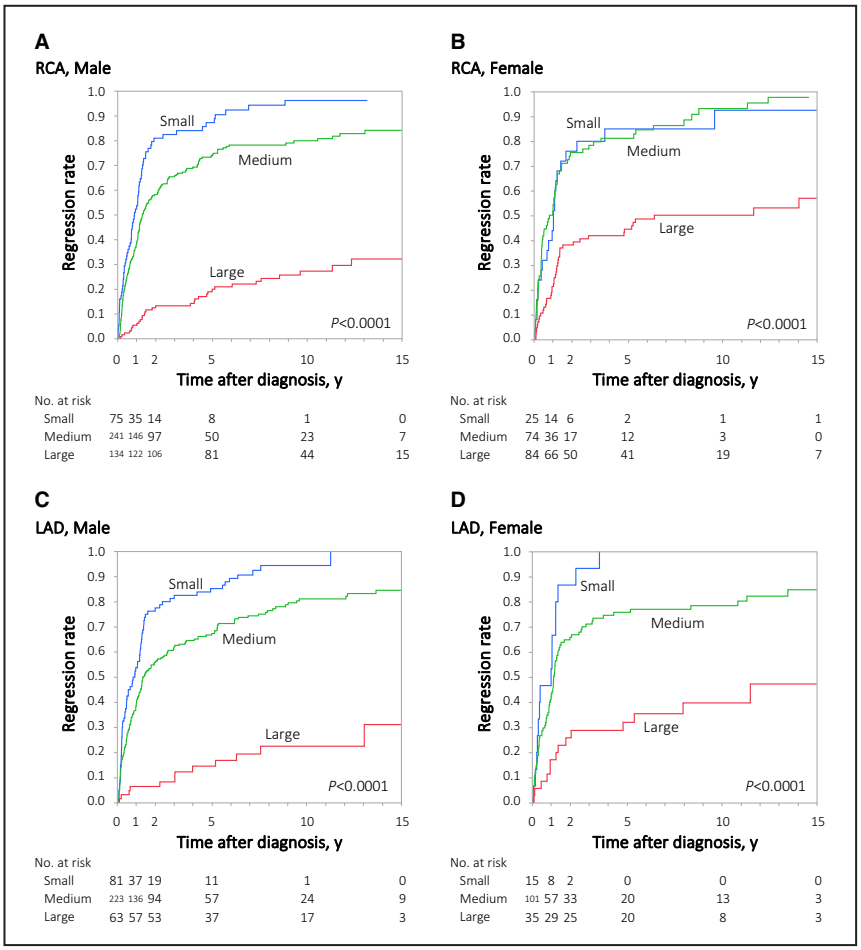

Figure 2. Kaplan–Meier curves for the coronary arterial aneurysm (CAA) regression rate classified by CAA severity in male and female patients.
A and **B**, Regression rate of the right coronary artery (RCA) classified by CAA severity in male (**A**) and female (**B**) patients. **C** and **D,** Regression rate of the left anterior descending artery (LAD) classified by CAA severity in male (**C**) and female (**D**) patients.

of CAA compared with other age groups.[14–16] In the pre-IVIG era, children younger than 1 year at the onset of KD showed a higher incidence of regression compared with patients older than 1 year.[17] Pathologically, CAA regression has been reported to result from intimal thickening mainly caused by the proliferation of smooth muscle cells.[18,19] Recently, the pathological process of the CAA was reported to include LMP by smooth muscle cell–derived myofibroblasts using light microscopy of semithin resin sections, transmission electron microscopy, and immunohistochemistry. LMP plays an important role in the process of normalizing the lumen diameter of CAA. Vascular smooth muscle cells lose the ability to proliferate with age.[20,21] The tendency for a higher regression rate in young patients compared with older patients may be associated, in part, with the altered characteristics of vascular smooth muscle cells with age.

There is a sex difference in the prognosis of CAAs in KD. Regression has been more frequently observed in female patients than in male patients, which was consistent with the present study.[17,22] On the other hand, male patients have a high risk of initial treatment resistance and developing CAAs.[23–26] Furthermore, our previous study showed that male sex was significantly associated with coronary events.[10] It is known that there are sex differences in the pathophysiology of cardiovascular diseases such as coronary heart disease. The effects of sex hormones on coronary heart diseases have been reported.[27,28] Among them, estrogen is known to have various cardiovascular protective effects.[29] In addition to sex hormones, lifestyle and behavior have also been suggested to be involved in the pathophysiology of coronary heart disease.[30] These factors may also affect the prognosis of the coronary arteries in KD.

The present study shows that the CAA regression rate was the highest in the more recent period in both the RCA and the LAD, and onset of KD in the most

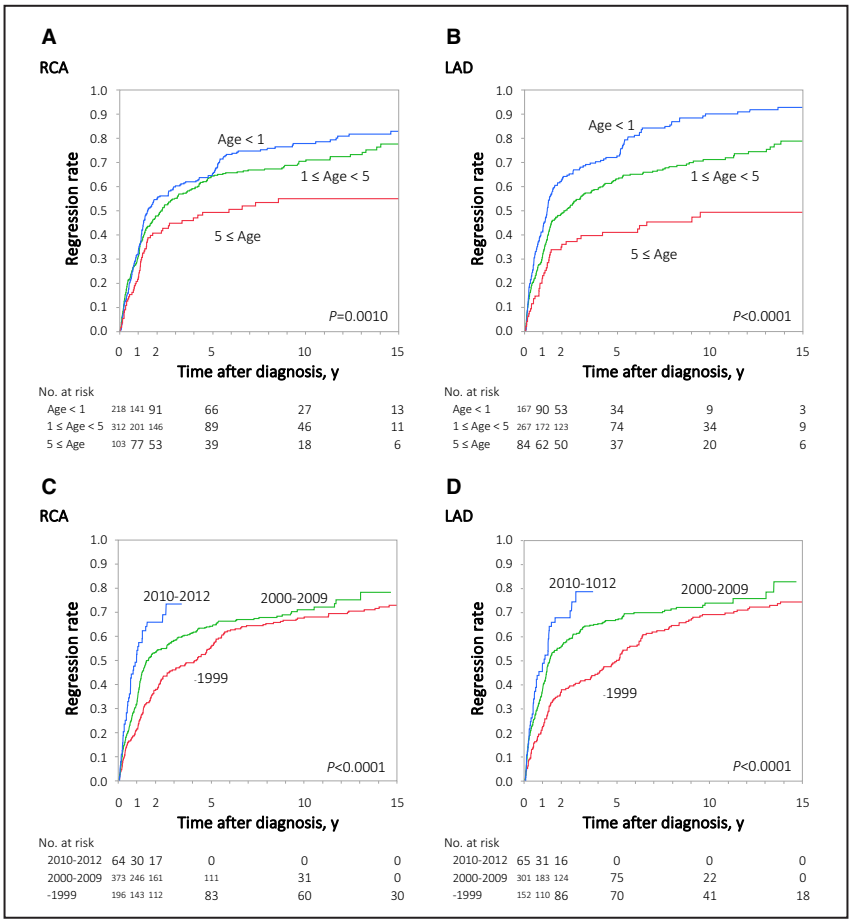

Figure 3. Kaplan–Meier curves for the coronary arterial aneurysm (CAA) regression rate by the age at onset and the decade at onset.
A and **B**, Regression rate classified by the age at onset in the right coronary artery (RCA) (**A**) and the left anterior descending artery (LAD) (**B**). **C** and **D**, Regression rate classified by the decade at onset in the RCA (**C**) and the LAD (**D**).

recent period was the factor associated with regression. The recent report of a US cohort was consistent with the present data showing that the CAA regression rate was 91%, 77%, and 49% in patients treated in 2010 to 2014, 2000 to 2009, and 1984 to 1999, respectively.[7] Improved recognition of incomplete KD, earlier commencement of treatment, and recent intensified treatment including initial treatment and additional treatment may contribute to rapid resolution of coronary arterial inflammation, which may have resulted in the improvement of the CAA regression rate in the recent period.

Resistance to initial IVIG treatment was not associated with a decreased regression rate, whereas resistance to initial IVIG treatment was associated with coronary events in our previous study.[10] There have been reports of patients with acute coronary syndrome after CAA regression.[31,32] Furthermore, abnormal endothelial function at the site of regressed CAAs was reported.[9] These findings suggest that regression and coronary events are not simple opposites in the clinical course. One of the possible reasons is that regression results mainly from LMP by smooth muscle cell–derived myofibroblasts, whereas coronary events may be associated with vascular endothelial cell dysfunction. The precise reason why resistance to initial IVIG treatment is associated with coronary events but not regression should be studied in the future, which may lead to an understanding of the impact of resistance to initial IVIG treatment in the long-term prognosis of KD. In this study, the initial IVIG-none group was shown to be the least likely to undergo regression for the first 5 years following diagnosis, but then abruptly closed the gaps with and even surpassed both the initial IVIG-responsive and the initial IVIG-resistant groups. This suggests that in the initial IVIG-none group there appear to be two different mechanisms of regression at play, perhaps the early phase of smooth muscle cell hypertrophy followed by a more dysplastic LMP phase.

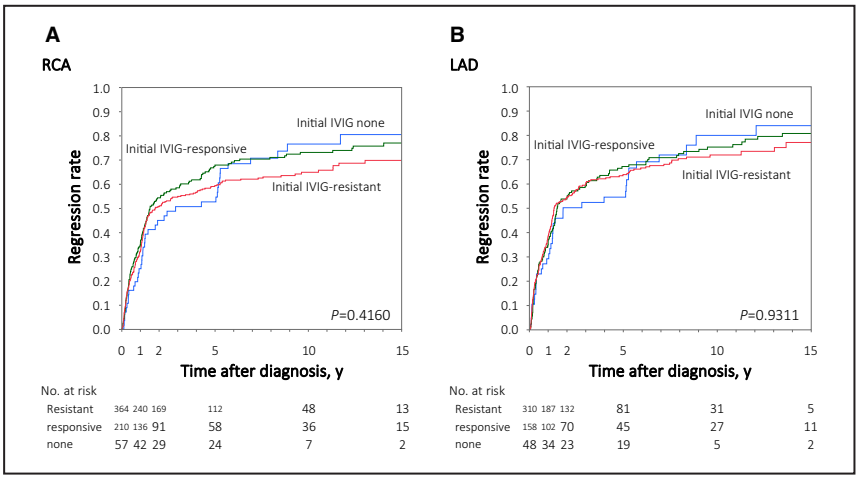

Figure 4. Kaplan–Meier curves for the coronary arterial aneurysm (CAA) regression rate by initial treatment and response.
A and **B**, Regression rate by initial treatment and response in the right coronary artery (RCA) **(A)** and left anterior descending artery (LAD) **(B)**.

Limitations

The present study has limitations that require caution in interpretation. In this study, the lower limit of small CAA was defined based on the Japanese Ministry of Health, Labour and Welfare criteria, not on the *z* score of coronary arterial internal diameter. This study also has other limitations, which are mainly attributable to its retrospective design. First, the initial and additional treatments and the antiplatelet or anticoagulation regimens were not standardized, which may affect the suppression of coronary arterial inflammation and CAA prognosis. Second, the timing of coronary angiography was not standardized. Therefore, the precise timing of regression may be earlier than the timing of

Table 3. Cox Regression Analysis for CAA Regression

Associated factor	Unadjusted		Adjusted	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
RCA				
Medium CAA (reference: small)	0.67 (0.53–0.84)	0.0006	0.62 (0.48–0.79)	0.0001
Large CAA (reference: small)	0.17 (0.12–0.23)	<0.0001	0.14 (0.10–0.19)	<0.0001
Female	1.24 (1.01–1.53)	0.0410	1.61 (1.30–2.00)	<0.0001
Age at diagnosis <1 y (reference: 1–4)	1.12 (0.91–1.37)	0.2732	1.43 (1.16–1.77)	0.0010
Age at diagnosis ≥5 y (reference: 1–4)	0.66 (0.49–0.91)	0.0105	0.72 (0.53–0.98)	0.0364
Initial IVIG-resistant (reference: none)	0.95 (0.70–1.27)	0.7220	1.22 (0.87–1.70)	0.2443
Initial IVIG-responsive (reference: none)	1.09 (0.80–1.48)	0.5874	1.18 (0.85–1.64)	0.3301
Date at diagnosis 2000–2009*	1.21 (0.99–1.50)	0.0687	1.28 (1.02–1.61)	0.0308
Date at diagnosis 2010–2012*	1.84 (1.30–2.63)	0.0007	1.96 (1.36–2.82)	0.0003
LAD				
Medium CAA (reference: small)	0.57 (0.45–0.71)	<0.0001	0.51 (0.40–0.65)	<0.0001
Large CAA (reference: small)	0.12 (0.08–0.18)	<0.0001	0.11 (0.07–0.17)	<0.0001
Female	1.05 (0.83–1.32)	0.6841	1.25 (1.00–1.58)	0.0522
Age at diagnosis <1 y (reference: 1–4)	1.51 (1.22–1.86)	0.0001	1.66 (1.33–2.09)	<0.0001
Age at diagnosis ≥5 y (reference: 1–4)	0.47 (0.32–0.68)	0.0001	0.55 (0.37–0.81)	0.0023
Initial IVIG-resistant (reference: none)	1.01 (0.73–1.41)	0.9309	1.13 (0.79–1.63)	0.5014
Initial IVIG-responsive (reference: none)	1.06 (0.75–1.49)	0.7601	1.23 (0.84–1.79)	0.2823
Date at diagnosis 2000–2009*	1.30 (1.04–1.63)	0.0232	1.50 (1.18–1.91)	0.0010
Date at diagnosis 2010–2012*	1.79 (1.28–2.52)	0.0007	2.05 (1.46–2.89)	<0.0001

CAA indicates coronary arterial aneurysm; HR, hazard ratio; IVIG, intravenous immunoglobulin; LAD, left anterior descending artery; and RCA, right coronary artery.

*Date at diagnosis in 1981 to 1999 was used as the reference.

confirmation of regression by coronary angiography. Third, the present cohort consisted of Japanese patients, and whether these data are applicable to other ethnic groups is unknown.

CONCLUSIONS

The severity of CAA classified by the *z* score of coronary arterial internal diameter was significantly associated with the CAA regression rate, and even large aneurysms could undergo regression. Small CAA, age at diagnosis older than 1 year, onset of KD in the most recent period, or female sex with a CAA in the RCA were significantly associated with regression. The present data may contribute to the investigation of the regression mechanisms and the long-term management of CAAs. Prospective studies to evaluate these data are warranted.

APPENDIX

The Z-Score Project 2nd Stage Study Group

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