ORIGINAL RESEARCH

Coronary Artery Aneurysms in Kawasaki Disease: Risk Factors for Progressive Disease and Adverse Cardiac Events in the US Population

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***Background*—**The natural history of coronary artery aneurysms (CAA) after intravenous immunoglobulin (IVIG) treatment in the United States is not well described. We describe the natural history of CAA in US Kawasaki disease (KD) patients and identify factors associated with major adverse cardiac events (MACE) and CAA regression.

***Methods and Results*—**We evaluated all KD patients with CAA at 2 centers from 1979 to 2014. Factors associated with CAA regression, maximum CA *z*-score over time (*z*Max), and MACE were analyzed. We performed a matched analysis of treatment effect on likelihood of CAA regression. Of 2860 KD patients, 500 (17%) had CAA, including 90 with CAA *z*-score >10. Most (91%) received IVIG within 10 days of illness, 32% received >1 IVIG, and 27% received adjunctive anti-inflammatory medications. CAA regression occurred in 75%. Lack of CAA regression and higher CAA *z*Max were associated with earlier era, larger CAA *z*-score at diagnosis, and bilateral CAA in univariate and multivariable analyses. MACE occurred in 24 (5%) patients and was associated with higher CAA *z*-score at diagnosis and lack of IVIG treatment. In a subset of patients (n=132) matched by age at KD and baseline CAA *z*-score, those receiving IVIG plus adjunctive medication had a CAA regression rate of 91% compared with 68% for the 3 other groups (IVIG alone, IVIG ≥2 doses, or IVIG ≥2 doses plus adjunctive medication).

***Conclusions*—**CAA regression occurred in 75% of patients. CAA *z*-score at diagnosis was highly predictive of outcomes, which may be improved by early IVIG treatment and adjunctive therapies. **(*J Am Heart Assoc*. 2016;5:e003289 doi: 10.1161/JAHA.116.003289)**

Key Words: cardiovascular outcomes • coronary aneurysm • Kawasaki disease

Kawasaki disease (KD) is an acute vasculitis that preferentially affects medium-sized arteries, particularly the coronary arteries (CA).[1-3] CA involvement can range from transient mild dilatation or ectasia, occurring in up to 40% of patients, to giant coronary artery aneurysms (CAA).[4,5] In the pre–intravenous immunoglobulin (IVIG) era, CAA occurred in 20% to 25% of KD patients.[6] With IVIG therapy, persistent CAAs are considerably less common but still occur in 4% to 6% of patients, with ≈1% developing giant CAA[7-9] using 1984 Japanese Ministry of Health criteria (absolute CA dimension ≥8 mm).[10] The incidence of coronary abnormalities is greater using *z*-score criteria.[4,8,11,12] A recent, 2-center US study found that 2.6% of patients met the *z*-score definition for giant aneurysms (any CA segment with *z*≥10).[8] Patients with large or giant CAAs are at risk for cardiac events including CA thrombosis or stenosis, myocardial infarction (MI), ventricular tachycardia, and death.[6,13–15] Large case series of Japanese patients with giant CAA have shown good overall survival but high cardiac event rates.[6,13,15]

The long-term natural history of CAA after treatment with IVIG in the US population is not well described. Many patients have regression of CAA to normal internal lumen diameter as a result of luminal myofibroblastic proliferation and layering of thrombus in larger CAA.[16] A large Japanese study from the pre-IVIG era analyzed serial angiograms in KD patients with CAA and showed that 55% to 60% have CAA regression, typically within 1 to 2 years of the acute illness.[6] In the US

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Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/5/9/e003289/DC1/embed/inline-supplementary-material-1.pdf

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population, only small cohorts of patients with large and giant CAA have been reported,[14,17,18] limiting the ability to assess risk factors associated with persistent CAA and major adverse cardiac events (MACE). The aims of this study were to describe the natural history of CAA in a contemporary cohort of US KD patients and to identify factors associated with MACE and CAA regression.

Methods

Subjects

In this 2-center retrospective study, we reviewed all patients with KD managed at Boston Children's Hospital and Rady Children's Hospital, San Diego, between 1979 and 2014. We included all patients with CAA at any time in their illness. We defined CAA as left anterior descending coronary artery (LAD) and/or right coronary artery (RCA) *z*-score >3 or original Japanese Ministry of Health and Welfare criteria for CAA in CA segments for which *z*-scores are not available (CA dimension >3 mm for patients <5 years of age and >4 mm in patients ≥5 years of age).[2] Left main CA (LMCA) *z*-score was not used for inclusion due to previously reported variability in LMCA anatomy and measurement.[2,11,19] Of the 500 patients included, 498 were included based on *z*-score criteria, and 2 by Japanese Ministry of Health criteria. There were no patients in the data base with isolated LMCA CAA. Second episodes of KD were excluded, defined as repeat episode of complete or incomplete KD after complete resolution of the previous episode, or presence of congenital heart disease, except for bicommissural aortic valve, mitral valve prolapse, and hemodynamically insignificant ventricular septal defects.

Demographic, clinical, and cardiac imaging data were collected from medical records. Clinical data included

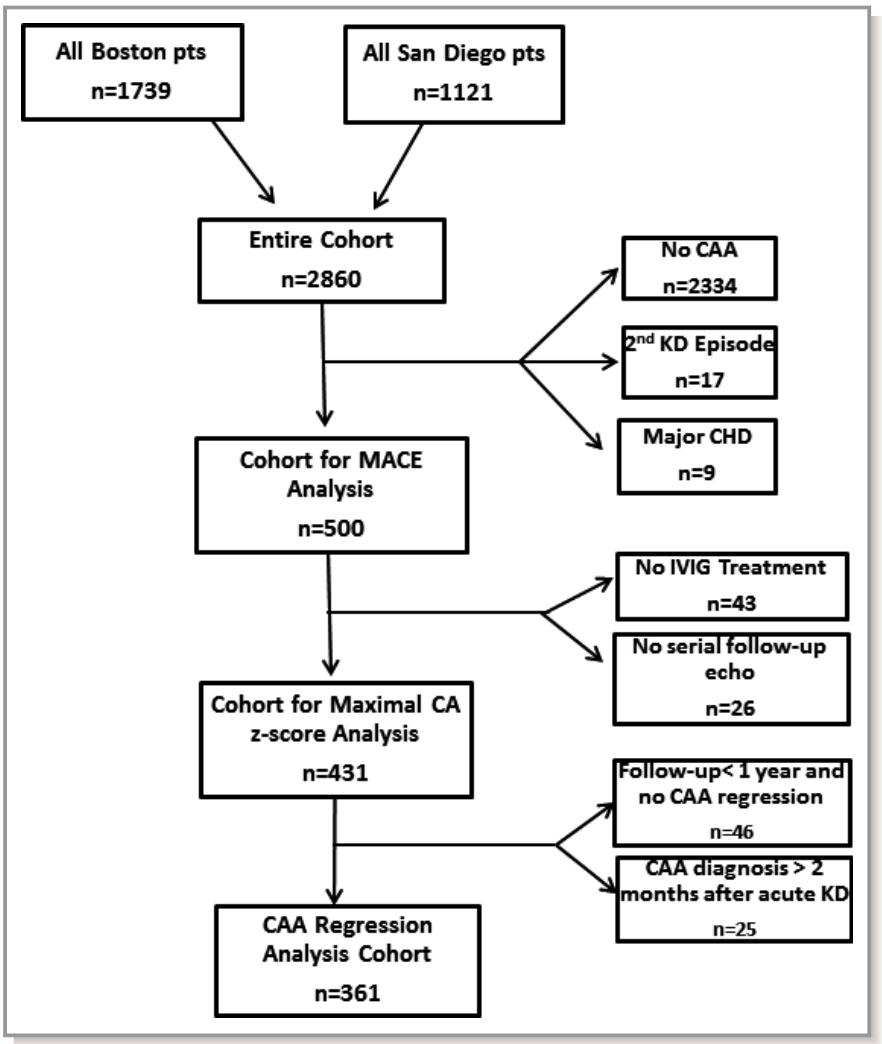

Figure 1. Patient selection. CAA indicates coronary artery aneurysm; CHD, congenital heart disease; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MACE, major adverse cardiac events.

demographics, date of KD onset, treatment center, KD diagnostic criteria met, and KD treatment. First-line treatment for KD at both participating institutions since 1986 has been IVIG (2 g/kg) and aspirin. IVIG treatment was considered delayed if given after day 10 of illness. For patients who were IVIG-resistant, had CAA at diagnosis (CA *z*-score >3 or Japanese Ministry of Health Criteria), and/or were deemed to be at high risk by clinical criteria,[20,21] second-line therapy has varied over time and by site and has included repeat IVIG (2 g/kg), oral or intravenous steroids (varying dosing and duration regimens), infliximab, cyclosporine, and/or cyclophosphamide.[22–27] Patients with giant CAA (CA *z*-score ≥10 or absolute dimension >8 mm) were chronically anticoagulated with either warfarin or low-molecular-weight heparin. This study was conducted with approval from the Committee for Clinical Investigation at Children's Hospital Boston and the Institutional Review Board at Children's Hospital Boston and Rady Children's Hospital with requirement for consent waived.

Imaging Data

Echocardiographic data were collected from reports produced at the time of the study. We collected CA measurements for the following segments: LMCA, proximal and distal LAD, circumflex, proximal and distal RCA, and posterior descending CA. Using the reported measurements, we calculated *z*-scores for the proximal LAD and proximal RCA using *z*-score equations derived from previously described normative data.[4] Prior studies from our institution have shown high inter- and intraobserver reliability for proximal LAD and RCA measurement.[11,19] In cases where additional imaging modalities were performed, including cardiac magnetic resonance imaging, cardiac computed tomography, or cardiac catheterization, CA dimensions were collected from reports produced at the time of the study. The *z*-scores for the proximal RCA and proximal LAD were recalculated for all subjects using the echo-derived CA *z*-score formula for the respective CA segment. We classified CAA as small (*z*-score=3.0-4.9), moderate (*z*-score=5-9.9), or giant (*z*-score ≥10).[12] The *z*Max was defined as the higher value between RCA and LAD *z*-scores on each echocardiogram. Analysis included CA size and *z*-score at initial echocardiogram, maximum RCA or LAD *z*-score over follow-up (highest *z*Max), and most recent echocardiogram.

Patient Outcomes

All patients who met inclusion/exclusion criteria were included in analysis of MACE (Figure 1). We reviewed all available clinical information including echocardiogram, catheterization reports, nuclear perfusion studies, stress

Table 1. Summary of Cohorts

	MACE Analysis (n=500)	Follow-Up (n=431)
Decade of KD episode		
1977–1989, n (%)	32 (6%)	13 (3%)
1990–1999	111 (22%)	87 (20%)
2000–2009	254 (51%)	234 (54%)
2010–2014	103 (21%)	97 (23%)
Site		
Boston	316 (63%)	265 (61%)
San Diego	184 (37%)	166 (39%)
Age at fever onset, y		
<1	167 (33%)	143 (33%)
1 to 4	235 (47%)	207 (48%)
≥5	98 (20%)	81 (19%)
Male sex	360 (72%)	312 (72%)
Asian race	112 (22%)	104 (24%)
Location of aneurysm		
Left anterior descending	221 (44%)	202 (47%)
Right coronary	117 (23%)	95 (22%)
Both	162 (33%)	134 (31%)
z-Score of largest CAA at diagnosis, median (IQR)*	4.3 (3.4, 7.0)	4.6 (3.6–8.9)
z-Score of largest CAA at diagnosis*		
z-Score <5.0	313 (63%)	289 (67%)
z-Score ≥5, <10	97 (19%)	78 (18%)
z-Score ≥10	90 (18%)	64 (15%)
IVIG treatment		
Yes	456 (91%)	431 (100%)
No	31 (6%)	0
Unknown	13 (3%)	0
If IVIG Yes, IVIG re-treatment		
Yes	164/456 (36%)	148/431 (34%)
No	290/456 (64%)	282/431 (65%)
Unknown	2/456 (<1%)	1/431 (<1%)
Adjunctive anti-inflammatory medication		
Yes	133 (27%)	123 (29%)
No	356 (71%)	308 (71%)
Unknown	11 (2%)	0 (0%)

IVIG indicates intravenous immunoglobulin; KD, Kawasaki disease; MACE, major adverse cardiac event.
*Larger coronary artery between left anterior descending and right coronary artery used.

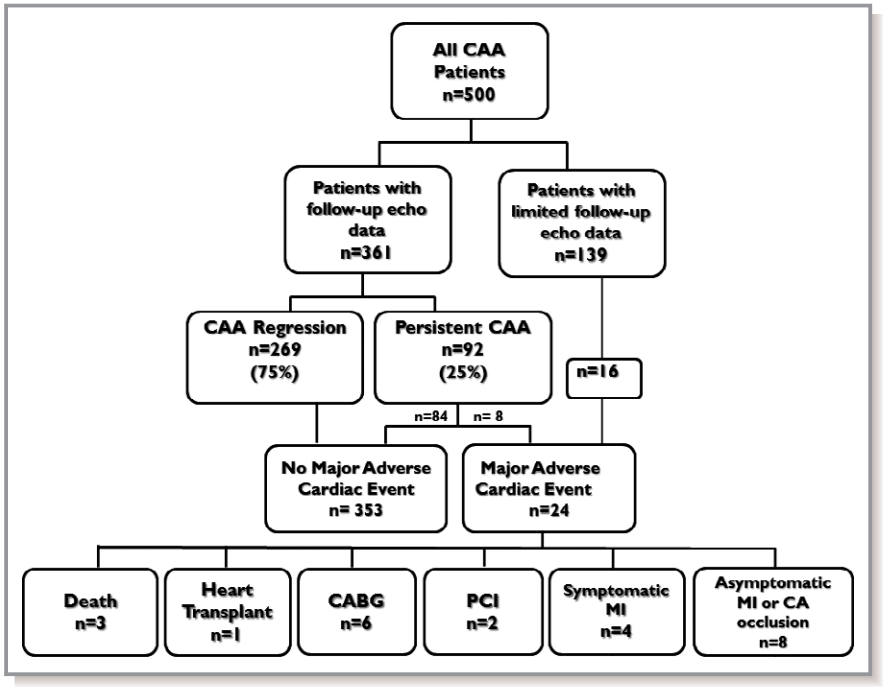

Figure 2. Patient outcomes. CA indicates coronary artery; CAA, coronary artery aneurysm; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary artery intervention.

echocardiograms, internal and external clinic notes, and operative notes. Patients were classified as having MACE if they had any of the following at any time point: complete proximal CA occlusion, clinical or imaging evidence of MI, coronary artery bypass graft (CABG), percutaneous CA intervention (PCI), cardiac death, ventricular tachycardia, or orthotopic heart transplant (OHT). Asymptomatic CA stenosis was not included as MACE. The primary MACE analysis was performed on the entire cohort of CAA patients. A subgroup analysis for MACE was performed using only patients treated with IVIG within 10 days of fever onset.

Additional analyses were restricted to patients who were treated with IVIG at one of the participating institutions and had serial follow-up echocardiograms (≥1 study with CA measurements after the initial diagnosis of CAA) (Figure 1). The follow-up cohort was used to analyze factors associated with the highest *z*Max over follow-up and for analysis of time to CAA regression. To avoid selection bias in analyses of time to regression of CAA, we excluded patients who had CAA diagnosed >2 months after acute KD or who had <1 year of follow-up and no CAA regression. Regression of CAA was defined on a patient basis (rather than individual CA segment). We considered CAA regression to have occurred when echocardiograms showed *z*-score <2.5 for proximal LAD and proximal RCA as well as CA dimensions below the thresholds for the Japanese Ministry of Health criteria for CA segments for which *z*-scores are not available.

Statistics

Demographic and clinical data are presented as count (percentage) or median with (interquartile range) or (range) as specified. Factors associated with MACE were analyzed using logistic regression. Model discrimination for MACE was assessed using the area under the receiver-operator characteristic curve (c statistic). Associations with highest *z*Max over follow-up were evaluated using median regression. Time to CAA regression was estimated using the Kaplan-Meier method, with follow-up censored at 2 years after diagnosis of CAA. Factors associated with CAA regression were explored using the log-rank test and Cox proportional hazards regression. All multivariable analyses were performed using forward selection. A matched subgroup analysis was performed across 4 treatment groups: single dose of IVIG, repeat IVIG (≥2 IVIG doses), single IVIG plus adjunctive anti-inflammatory (infliximab, steroids, cyclosporine, etc), or both repeat IVIG (≥2 IVIG doses) and adjunctive anti-inflammatory medication. Patients were matched on CAA *z*-score at diagnosis (small, moderate, and large/giant) and age at diagnosis (<1 year of age or ≥1 year of age). Comparisons across groups were performed using the Fisher exact test or the Kruskal-Wallis test. Time to CAA was compared using Cox regression, with patients with only a single

Table 2. Description of MACE

	MACE	Age at KD, years	KD Year	IVIG	Age at MACE, y	MACE Description
1	MI, OHT	2.5	1981	No	29.3	Acute KD with 6-mm bilateral CAA, represented at 29 years with cardiomyopathy (EF ≈15%), severe LAD stenosis
2	MI, PCI	0.8	1982	No	21.6	Giant CAA, lost to follow-up until he presented with acute chest pain and MI due to high-grade stenosis of proximal LAD
3	CA occlusion	1.3	1983	No	22.4	Asymptomatic LAD occlusion on surveillance catheterization
4	CA Occlusion	12.2	1984	No	33.0	Asymptomatic, incidentally found to have calcified chest mass at 33 years old, giant/thrombosed RCA CAA
5	CA occlusion	3.8	1985	No	6.9	Asymptomatic, cath 3 years post-KD with RCA occlusion
6	MI, Death	1.1	1988	Late	1.2	Acute thrombosis and fatal MI CAA 3 weeks post-acute KD
7	MI, CABG, Death	0.6	1988	Late	0.7	Thrombosis of giant LAD CAA 8 weeks post-acute KD, failed thrombolysis and attempted CABG
8	CA occlusion	0.5	1989	No	20.0	Asymptomatic, lost to follow-up, surveillance catheterization with occluded RCA
9	MI, CA occlusion	0.9	1990	Yes	5.2	Asymptomatic, LAD occlusion by cath with rwma on resting echocardiogram
10	MI, VT, CABG, PCI	4.1	1993	Late	6.0	Giant bilateral CAA, complete LAD occlusion, high-grade RCA stenosis with inducible perfusion defect on dobutamine MRI
11	CABG, MI	1.3	1994	Late	4.1	Thrombotic LAD occlusion in acute phase with rwma and inducible ischemia on dobumatine MRI
12	MI, CA occlusion	9.1	1994	No	21.2	Asymptomatic, RCA occlusion, delayed enhancement and rwma on dobutamine MRI
13	MI	0.6	1994	Late	0.6	Acute phase LAD thrombosis with apical MI
14	MI, PCI	4.7	1995	Late	14.4	Severe stenosis of proximal LAD CAA with exertional chest pain and reversible perfusion defect on stress MIBI
15	CABG	0.6	1997	No	11.9	RCA occlusion, severe LAD stenosis, ST elevation on exercise stress test
16	MI, CABG	1.6	1999	Late	4.5	Acute chest pain and MI due to thrombotic occlusion of giant RCA CAA
17	MI, CA occlusion	0.4	1999	Late	1.3	Asymptomatic, thrombotic LAD occlusion with apical/anterior rwma, fixed perfusion defect and +MDE on MRI
18	PCI	0.3	2002	Late	5.4	Exertional angina at age 5 years leading to catheterization showing severe RCA stenosis, failed attempt at RCA angioplasty
19	MI, CA occlusion	2.5	2002	Late	2.6	Thrombotic occlusion of giant circumflex CAD 1 month post-acute KD, residual +MDE and resting rwma
20	MI, Death	0.1	2003	Yes	0.3	Giant bilateral CAA. Sudden cardiac arrest at home 10 weeks post-KD.
21	MI	0.3	2003	Late	4.7	Asymptomatic, severe RCA stenosis with rwma on rest echo and +MDE on MRI
22	CABG	9.4	2007	Yes	11.6	RCA occlusion, reversible perfusion defect on stress MIBI and inducible rwma on stress echo
23	MI, CA occlusion	0.6	2007	Yes	0.7	Occlusive LAD thrombus and MI in acute stage treated with heparin
24	CA Occlusion	1.7	2010	Yes	0.7	LAD thrombosis in acute phase, successfully treated with thrombolytic

CAA indicates coronary artery aneurysm; CABG, coronary artery bypass graft; KD, Kawasaki disease; LAD, left anterior descending; MACE, major adverse cardiac event; MDE, myocardial delayed enhancement; MI, myocardial infarction, MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; RCA, right coronary artery; rwma, regional wall motion abnormality; VT, ventricular tachycardia.

dose of IVIG serving as the reference group. Analyses were performed with SAS version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Demographic and clinical data for the entire cohort (n=500) and for the subgroup of patients who were treated with IVIG and had follow-up imaging data (follow-up cohort, n=431) are in Table 1. There were more patients from the more recent era (after 2000) than earlier time periods. Patients younger than 1 year of age comprised one-third of both cohorts. In the follow-up cohort, the median CA *z*-score at diagnosis was 4.6 (IQR 3.6–8.9), with 15% having large/giant CAA. In the entire cohort, 94% of patients were treated with IVIG. The

Table 3. Multivariable Analysis of Factors Associated With Major Adverse Cardiac Events

	Odds Ratio	*P* Value	c-Statistic
Size of CAA at diagnosis (for each 1 unit increase in *z*-score)*	1.1	<0.001	0.93
No IVIG treatment	9.0	<0.001	

CAA indicates coronary artery aneurysm; IVIG, intravenous immunoglobulin.
*Larger coronary artery between left anterior descending and right coronary artery used.

percentage of patients treated with IVIG increased over time with 44% treated in 1977–1989, 87% treated in 1990–1999, and 97% treated in 2000–2014 ($P<0.001$). Re-treatment with IVIG (32%) and use of adjunctive anti-inflammatory medications (1 or more adjunctive medications given in 27% of patients) were common. Adjunctive anti-inflammatory medication usage consisted of steroids in 91 patients (18%), infliximab in 69 (14%), cyclosporine in 6 (1.2%), cyclophosphamide in 1 (0.2%), and anakinra in 1 (0.2%) patient. Comparisons of patient characteristics between the 2 sites are shown in Table S1.

Patient outcomes for all 500 CAA patients are shown in Figure 2. Of the 361 patients with adequate follow-up imaging data, 269 (75%) had CAA regression within 2 years of KD episode. MACE occurred in 24 patients (Table 2), 8 of whom had known persistent CAA and 16 who did not have serial follow-up imaging (12 followed at outside institutions and 4 lost to follow-up). No patients with CAA regression had MACE. MACE occurred at a median age of 3.5 years (range 0.2-29.7 years) and median time from KD of 1.5 years (range 14 days to 27 years). Median follow-up time for the entire cohort was 11.7 years (IQR 6.9–16.6 years).

MACE included 3 deaths, 1 orthotopic heart transplant (OHT), 6 CABG, and 2 PCI (Table 2). The deaths all occurred

Table 4. Multivariable Analysis of Factors Associated With Higher Maximal CA *z*-Score

	Coefficient	*P* Value
Largest CAA size at diagnosis*		
z<5.0	1.00	—
z≥5, <10	2.65	<0.001
z≥10	18.2	<0.001
CAA location		
LAD or RCA alone	1.00	—
Both LAD and RCA	1.10	0.01

CA indicates coronary arteries; CAA, coronary artery aneurysm; LAD, left anterior descending coronary artery; RCA, right coronary artery.
*Larger coronary artery between left anterior descending and right coronary artery used.

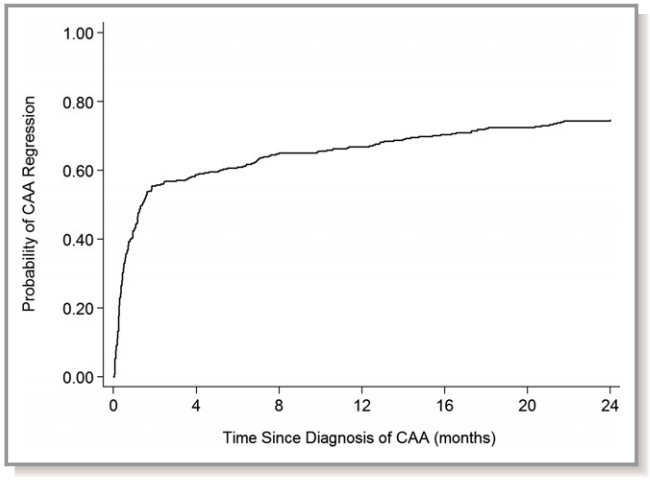

Figure 3. Kaplan-Meier curve for coronary artery aneurysm regression: entire cohort. CAA indicates coronary artery aneurysm.

in infants who had thrombosis of the LAD in the acute or subacute period. First, a 13-month-old male 3 weeks after illness onset suffered acute thrombosis of giant proximal LAD CAA and fatal MI. Second, a 7-month-old male 8 weeks after illness onset had thrombosis of a giant LAD aneurysm and acute MI. After thrombolytic therapy failed, he was taken to the operating room for a CABG, which was unsuccessful, and the patient died in the early postoperative period. Third, a 6-week-old female with giant bilateral CAA who died suddenly at home 2.5 months into illness from presumed MI; her family refused autopsy. One patient underwent OHT. He developed KD at 2.5 years of age with large bilateral CAA. He presented again at age 29 years with congestive heart failure symptoms, high-grade LAD stenosis, and cardiomyopathy (ejection fraction ≈15%). Six patients underwent CABG, and 2 underwent PCI at a median age of 6 years (range 4.1-12.4 years) and median interval of 3 years post–acute KD (range 1.7-11.3 years). Of the 12 patients with MI or CA occlusion but no other MACE, 4 had clinical symptoms of MI, and 8 had no recognized clinical symptoms and were diagnosed on surveillance imaging (eg, radionuclear imaging, cardiac MRI with myocardial delayed enhancement, or PET scan).

Factors associated with MACE in univariate and multivariable analysis are shown in Table S2 and Table 3, respectively. Larger CAA size at diagnosis had the highest discrimination for prediction of MACE, with a c-statistic of 0.92. MACE occurred in 21 of 90 patients (23%) with *z*-score ≥10 at diagnosis, 3 of 97 (3%) with *z*-score of 5 to 10 at diagnosis, and in none of 313 patients with CA *z*-score <5 at diagnosis. All patients with MACE had a history of giant CAA at some time point. The 3 patients with *z*-score 5 to 10 at diagnosis who experienced MACE all had progression in size of CAA to *z*-score >10 during follow-up. Lack of IVIG

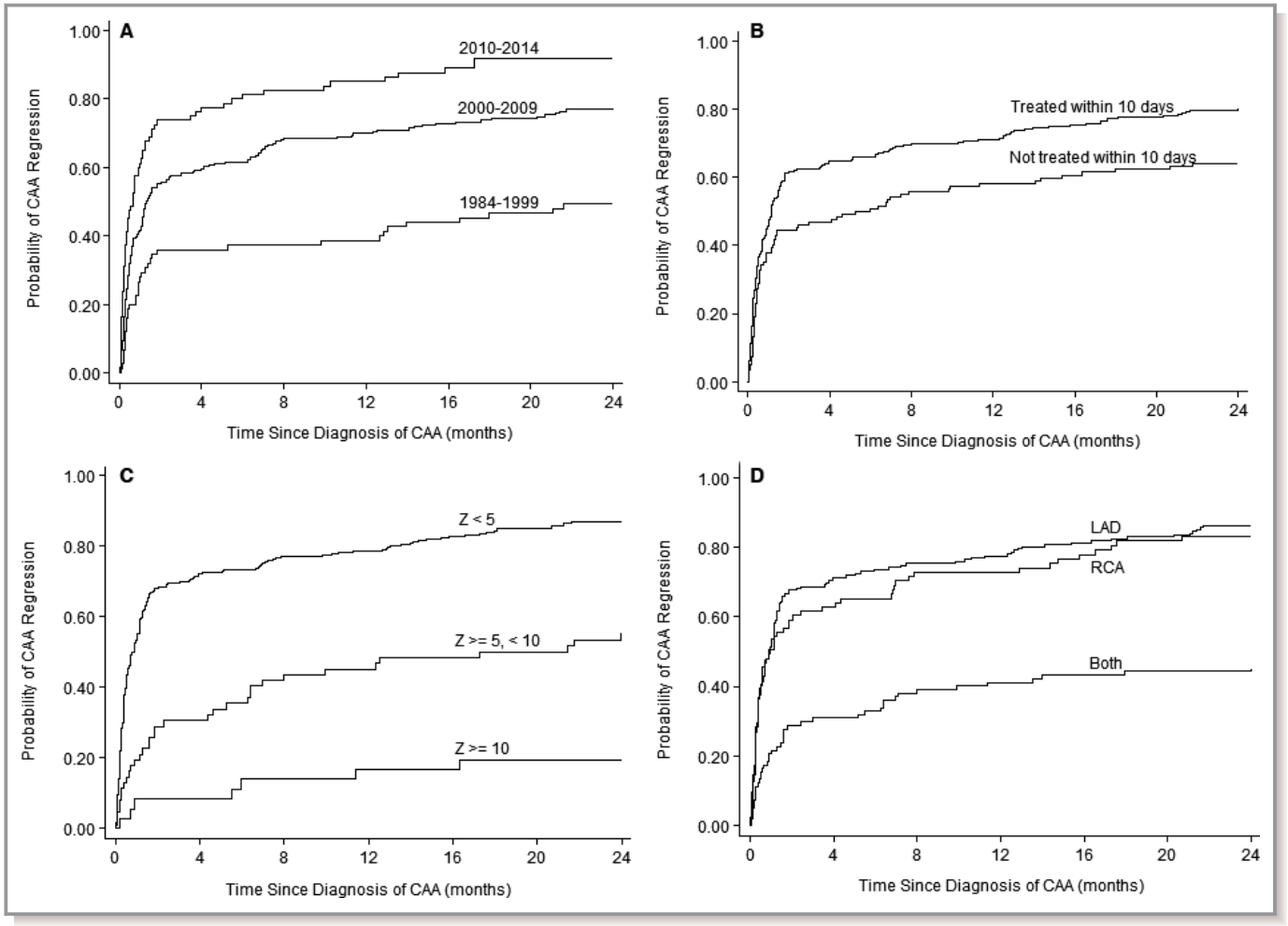

Figure 4. Kaplan-Meier curves for coronary artery aneurysm regression. A, Decade of Kawasaki disease episode. B, IVIG treatment within 10 days of fever onset. C, Maximum coronary artery *z*-score at diagnosis. D, Location of coronary artery aneurysm. CAA indicates coronary artery aneurysm; IVIG, intravenous immunoglobulin; LAD, left anterior descending coronary artery; RCA, right coronary artery.

treatment was also associated with MACE in multivariable analysis. MACE occurred in 11/44 (25%) patients who did not receive IVIG, 9/171 (5%) patients who received IVIG ≥10 days after fever onset, and in only 4/285 (1.4%) patients who were treated within 10 days. When follow-up duration is included in the multivariate model, both size of CAA at diagnosis (OR 1.1, $P<0.001$) and lack of IVIG treatment (OR 4.4, $P=0.03$) as well as follow-up duration (OR=1.1, $P=0.02$) are associated with MACE. Demographic factors, decade of treatment, site of treatment, use of additional IVIG doses and/or adjunctive anti-inflammatory medications were not independent risk factors for MACE. In a subgroup analysis restricted to patients who received IVIG within 10 days of treatment, CAA size at diagnosis was the only factor associated with MACE.

In the 431 patients with follow-up CA imaging, the highest *z*Max occurred on the baseline echocardiogram, ie, at diagnosis, in 273 patients (63%) and at follow-up in 158 patients (37%). In the latter group the median time to highest *z*Max was 12 days (interquartile range 0-27 days). Median highest *z*Max was 4.5 (range 3.1-29.9). Univariate and multivariable analyses of factors associated with *z*Max are shown in Table S3 and Table 4, respectively. In multivariable analysis only larger CAA *z*-score at diagnosis and bilateral CAA remained associated with higher *z*Max. Although IVIG re-treatment and treatment with adjunctive anti-inflammatory medications were both associated with higher *z*Max in univariate analysis, additional KD treatments were not associated with larger *z*Max after adjustment for baseline CA *z*-score.

CAA regression to normal internal lumen diameter within 2 years occurred in 269 of 361 patients (75%) (Figure 3). Kaplan-Meier curves (Figure 4) and Table 5 show factors associated with CAA regression. In multivariable analysis, lack of CAA regression was associated with earlier era, larger CAA *z*-score at diagnosis, and bilateral CAA. The CAA regression rate in the most recent 5-year period was 91% compared with 77% from 2000 to 2009 and 49% prior to

Table 5. Factors Associated With CAA Regression

	n	Number (%) With CAA Regression	Hazard Ratio	*P* Value
Univariate analysis	361	269 (75)		
Time period of KD				
1979–1999	75	37 (49)	1.00	—
2000–2009	206	159 (77)	2.13	<0.001
2000–2014	80	73 (91)	3.58	<0.001
Site				
Boston	208	143 (69)	1.00	—
San Diego	153	126 (82)	1.37	0.01
Sex				
Female	99	68 (69)	1.00	—
Male	262	201 (77)	1.15	0.33
Age at fever onset				
≥5 y	69	52 (75)	1.00	—
1 to 4 y	178	146 (82)	1.17	0.33
<1 y	114	71 (62)	0.72	0.07
Asian race				
No/unknown	269	189 (70)	1.00	—
Yes	92	80 (87)	1.47	0.004
Largest CAA size at diagnosis*				
z<5.0	263	228 (87)	9.48	<0.001
z≥5, <10	62	34 (55)	3.53	0.002
z≥10	36	7 (19)	1.00	—
Size of CAA at diagnosis (for each 1 unit increase in *z*-score)*	—	—	0.87	<0.001
CAA location				
Left anterior descending coronary artery	183	158 (86)	3.16	<0.001
Right coronary artery	81	67 (83)	2.88	<0.001
Both	97	44 (45)	1.00	—
Timing of IVIG treatment				
<10 days of fever	239	191 (80)	2.06	<0.001
>10 days of fever	55	29 (53)	1.00	—
Unknown timing	67	49 (73)	1.69	0.03
IVIG re-treatment				
No	234	193 (82)	1.00	—
Yes	111	71 (64)	0.65	0.002
Use of adjunctive anti-inflammatory meds				
No	259	195 (75)	1.00	—
Yes	102	74 (73)	1.00	0.98
Multivariable analysis				
Time period of KD				
1977–1999			1.00	—
2000–2009			2.17	<0.001
2000–2014			3.49	<0.001
Largest CAA size at diagnosis				
z<5.0			6.73	<0.001
z≥5, <10			3.00	0.009
z≥10			1.00	—
CAA location—both RCA and LAD			0.61	0.007

CAA indicates coronary artery aneurysm; KD, Kawaski disease; IVIG, intravenous immunoglobulin.
*Larger coronary artery between left anterior descending and right coronary artery use.

2000. Only 19% of patients with CAA *z*-score ≥10 at diagnosis had CAA regression, whereas 55% with *z*-score between 5 and 9.99 and 87% with *z*<5 had CAA regression. Patients with bilateral CAA had a lower incidence of regression (45%) than those with only LAD (86%) or RCA (84%) CAA. IVIG re-treatment and/or use of adjunctive anti-inflammatory medications were not associated with time to CAA regression. Evaluation of CAA regression of individual CA segments showed 458 total aneurysmal CA segments (LAD and RCA) in the 361 patients. The regression rate was modestly higher in LCA (211/280, 75%) compared to RCA (119/178, 65%). When the analysis is limited to patients who received IVIG within 10 days of fever onset (n=250), the same risk factors remain significant for lack of CAA regression in multivariable analysis: earlier time period of KD (1984-1999 HR=1.00, 2000-2009 HR=2.08, 2010-2014 HR=3.40, *P*<0.001); larger CAA (CAA *z*-score ≥10 HR=1.00, *z*≥5, <10 HR=4.83 [*P*=0.01], *z*<5 HR=11.70 [*P*<0.001]); and bilateral CAA (HR=0.38, *P*<0.001).

Finally, we analyzed the effects of treatment strategy on likelihood of CAA regression within 2 years of disease onset using 4 matched groups of 34 patients each, with matching based on age group and CAA *z*-score at diagnosis (Table 6). Median age (1.7-2.0 years) and CAA *z*-score at diagnosis (4.2-4.4) were similar between groups. The CAA regression rate was 91% in patients who received IVIG and adjunctive anti-inflammatory medication compared to 68% in the other 3 groups (single dose of IVIG, IVIG ≥2 doses, IVIG ≥2 doses and adjunctive anti-inflammatory medication) (OR=1.95, *P*=0.02). Treatment strategy was collinear with site and era of treatment and differed between comparison groups (Table 6).

Table 6. Matched Treatment Effect Analysis

	IVIG Alone (n=34)	IVIG×2 Doses (n=34)	IVIG+Anti-inflammatory (n=34)	IVIG×2 Doses and Anti-inflammatory (n=34)	*P* Value
CAA regression rate	68%	68%	91%	68%	0.02
Age at fever onset, y	1.9 (0.8, 4.4)	2.0 (0.7, 4.3)	1.7 (0.6, 4.3)	1.8 (0.7, 4.0)	0.94
<1 year	12 (35%)	12 (35%)	12 (35%)	12 (35%)	1.0
≥1 year	22 (65%)	22 (65%)	22 (65%)	22 (65%)	
CAA *z*-score at diagnosis	4.0 (3.5, 5.2)	4.3 (3.4, 5.2)	4.1 (3.4, 5.4)	3.9 (3.5, 5.0)	0.99
z-score <5.0	25 (74%)	25 (74%)	25 (74%)	25 (74%)	1.0
z-score ≥5.0, <10.0	6 (18%)	6 (18%)	6 (18%)	6 (18%)	
z-score ≥10.0	3 (9%)	3 (9%)	3 (9%)	3 (9%)	
Male sex	23 (68%)	29 (85%)	24 (71%)	24 (71%)	0.34
Asian race	10 (29%)	5 (15%)	10 (29%)	9 (26%)	0.44
Time period of KD					<0.001
1984–1999	7 (21%)	13 (38%)	1 (3%)	5 (15%)	
2000–2009	18 (53%)	19 (56%)	13 (38%)	17 (50%)	
2010–2014	9 (26%)	2 (6%)	20 (59%)	12 (35%)	
Treatment ≥10 days of fever	5 (21%)	2 (6%)	5 (16%)	3 (10%)	0.41
Site					<0.001
Boston	17 (50%)	28 (82%)	5 (15%)	20 (59%)	
San Diego	17 (50%)	6 (18%)	29 (85%)	14 (41%)	
CAA location					0.79
LAD	20 (59%)	19 (56%)	20 (59%)	17 (50%)	
RCA	5 (15%)	8 (24%)	7 (21%)	5 (15%)	
Both LAD and RCA	9 (26%)	7 (21%)	7 (21%)	12 (35%)	

CAA indicates coronary artery aneurysm; KD, Kawasaki disease; LAD, left anterior descending; RCA, right coronary artery.

Discussion

In this 2-center study, we describe outcomes in the largest cohort of US KD patients with CAA reported to date. We found an overall CAA regression rate of ≈75%. MACE occurred in ≈5% of CAA patients, almost exclusively in those with large/giant CAA at diagnosis. Initial CA *z*-score was highly predictive of CA regression, highest CA *z*Max over time, and clinical events. Because echocardiograms are now routinely obtained at diagnosis, it has become increasingly clear that initial CAA size provides excellent risk stratification.[8,28] This study adds to existing evidence that CAA size at diagnosis is highly predictive of both CAA persistence and cardiac events.[28,29]

The CAA regression rate of 75% in our cohort is higher than reported by prior studies.[6,17,18] A large Japanese study from the pre-IVIG era performed serial angiograms in KD patients with CAA and showed that ≈55% to 60% had CAA regression, typically within 1 to 2 years of KD.[6] Notably, none of the patients with giant aneurysms (n=26) in that study had CAA regression. Similarly, we found that CAA size at diagnosis is highly predictive of CAA regression rate, with a low CAA regression rate (16%) in patients with large/giant CAA and a high regression rate in those with small CAA at diagnosis (85%). More aggressive therapy, particularly increased use of repeat IVIG or additional anti-inflammatory medications, may decrease CA inflammation and progressive dilation and thereby account for improved CAA regression rate.[26,30,31] Improved echocardiographic techniques and routine use of CA *z*-scores for definition of CAA may lead to identification of more small CAA, and this may also contribute to the higher CAA regression rate in our study compared to prior studies.[19]

MACE occurred exclusively in patients with giant CAA; 23% of patients in this group had at least 1 MACE. The cardiac event rate in the current study is lower than that in prior Japanese studies, which report cardiac event-free survival ranging from ≈30% to 50% in KD patients with giant CAA.[13,15,32] Possible explanations for this difference include the definition of giant CAA; *z*-score >10 in this study compared to >8 mm absolute dimension in older literature, which uses Japanese Ministry of Health Criteria. Additionally, more aggressive anticoagulation and medical management may play a role in improved outcomes in this

population.[12,17,33] Duration of follow-up in this study was shorter than those in Japanese studies of KD patients in the pre-IVIG era. Conversely, 8 events were clinically silent and were only detected on surveillance imaging showing myocardial scar and/or fixed perfusion defect. Importantly, absence of IVIG administration was an independent risk factor for MACE. In the entire cohort only 4 patients treated with IVIG within 10 days of fever onset developed MACE, whereas 19 patients who had late or no IVIG treatment developed MACE. This provides a strong argument that the most effective intervention for reducing cardiac sequalae from KD involves improved education and awareness in order to prevent missed or delayed diagnosis of KD.[34-36]

Our results also suggest that KD recognition and prompt treatment have improved over time with resultant improvement in outcomes. Specifically, in the most recent 5-year period, the CAA regression rate was ≈90%, and there was only 1 MACE. This CAA regression rate is higher than those of prior eras (50% to 75%) and also higher than those previously reported.[6] Improvement in outcomes may be related to greater recognition of KD, leading to fewer patients with late and missed diagnoses. It is also possible that better outcomes are a consequence of more aggressive acute-phase therapies for patients with CA abnormalities at diagnosis in the more recent era.[26,30,31] The latter hypothesis is supported by a subgroup analysis of our patients who received IVIG within 10 days of fever onset; those treated in the most recent 5-year period were more likely to receive additional KD medications and had a higher rate of CAA regression than patients treated in prior eras. Although administration of anti-inflammatory medications adjunctive to IVIG was associated with improved outcomes, our study design did not permit causal inference and should be viewed as hypothesis generating. Future large randomized controlled trials are needed to determine optimal therapy in KD patients who present with CAA.

Other limitations of this study include its retrospective design, with less optimal data capture in the early era. The precision of our estimates of MACE was limited by losses to follow-up and inability of young children to report symptoms, such as MI. There is potential ascertainment bias in diagnosis of MACE, particularly clinically silent MI, as follow-up diagnostic testing and follow-up duration varied. Both centers in this study are referral centers for management of KD with CA complications, and this may bias the MACE rate. Many covariates were highly correlated, eg, treatment regimen and era, preventing causal inference. The matched analysis of treatment effect is subject to confounding by indication; we attempted to mitigate this by matching based on CAA size at diagnosis. KD therapy varied over time and by site. Indications for additional IVIG and adjunctive anti-inflammatory medications were not standardized over the study period. We cannot determine if anticoagulation had an effect on CAA regression rate or MACE in patients with giant CAA because all giant CAA patients were on long-term anticoagulants. Because the sample size in our matched treatment analysis was small, we grouped all adjunctive anti-inflammatory medications together and had insufficient power to analyze the treatment effect of specific anti-inflammatory medications or steroid regimens. The matched analysis was further limited by the small number of patients with large/giant CAA who could be matched (n=5 in each group), as well as the inability to evaluate the timing of adjunctive anti-inflammatory therapies relative to disease onset. Finally, regression of lumen diameter in CAA is not equivalent to normalization of the arterial wall, particularly after remodeling of large and giant CAAs in which layering thrombus and luminal myofibroblastic proliferation occur, leaving these patients at risk for cardiac events.[37,38]

Conclusions

In summary, in the largest cohort of US patients with KD and CAA reported to date, 71% had CAA regression over a 2-year period. Clinical outcomes were associated with CAA *z*-score at diagnosis as well as with prompt treatment with IVIG and adjunctive therapies. Once large/giant CAAs develop, the risks of CAA persistence and MACE are high; early recognition of KD and mitigation of CAA progression are thus key.[28,39-41] Randomized, clinical trials of adjunctive anti-inflammatory therapies for KD patients who present with CAA are needed to improve outcomes for this vulnerable patient population.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1

	Boston n=316	San Diego n=184	P Value
Decade of KD episode			<0.001
1977-1989 (n, %)	31 (10%)	1 (1%)	
1990-1999	94 (30%)	17 (9%)	
2000-2009	136 (43%)	118 (64%)	
2010-2014	55 (17)%	48 (26%)	
Age at Fever Onset (years)			<0.001
<1	109 (34%)	58 (32%)	
1-4	131 (41%)	104 (57%)	
≥ 5	76 (24%)	22 (12%)	
Male Sex	230 (73%)	130 (71%)	0.61
Asian Race	52 (16%)	60 (33%)	<0.001
Location of Aneurysm			0.007
Left Anterior Descending	131 (41%)	90 (49%)	
Right Coronary	67 (21%)	50 (27%)	
Both	118 (37%)	44 (24%)	
z-score of Largest CAA at Diagnosis (median, IQR)*	4.5 [3.5, 9.4]	4.0 [3.4-5.2]	<0.001
z-score of Largest CAA at Diagnosis*			<0.001
z-score < 5.0	179 (57%)	134 (73%)	
z-score ≥ 5, < 10	63 (20%)	34 (18%)	

z-score ≥ 10	74 (23%)	16 (9%)	
IVIG Treatment			0.30
Yes	285 (90%)	171 (93%)	
No	20 (6%)	11 (6%)	
Unknown	11 (4%)	2 (1%)	
If IVIG Yes, IVIG retreatment			<0.001
Yes	129/285 (45%)	35/171 (20%)	
No	155/285 (54%)	135/171 (79%)	
Not reported	1	1	
Adjunctive Anti-Inflammatory Medication			<0.001
Yes	71 (22%)	62 (34%)	
No	245 (78%)	112 (61%)	
Not reported	0 (0%)	10 (5%)	

IVIG, intravenous immunoglobulin

*Larger coronary artery between left anterior descending and right coronary artery used.

Table S2. Univariate Analysis of Factors Associated with Major Adverse Cardiac Events

	Odds Ratio	p-value	c-statistic
Decade of KD			0.73
1977-1989	14.5	<0.001	
1990-1999	3.4	0.02	
2000-2014	1.0	--	
Site Boston	2.3	0.11	0.58
Asian Race	0.14	0.06	0.60
Bilateral CAA	3.1	0.008	0.64
Size of CAA at Diagnosis (for each 1 unit increase in z-score)*	1.1	<0.001	0.92
Largest CAA z-score at Diagnosis ≥10*	41.3	<0.001	0.87
No IVIG Treatment	11.9	<0.001	0.67
Adjunctive Anti-Inflammatory Medication	2.0	0.11	0.58

KD, Kawasaki Disease; CAA, coronary artery aneurysm; IVIG, intravenous immunoglobulin

* Larger coronary artery between left anterior descending and right coronary artery used.

Table S3. Univariate Analysis of Factors Associated with Higher Maximal CA Z-score

	n	Median Zmax	IQR	p-value
Time Period of KD				0.16
1979-1999	100	5.1	3.7, 11.2	
2000-2009	234	4.6	3.6, 8.9	
2000-2014	97	4.2	3.4, 6.0	
Site				0.02
Boston	265	4.8	3.7, 11.0	
San Diego	166	4.3	3.5, 6.2	
Sex				0.06
Female	119	4.9	3.7, 11.0	
Male	312	4.5	3.5, 7.8	
Age at Fever Onset				<0.001
< 1 year	143	5.5	3.8, 12.1	
1-4 years	207	4.2	3.5, 6.0	
≥ 5 years	81	4.4	3.5, 6.9	
Asian Race				0.009

Yes	104	4.4	3.4, 5.5	
No/unknown	327	4.6	3.7, 10.1	
Largest CAA size at Diagnosis*				<0.001
z< 5.0	289	3.9	3.4, 4.6	
z≥ 5, <10	78	7.0	5.7, 10.9	
z≥ 10	64	22.7	15.3, 31.2	
CAA Location				<0.001
LAD	202	3.9	3.4, 5.0	
RCA	95	3.9	3.4, 4.9	
Both	134	10.3	5.6, 20.4	---
Timing of IVIG Treatment				0.008
≤ 10 days of fever	273	4.4	3.5, 7.0	
>10 days of fever	71	6.0	3.8, 16.1	
Unknown timing	87	4.6	3.7, 9.8	
IVIG retreatment				<0.001
No	255	4.1	3.4, 5.2	
Yes	130	5.8	3.9, 14.3	
Use of Adjunctive Anti-				<0.001

Inflammatory Meds			
No	308	4.3	3.5, 6.4
Yes	123	5.6	4.2, 14.5

CA, coronary artery; KD, Kawasaki Disease; CAA, coronary artery aneurysm; LAD, left anterior descending coronary artery; RCA, right coronary artery IVIG, intravenous immunoglobulin

* Larger coronary artery between left anterior descending and right coronary artery used