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ORIGINAL RESEARCH

Medium-Term Complications Associated With Coronary Artery Aneurysms After Kawasaki Disease: A Study From the International Kawasaki Disease Registry

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BACKGROUND: Coronary artery aneurysms (CAAs) may occur after Kawasaki disease (KD) and lead to important morbidity and mortality. As CAA in patients with KD are rare and heterogeneous lesions, prognostication and risk stratification are difficult. We sought to derive the cumulative risk and associated factors for cardiovascular complications in patients with CAAs after KD.

METHODS AND RESULTS: A 34-institution international registry of 1651 patients with KD who had CAAs (maximum CAA Z score ≥ 2.5) was used. Time-to-event analyses were performed using the Kaplan–Meier method and Cox proportional hazard models for risk factor analysis. In patients with CAA Z scores ≥ 10 , the cumulative incidence of luminal narrowing ($>50\%$ of lumen diameter), coronary artery thrombosis, and composite major adverse cardiovascular complications at 10 years was $20\pm 3\%$, $18\pm 2\%$, and $14\pm 2\%$, respectively. No complications were observed in patients with a CAA Z score < 10 . Higher CAA Z score and a greater number of coronary artery branches affected were associated with increased risk of all types of complications. At 10 years, normalization of luminal diameter was noted in $99\pm 4\%$ of patients with small ($2.5 \leq Z < 5.0$), $92\pm 1\%$ with medium ($5.0 \leq Z < 10$), and $57\pm 3\%$ with large CAAs ($Z \geq 10$). CAAs in the left anterior descending and circumflex coronary artery branches were more likely to normalize. Risk factor analysis of coronary artery branch level outcomes was performed with a total of 893 affected branches with Z score ≥ 10 in 440 patients. In multivariable regression models, hazards of luminal narrowing and thrombosis were higher for patients with CAAs of the right coronary artery and left anterior descending branches, those with CAAs that had complex architecture (other than isolated aneurysms), and those with CAAs with Z scores ≥ 20 .

CONCLUSIONS: For patients with CAA after KD, medium-term risk of complications is confined to those with maximum CAA Z scores ≥ 10 . Further risk stratification and close follow-up, including advanced imaging, in patients with large CAAs is warranted.

Key Words: cardiovascular outcomes ■ coronary artery ■ Kawasaki disease ■ risk factors

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*The members of the International Kawasaki Disease Registry are listed in the Appendix.

For Sources of Funding and Disclosures, see page 13.

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CLINICAL PERSPECTIVE

What Is New?

- Medium-term cardiac complications of coronary artery aneurysms secondary to Kawasaki disease are relatively frequent but generally limited to patients with maximum coronary artery Z scores >10.
- While patients with coronary artery Z scores >10 were previously thought to represent a common risk category, increased risk profile was observed for patients with coronary artery Z scores >20.
- Physical properties of coronary artery aneurysms are associated with the risk of complications potentially by affecting blood rheology.

What Are the Clinical Implications?

- While still requiring ongoing follow-up, patients with small or medium coronary artery aneurysms can likely be managed with low-intensity, antiplatelet-based thromboprophylaxis and are unlikely to need anticoagulation.
- Given the substantial risk of complications, combined thromboprophylaxis with both anticoagulation and antiplatelet agents should be considered in patients with giant coronary artery aneurysms, particularly those with coronary artery Z scores >20.

Nonstandard Abbreviations and Acronyms

AHA	American Heart Association
CAA	coronary artery aneurysm
CI	cumulative incidence
IKDR	International Kawasaki Disease Registry
IQR	interquartile range
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
LAD	left anterior descending coronary artery
LCX	left circumflex artery
LMCA	left main coronary artery
MI	myocardial infarction
RCA	right coronary artery
REDCap	Research Electronic Data Capture

as the most important complication of KD, leading to significant morbidity and mortality. As a result, KD is now thought to be the leading cause of acquired heart disease in children of developed countries.^{1,2} Despite optimal acute management, CAAs still develop in ~4% of cases. The prevalence of CAAs increases to 25% if the diagnosis of KD is missed or treatment is delayed.¹ Thrombosis in large CAAs can lead to total occlusion and myocardial infarction (MI) and sudden death.¹ In the long-term, CAAs accompanied by chronic inflammation and luminal myofibroblastic proliferation have the potential to reduce the size of CAA, but the process may eventually cause luminal narrowing. Additionally, nonocclusive organized thrombus and recanalized occlusive thrombus can contribute to luminal narrowing.¹ An angiographic study published in 1986 found that there was low prevalence of occlusion and stenosis early on after the acute KD period, and that complications often occurred at least 1 year from disease onset.³ These findings were later supported by a large historical Japanese cohort reported by Kato et al.⁴ This highlights the importance of uninterrupted long-term follow-up with serial imaging to determine the risks of cardiac complications in patients with KD and inform tailored management strategies.

Given the heterogeneity of patients with CAAs and their rarity at any single institution, there are a paucity of data available to inform more precise risk stratification for outcomes in this population. In addition, a limited number of risk factors have been identified for adverse outcomes, which has impeded the development and evaluation of long-term surveillance and management strategies calibrated to individual risk. Therefore, we sought to determine the cumulative risk and associated factors for adverse cardiovascular outcomes for patients with KD and CAAs using data from the IKDR (International Kawasaki Disease Registry), a large, curated, multi-institutional registry including medium- to long-term clinical follow-up.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the research ethics board of The Hospital for Sick Children at researchethics.board2@sickkids.ca and to the corresponding author of this study to initiate the process. Authorization from all institutions who participated in this study will be required to access the data set.

Study Population

Data for this study was collected by the IKDR, which included 34 pediatric referral centers in Canada, the

Kawasaki disease (KD) is a pediatric systemic vasculitis with a predilection for the coronary arteries. Coronary artery aneurysms (CAAs) are recognized

United States, and Taiwan. To be eligible for the registry, patients younger than 18 years must have been diagnosed with complete or incomplete KD between 1999 and 2017 and have at least 1 CAA with a maximum coronary artery Z score ≥ 2.5 at any time after diagnosis based on the American Heart Association (AHA) recommendations for risk stratification.¹ Patients seen at participating centers only for a single consultation (or in the acute phase only) and patients seen for the first time at the reporting center >3 months after the acute phase were not eligible for the registry. For the purpose of this study, data harvest was performed on March 1, 2018, and included all follow-up information up to December 31, 2017. Participating centers were required to submit all cases that met all inclusion criteria and none of the exclusion criteria, thus preventing potential selection bias.

Data Acquisition

Data were retrospectively collected by participating centers and entered using centralized Research Electronic Data Capture (REDCap) tools, which is a secure, web-based application designed to support data capture for research studies, hosted at SickKids Hospital (Toronto, Canada).⁵ Personnel from the data coordinating center (also hosted at SickKids Hospital) reviewed patient data for eligibility and performed data validation and verification. Participation in the IKDR requires institutional review board or research ethics board approval for the study at the US and Canadian/Taiwanese sites, respectively, with the institutional review board/research ethics board approving a waiver of consent for the collection of retrospective data. SickKids Hospital was responsible for managing all bilateral data sharing agreements.

Data Collection

The IKDR collects deidentified information regarding patient demographics, details of hospitalization for the acute KD episode, short- and long-term management, imaging data, and complications. As per AHA guidelines, patients with prolonged fever but ≤ 3 of the classic clinical features of KD were classified as having incomplete KD. Copies of all imaging reports (echocardiograms, angiograms, computed tomography scans, and magnetic resonance imaging) were submitted to the data coordinating center for centralized data extraction, and the coronary arteries of all patients were characterized and classified. Serial absolute internal luminal diameters were retrieved from echocardiography reports, and the measurements were adjusted for body surface area (recalculated using the Haycock formula for all patients to ensure consistency) by calculation of Z scores using the Boston coronary artery Z score equations (the left anterior descending artery [LAD]

equation was used for the left circumflex artery [LCX]).² Based on maximal Z score, CAAs were classified as small ($2.5 \leq Z < 5$), medium ($5 \leq Z < 10$), and large ($Z \geq 10$), as per 2017 AHA guidelines.¹ Data extracted from written reports of imaging study included the number of coronary artery branches with CAAs and the maximum CAA Z score ever reached. The coronary artery architecture was classified as dilatation only, isolated CAA in an otherwise normal vessel, isolated CAA in a dilated vessel, or complex CAAs. Complex CAA was defined as any coronary artery branch with >1 discrete lesion or with CAAs extending into the bifurcation of the left main coronary artery. The CAA location within the branch, the CAA shape and length of the CAA when reported, the CAA diameter to length ratio, and the estimated CAA ellipsoid area (diameter multiplied by length $\times 0.80$) were also assessed. Normalization of CAA diameter was defined as the reduction of the internal diameter of a CAA during follow-up to achieve a Z score < 2.5 .

Patient Outcomes

Complications of CAAs were defined as: (1) luminal narrowing clinically reported as significant coronary artery stenosis/obstruction confirmed on coronary artery angiography ($>50\%$ narrowing of lumen diameter); (2) coronary artery revascularization either by catheterization or surgery; (3) coronary artery thrombosis (occlusive or nonocclusive) diagnosed on any imaging modality; (4) MI reported clinically; and (5) major adverse cardiac complications, including a composite of surgical or catheter-based revascularization, MI, cardiac ischemia, heart transplantation, or death from cardiac causes.

Statistical Analysis

Data are presented as means with SDs, medians with interquartile ranges (IQRs), and frequencies as appropriate. Time-related freedom from outcomes was calculated using the Kaplan–Meier method (presented as cumulative incidence rate rather than freedom from event). Patient follow-up intervals were censored at last follow-up or death. Multivariable risk factor analysis was performed using Cox proportional hazard analysis, with variable selection informed using bootstrap resampling (500 random samples, $P < 0.05$ to enter and $P < 0.10$ to remain).⁶ Variables with high reliability (ie, selected in $>50\%$ of the random samples) were then included in a multivariable Cox proportional hazard model. Backward selection of variables was then used to obtain a final model. Proportional hazard assumption was tested by assessing the statistical significance of the time-dependent covariate (interaction between the time component and each parameters) in the regression models; none of which demonstrated

a violation of the proportional hazard assumption. A complete list of variables considered in the risk factor analysis can be found in Table 1. Note that acetylsalicylic acid use was not included in risk factor analysis given that >99% of patients were taking this medication, and long-term treatments (eg, antithrombotics, β -blockers, and statins) were not included given their time-varying nature. Pertinent negatives are reported. For the analysis by affected coronary artery branch, only branches with CAA maximal Z score ≥ 10 were included. While each branch is unique, patients could have had >1 branch with CAA Z score ≥ 10 . For this analysis, adjustment for repeated measures (multiple branches included from the same patient) was

performed by including the model-based estimate for the covariance matrix as a regression term in the Cox proportional hazard model. Kaplan–Meier analyses were performed for up to 10 years postdiagnosis, after which the number of patients remaining at risk was deemed too low to generate valid estimates. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Table 1. Patients and CAA Characteristics Considered in the Risk Factor Analysis for Cardiac Complications and Outcomes

Risk Factors
Age at KD
Sex
Type of KD (complete/incomplete)
Arthritis at diagnosis
Laboratory values during acute phase
Hemoglobin, g/L
Hematocrit, %
ESR, mm/h
White blood cell count, $\times 10^9/L$
Platelets, $\times 10^9/L$
Albumin, g/L
C-reactive protein, mg/L
Red blood cell count, $\times 10^{12}/L$
Aspartate transaminase, U/L
Alanine aminotransferase, U/L
Duration of fever before IVIGs
Total duration of fever
IVIG treatment
No. of IVIG doses
Intravenous steroids in the acute phase
Oral steroids in the acute phase
Infliximab in the acute phase
Any use of nonsteroidal anti-inflammatory drugs in the acute phase
Coronary artery branch
Maximum coronary artery Z score
Involvement of the LAD/LMCA/LCX bifurcation
Aneurysm architecture
Aneurysm location within coronary branch
Aneurysm shape
Aneurysm width to height ratio
Aneurysm estimated area

CAA indicates coronary artery aneurysm; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LAD, left anterior descending artery; LCX, left circumflex artery; and LMCA, left main coronary artery.

RESULTS

Patient and CAA Characteristics

A total of 1651 patients were included in this analysis, of whom 1184 (72%) were men, as expected given the sex distribution of KD. The median age at diagnosis was 2 years (IQR, 0.67–4.67 years; range 1 month–17.9 years), with 744 (45%) aged between 1 and 5 years. Patients had a median fever duration of 9 days (IQR, 7–13 days), and 973 of 1633 (60%) had complete KD. Maximum Z scores of any of the 4 coronary artery branches (right coronary artery [RCA], left main coronary artery [LMCA], LAD, or LCX) were used to categorize patients as having small 854 (52%), medium 357 (22%), and large 440 (27%) CAAs. Notably, a greater degree of coronary artery complications was associated with extremes of the age spectrum (younger and older), having incomplete rather than complete KD, longer duration of fever before treatment, nonresponse to first treatment with intravenous immunoglobulins (IVIGs) as indicated by need for immunosuppressive therapy beyond the initial IVIG cycle, and longer total duration of fever. Complete patient characteristics stratified by degree of coronary artery involvement are presented in Table 2.

Complications of CAAs

Median duration of follow-up was 2.1 years (IQR, 0.9–6.4; 5th–95th percentile: 0.1–12.5) (total of 6366 patient-years of follow-up) for all patients. Follow-up was substantially longer for patients with large CAAs, with a median of 5.2 years (IQR, 1.9–8.9; 5th–95th percentile: 0.3–14.3) ($P < 0.001$). No complications were reported for patients with small CAAs. Only 1 patient with a medium CAA (maximum Z score of 8.5) experienced a cardiac complication (chronic cardiac ischemia resulting in heart failure and death); this patient happened to have CAAs in all 4 coronary artery branches. Figure 1 presents the cumulative incidence (CI) of 6 major complications in patients with large CAAs, including luminal narrowing (10-year CI, $20 \pm 3\%$), coronary artery interventions (10-year CI, $10 \pm 2\%$), coronary artery thrombosis (10-year CI, $18 \pm 2\%$), MI (10-year CI, $5 \pm 2\%$), composite major adverse cardiac complications (10-year CI, $14 \pm 2\%$), and death from cardiac causes or heart transplantation (10-year CI, $2 \pm 1\%$).

Table 2. Patient Characteristics Stratified by Maximum Degree of Coronary Artery Involvement

	No.	All Patients	No.	Small CAA	No.	Medium CAA	No.	Large CAA	P Value
Acute phase presentation									
Men	1651	1184 (72%)	854	623 (73%)	357	245 (69%)	440	316 (72%)	0.32
Age at diagnosis, y	1651	2.0 (0.7–4.7)	854	2.4 (1.1–5.0)	357	1.5 (0.5–3.8)	440	1.4 (0.4–4.7)	<0.001
Age at diagnosis category, y	1651		854		357		440		<0.001
<0.5		282 (17%)		78 (9%)		76 (21%)		128 (29%)	
0.5 to <1		240 (15%)		113 (13%)		61 (17%)		66 (15%)	
1 to <5		744 (45%)		447 (52%)		155 (43%)		142 (32%)	
5 to <10		306 (19%)		171 (20%)		56 (16%)		79 (18%)	
≥10		79 (5%)		45 (5%)		9 (3%)		25 (6%)	
Any acute readmission	1508	223 (15%)	757	79 (10%)	331	44 (13%)	420	100 (23%)	<0.001
Fever pre-IVIGs, d	1578	7 (5–10)	824	6 (5–8)	348	7 (5–10)	406	9 (6–14)	<0.001
Fever post-IVIGs, d	1527	1 (0–3)	783	1 (0–2)	344	1 (0–3)	400	1 (0–5)	<0.001
Total fever duration, d	1553	9 (7–13)	798	8 (6–10)	348	9 (7–12)	407	13 (9–17)	<0.001
Length of hospital stay, d	1576	5 (3–8)	802	4 (3–6)	352	5 (3–9)	422	8 (4–15)	<0.001
Conjunctivitis	1616	1462 (91%)	835	756 (91%)	354	317 (90%)	427	389 (91%)	0.75
Cervical lymphadenopathy	1616	653 (40%)	835	367 (44%)	354	130 (37%)	427	156 (37%)	0.01
Rash	1618	1386 (86%)	837	717 (86%)	354	315 (89%)	427	354 (83%)	0.05
Erythema/edema of extremities	1593	978 (61%)	823	527 (64%)	348	206 (59%)	422	245 (58%)	0.08
Mucosal changes	1616	1237 (77%)	835	677 (81%)	354	256 (72%)	427	304 (71%)	<0.001
No. of KD symptoms	1597		828		351		418		0.006
1		56 (3%)		26 (3%)		12 (3%)		18 (4%)	
2		175 (11%)		71 (8%)		48 (13%)		56 (13%)	
3		436 (26%)		208 (24%)		101 (28%)		127 (29%)	
4		648 (39%)		363 (43%)		137 (38%)		148 (34%)	
5		282 (17%)		160 (19%)		53 (15%)		69 (16%)	
Type of KD reported	1633		845		355		433		<0.001
Complete		973 (60%)		549 (65%)		199 (56%)		225 (52%)	
Incomplete		660 (40%)		296 (35%)		156 (44%)		208 (48%)	
Arthritis	1384	170 (12%)	718	87 (12%)	310	24 (8%)	356	59 (17%)	0.002
Weight before first IVIG dose, kg	1401	13 (9–19)	700	13 (10–19)	309	12 (8–17)	392	11 (8–20)	<0.001
Duration of follow-up, y	1651	2.1 (0.9–6.4)	854	1.2 (0.4–3.4)	357	2.8 (1.0–6.3)	440	5.2 (1.9–8.9)	<0.001
Laboratory values at admission									
Hemoglobin, g/L	1350	105.7±14.2	732	108.6±12.8	295	103.6±14.2	323	101.2±15.7	<0.001
Hematocrit, %	1300	0.31±0.04	716	0.32±0.04	282	0.31±0.04	302	0.30±0.04	<0.001
Red blood cell count, ×10 ¹² /L	1042	4.0 (3.6–4.3)	526	4.1 (3.8–4.4)	246	3.9 (3.6–4.3)	270	3.8 (3.4–4.2)	<0.001
White blood cell count, ×10 ⁹ /L	1358	16.1±6.8	729	14.9±5.7	303	16.6±6.7	326	18.2±8.4	<0.001
Platelets, ×10 ⁹ /L	1339	442±220	719	395±170	295	467±242	325	523±265	<0.001
ESR, mm/h	1166	62 (46–88)	647	60 (45–85)	257	61 (46–85)	262	70 (50–100)	<0.001
C-reactive protein, mg/L	1140	20 (9–84)	629	18 (8–69)	246	20 (8–96)	265	25 (12–106)	0.004
Albumin, g/L	1003	31.6±6.4	553	33.1±6.2	222	30.8±6.1	228	28.8±6.2	<0.001
Aspartate transaminase, U/L	946	36 (25–58)	494	37 (27–61)	220	34 (24–55)	232	33 (24–53)	0.02
Alanine aminotransferase, U/L	1202	35 (19–74)	684	38 (20–90)	259	33 (18–64)	259	32 (19–57)	0.04
Acute treatment									
At least 1 IVIG course	1646	1592 (97%)	852	828 (97%)	357	350 (98%)	437	414 (95%)	0.03
No. of IVIG doses	1643		852		357		434		<0.001
0		54 (3%)		24 (3%)		7 (2%)		23 (5%)	
1		1009 (61%)		600 (70%)		207 (58%)		202 (46%)	

(Continued)

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Table 2. Continued

	No.	All Patients	No.	Small CAA	No.	Medium CAA	No.	Large CAA	P Value
2		506 (31%)		214 (25%)		125 (35%)		167 (38%)	
3		66 (4%)		14 (2%)		16 (5%)		36 (8%)	
≥4		8 (1%)		0 (0%)		2 (1%)		6 (1%)	
Infliximab	1642	214 (13%)	851	86 (10%)	355	51 (14%)	436	77 (18%)	<0.001
Pentoxifylline	1591	7 (0.4%)	816	0 (0%)	346	2 (1%)	429	5 (1%)	0.01
Immunotherapy	1591	46 (3%)	816	10 (1%)	346	11 (3%)	429	25 (6%)	<0.001
Any steroids	1594	342 (21%)	817	104 (13%)	348	73 (21%)	429	165 (38%)	<0.001
Oral steroids	1592	216 (14%)	817	58 (7%)	346	44 (13%)	429	114 (27%)	<0.001
Intravenous steroids	1525	288 (19%)	761	85 (11%)	336	62 (19%)	428	141 (33%)	<0.001

Small CAA: $2.5 \leq Z < 5$; Medium CAA: $5 \leq Z < 10$; Large CAA: $Z \geq 10$.

CAA indicates coronary artery aneurysm; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; and KD, Kawasaki disease.

There were 8 deaths overall: 1 with medium and 7 with large CAAs. The 1 patient with medium CAAs in all 4 branches (mentioned above) died of chronic ischemia 6 months after the acute phase. Four deaths were secondary to MI (3 within 6 weeks of the acute phase and 1 that occurred 18 months after the acute phase). The other 3 patients died of noncardiac causes (1 mitochondrial disorder and 2 trauma). In addition, 2 patients with large CAAs underwent heart transplantation at 5 months and 4 years after the acute phase. A higher maximum CAA Z score and higher number of coronary artery branches affected were strongly associated with the composite outcome of major cardiac complications (Table 3).

Branch Level Outcomes

Given that the risk of complications was associated with specific CAA characteristics (as opposed to being determined solely at the patient level), risk factor analyses were performed at the coronary artery branch level for branches with at least 1 CAA with a Z score ≥ 10 . CAAs with Z scores < 10 were not included in this analysis because of our finding that there was no substantial risk of complications in those patients. A total of 893 CAAs in 440 patients were included in this analysis, with 370 (42%) in the LAD, 297 (33%) in the RCA, 135 (15%) in the LCX, and 91 (10%) in the LMCA. The majority (603, 68%) of branches included had maximum CAA Z scores 10 to 19.9, 195 (22%) had Z scores 20 to 29.9, 48 (5%) had Z scores 30 to 39.9 (5%), and 47 (5%) had Z scores ≥ 40 . Complete details of the architecture of CAAs by branch are presented in Table 4. This analysis focused on 3 branch-level outcomes: narrowing of luminal diameter $> 50\%$ of normal, coronary artery thrombosis, and normalization of luminal diameter. Given that vascular interventions and MIs may be a consequence of the first 2 categories, risk factors are presumed likely to be the same. Vascular interventions and MIs were not analyzed as separate outcomes.

At 10 years, luminal narrowing affected $12 \pm 1\%$ of all branches with large CAAs, with substantially higher rates of narrowing for CAAs in the RCA and the LAD (versus LMCA and LCX) and in branches with CAAs with Z scores ≥ 20 (Figure 2). The complete list of factors associated with luminal narrowing in multivariable Cox regression models is provided in Table 5. Other than CAA branch and higher CAA size, complex CAA architecture was also associated with greater hazard of luminal narrowing. Some characteristics of the acute phase were also associated with an increased hazard of luminal narrowing, namely lower number of IVIG doses (ie, cycles) during the acute phase, lower serum albumin levels, and higher total number of days of fever before treatment with IVIGs.

Thrombosis affected $11 \pm 1\%$ of all branches with large CAAs by 10 years, with a predilection for the RCA and the LAD, and for branches with CAAs with Z score ≥ 20 (Figure 2). The complete list of factors associated with coronary artery thrombosis in multivariable Cox regression models is provided in Table 6. Factors associated with an increased risk of thrombosis included greater maximum CAA Z score, no treatment with IVIGs in the acute phase, complex CAA architecture, and lower serum C-reactive protein in the acute phase.

Normalization of luminal diameter at 10 years occurred in $57 \pm 3\%$ of branches with large CAAs, which was substantially lower than the rate of normalization for branches with medium ($92 \pm 1\%$) or small CAAs ($99 \pm 4\%$) (Figure 3). Large CAAs in the LAD and LCX were more likely to normalize in dimensions compared with those in the RCA or LMCA, and the hazard of normalization was inversely proportional to the maximum Z score of the CAA (Figure 2). The complete list of factors associated with normalization of luminal diameter in the multivariable regression model are shown in Table 7. Other than coronary artery branch and the maximum size of the CAA, factors associated with increased risk of normalization were lower total CAA ellipsoid area, treatment with IVIGs in the acute phase, female sex,

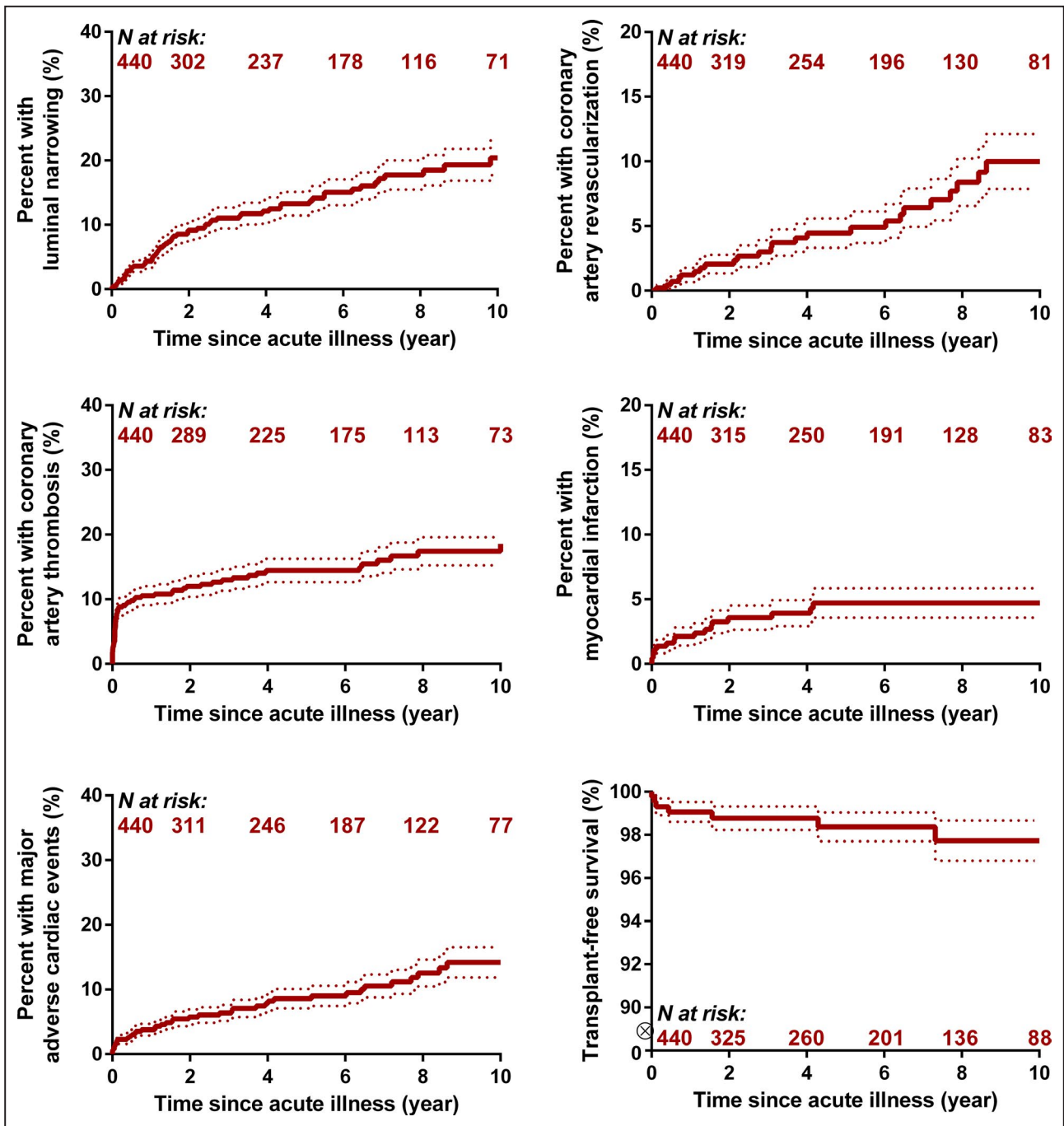


Figure 1. Cumulative incidence calculated using Kaplan–Meier survival analysis of complications for patients with coronary artery aneurysms after Kawasaki disease in patients with at least 1 lesion with a coronary artery Z score ≥ 10 . Dotted lines represent the estimated standard error around the cumulative incidence.

younger age at acute KD, incomplete KD, and lower initial erythrocyte sedimentation rate.

CAA shape (saccular or fusiform/irregular), location in the vessel (distal, extending, or proximal), and width to height ratio were not associated with any cardiac complications in multivariable models (although some associations were statistically significant at the univariable level) (data not shown).

DISCUSSION

In this study, we report that the occurrence of luminal narrowing, coronary artery thrombosis, and major adverse cardiac complications were nearly completely confined to patients with CAAs with Z scores ≥ 10 . Importantly, in those patients, the risk continued to increase over time, highlighting the importance of

Table 3. Univariable Factors Associated With Composite Risk Major Adverse Cardiac Complications in Cox Proportional Hazard Analysis for All Patients With KD and Maximum Coronary Artery Z Score ≥ 2.5

Univariable Risk Factors	HR	Lower 95% CI	Upper 95% CI	P Value
Maximum CAA Z score				
≥ 2.5 to <10	0.19	0.09	0.42	<0.001
≥ 10 to <20	Reference			
≥ 20 to <30	2.33	1.01	5.40	0.05
≥ 30	7.63	3.12	18.7	<0.001
No. of CAAs with Z score ≥ 10				
1	0.05	0.02	0.16	<0.001
2	Reference			
3	1.98	0.91	4.33	0.09
4	3.13	1.38	7.11	0.006

CAA indicates coronary artery aneurysm; HR, hazard ratio; KD, Kawasaki disease.

long-term and uninterrupted clinical follow-up. The highest risks were associated with CAAs in the LAD and RCA with maximum Z scores ≥ 20 and complex CAA architecture. Luminal normalization of coronary artery dimension was more likely to occur for CAAs in the LAD and LCX branches, with the likelihood of normalization inversely related to the initial maximum Z score of CAA. Additional factors such as IVIG treatment during the acute phase, lower erythrocyte sedimentation rate, and lower total CAA area were also associated with an increased likelihood of luminal normalization. This study has the advantages of being a large, multi-institutional, international study, which more precisely defines the prevalence of CAA-related cardiovascular complications, uses longitudinal Z scores, and defines associations with coronary artery branch, with over a 10-year follow-up.

Risk Stratification

Manliot et al⁷ first demonstrated that, regardless of absolute dimensions, a CAA Z score ≥ 10 represented the effective lower bound of risk for cardiac complications in the medium term after KD. However, we found that within groups with large CAAs (Z scores ≥ 10), the risk profile of large aneurysms with Z scores < 20 differs significantly from aneurysms with Z scores ≥ 20 , with the latter being at substantially higher risk of complications. This is a novel finding that may have important implications in the surveillance and management of patients with CAA Z scores ≥ 20 . We, therefore, propose that patients with CAAs that have Z scores ≥ 20 be further distinguished and be regarded as a separate and higher risk category than those with CAAs that have Z scores between ≥ 10 and < 20 . The change in risk stratification has important implications for the intensity

Table 4. Characteristics of Coronary Artery Branches With Aneurysms With Maximum Coronary Artery Z Score ≥ 10

Branch	
RCA	297 (33%)
LMCA	91 (10%)
LAD	370 (42%)
LCX	135 (15%)
Maximum coronary artery Z score	Median (IQR) 15.7 (12.3–22.3)
10.0–19.9	603 (68%)
20.0–29.9	195 (22%)
30.0–39.9	48 (5%)
40.0+	47 (5%)
Involvement of the LAD/LMCA/LCX bifurcation	
Yes	338 (38%)
No	555 (62%)
Aneurysm architecture	
Isolated aneurysm in normal vessel	161 (18%)
Isolated aneurysm in a dilated vessel	332 (37%)
Complex aneurysms*	251 (28%)
Undefined/unreported	149 (17%)
Aneurysm location within branch	
Proximal segment	343 (38%)
Distal segment	79 (9%)
Extending throughout segment	221 (25%)
Undefined/unreported	250 (28%)
Aneurysm shape	
Saccular	171 (20%)
Fusiform/irregular	306 (34%)
Undefined/unreported	416 (47%)
Aneurysm diameter to height ratio (n=312)	Median (IQR) 0.73 (0.53–1.06)
Aneurysm estimated area (n=312)	Median (IQR) 0.72 (0.44–1.34)

IQR indicates interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; LMCA, left main coronary artery; and RCA, right coronary artery.

*Architecture other than a single isolated aneurysm in a coronary artery branch.

and type of thromboprophylaxis that should be used in those patients. In small ($2.5 \leq Z < 5$) to medium ($5 \leq Z \leq 10$) CAAs, where platelet activation is a key factor in initiating thrombus formation, antiplatelet therapy is likely to be effective and is currently the mainstay of therapy. However, more aggressive thromboprophylactic therapy with the addition of an anticoagulant is necessary in patients with large (Z score ≥ 10 , and even more so in those with Z score ≥ 20) or progressive CAAs, where the low shear stress environment and flow stasis leads to activation of the clotting cascade.⁸

The 2017 AHA guidelines considered omitting echocardiographic evaluation in children with small

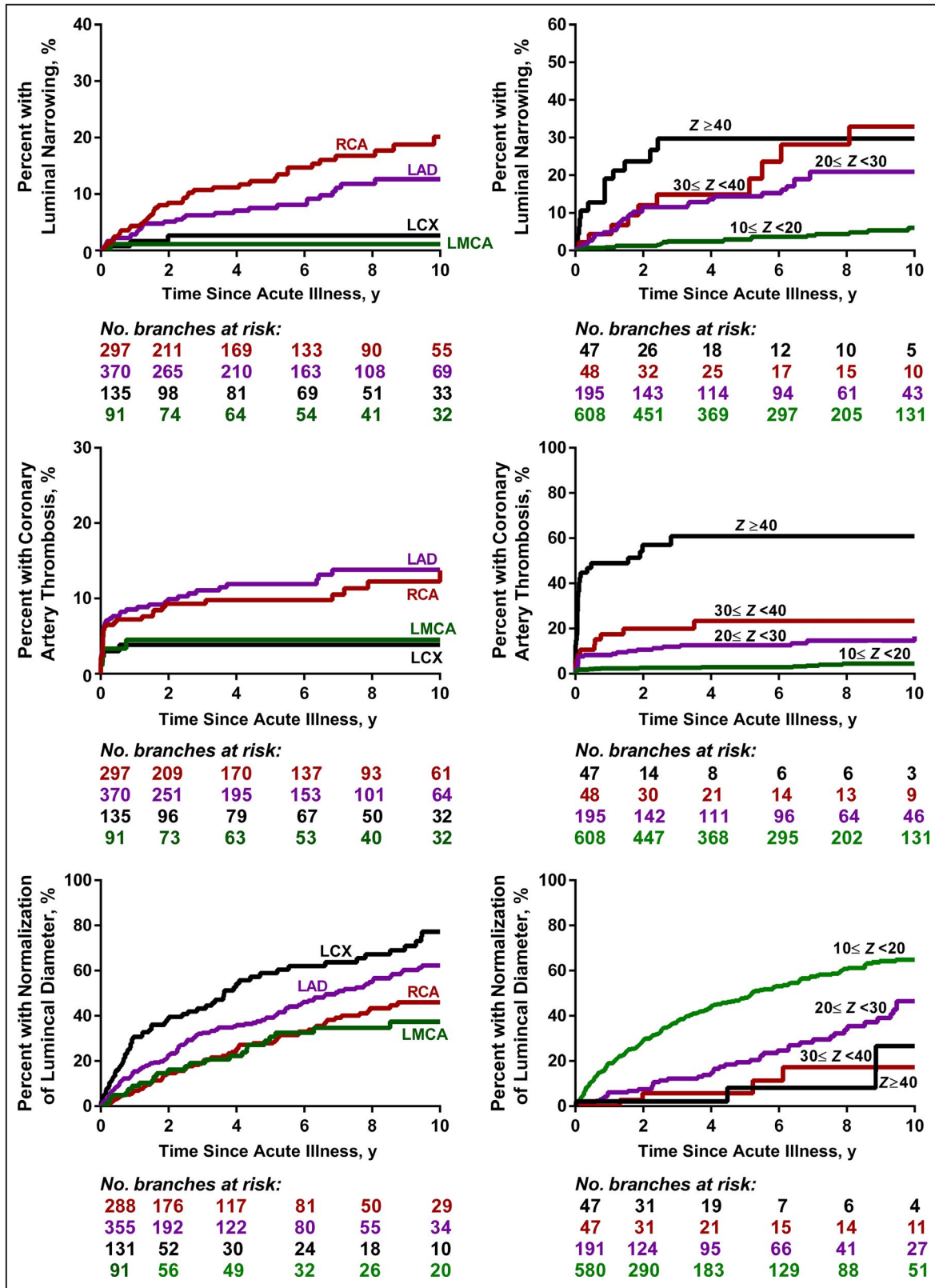


Figure 2. Cumulative incidence of luminal narrowing, coronary artery thrombosis, and normalization of luminal diameter, calculated using Kaplan–Meier survival analysis, for coronary artery aneurysms after Kawasaki disease in coronary artery branches with coronary artery Z score ≥10 stratified by coronary artery branches. LAD indicates left anterior descending coronary artery; LCX, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery; and maximum coronary artery Z scores.

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Table 5. Multivariable Factors Associated With Risk Luminal Narrowing Using Cox Proportional Hazard Analysis in Branches With CAAs With Z Score ≥10

Multivariable Risk Factors	Reliability, %	HR	Lower 95% CI	Upper 95% CI	P Value
Maximum CAA Z score	100				
≥10 to <20		Reference			
≥20 to <30		3.65	1.91	6.98	<0.001
≥30 to <40		4.24	2.00	9.01	<.0001
≥40		7.56	3.19	17.9	<0.001
No. of d of fever before IVIGs	98	1.04	1.01	1.07	0.01
Complex aneurysms architecture	97	1.93	1.24	3.01	0.004
Albumin level, g/L	94	0.92	0.86	0.98	0.008
No. of IVIG cycles	93				
0		Reference			
1		0.13	0.03	0.54	0.005
2		0.34	0.12	0.96	0.04
3+		0.48	0.18	1.29	0.15
Branch	78				
RCA		Reference			
LMCA		0.11	0.01	0.82	0.03
LAD		0.58	0.38	0.89	0.01
LCX		0.22	0.07	0.72	0.01

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

aneurysms who had normalization of the dimension of their coronary artery lumen (risk level 3.2). No patient with small CAAs had cardiac complications during the follow-up period, and 99% had normalization of their CAA luminal diameter. Given our data and a previous study by Dionne et al,⁹ which showed preserved endothelium continuity in patients with small CAAs but no actual anatomical aneurysms (ie, dilatation only), it would be reasonable to consider discharging these patients from cardiology follow-up. This recommendation is currently only true for children with lower risk levels (risk level 1 or 2).¹ As cardiologists and whenever evidence supports, we ought to empower our patients to achieve their maximal potential and not leave a cloud of being different for those with no evidence of

complications. Such a label might impact “self-image and lifestyle.”¹⁰

Examination of Additional Risk Factors

While Manlhiot et al proposed a risk classification system based solely on coronary artery Z scores, we found evidence that branch-level factors play an important role in determining the risk of luminal narrowing and thrombosis, as well as the likelihood of luminal diameter normalization.⁷ This supports findings from Tsuda et al¹¹ that branch CAAs had a higher risk of stenosis compared with bifurcation aneurysms. Rheological studies have reported a strong negative correlation between shear stress and risk of thrombus formation.^{8,12} In angiographic studies with

Table 6. Multivariable Factors Associated With Risk Coronary Artery Thrombosis, Using Cox Proportional Hazard Analysis, in Branches With CAAs With Z Score ≥10

Multivariable Risk Factors	Reliability, %	HR	Lower 95% CI	Upper 95% CI	P Value
Maximum CAA Z score	100				
≥10 to <20		Reference			
≥20 to <30		3.51	1.84	6.69	<0.001
≥30 to <40		5.74	2.50	13.16	<0.001
≥40		29.5	14.4	60.3	<0.001
Complex aneurysms architecture	88	2.08	1.32	3.26	0.002
Treatment with IVIG	87	0.38	0.19	0.76	0.006
C-reactive protein, 10 mg/L	76	0.95	0.90	0.99	0.02

CAA indicates coronary artery aneurysm; HR, hazard ratio; and IVIG, intravenous immunoglobulin.

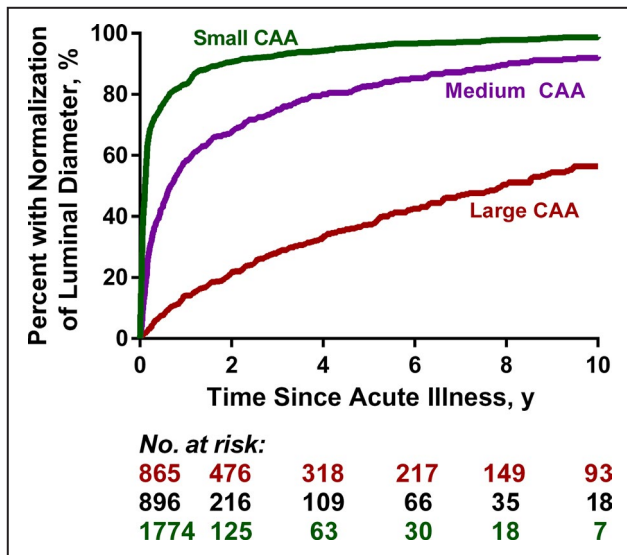


Figure 3. Cumulative incidence of normalization of luminal diameter, calculated using Kaplan–Meier survival analysis, for coronary artery aneurysms (CAAs) after Kawasaki disease stratified by level of coronary artery involvement.

Doppler flow, the average peak velocity in the CAA was found to decrease as the size of the CAA increased, suggesting that flow stagnation was also a risk factor for thrombosis.^{12–16}

In our analysis of CAA architecture, we found that both a higher number of CAAs within a coronary artery branch, and CAAs of the LAD/LCX involving the left bifurcation, increased the risk of complications in patients with large CAAs. Interestingly, research on atherosclerotic heart disease has found that the localization of atherosclerotic lesions to certain areas within the arterial system, particularly the branching sites, could be associated with rheological characteristics.^{14,15}

In terms of CAA location, the risk of thrombosis and luminal narrowing was higher in CAAs affecting the RCA and LAD coronary artery branches. We speculate that this could be a result of several reasons. First, reliability of LMCA measurements has been of concern, because of its anatomical variation.¹⁷ Second, being short and high-pressured, the walls of the LMCA may be less likely to weaken and facilitate sluggish flow. In terms of the LCX branch, its distal anatomical placement hinders visualization by echocardiography, which creates the possibility that stenosis and thrombus development in the area were missed.

Taken together, our findings support that these additional coronary artery branch–level risk factors should be taken into account when decisions are made regarding risk classification. While we

Table 7. Multivariable Factors Associated With Risk of Normalization of Luminal Diameter, Using Cox Proportional Hazard Analysis, in Branches With CAAs With Z Score ≥ 10

Multivariable Risk Factors	Reliability, %	HR	Lower 95% CI	Upper 95% CI	P Value
Maximum CAA Z score	100				
≥ 10 to <20		Reference			
≥ 20 to <30		0.50	0.38	0.66	0.002
≥ 30 to <40		0.24	0.12	0.51	<0.001
≥ 40		0.25	0.10	0.61	<0.001
Aneurysm area, cm ²	100				
>1.35		7.01	2.38	20.6	$<.001$
0.71 to 1.35		4.50	1.61	12.6	0.004
0.46 to 0.70		1.59	0.46	5.58	0.47
≤ 0.45		Reference			
Branch	99				
RCA		Reference			
LMCA		0.60	0.39	0.91	0.02
LAD		1.94	1.51	2.48	$<.001$
LCX		2.16	1.55	3.00	$<.001$
Treatment with IVIGs	94	3.22	1.28	8.13	0.01
Age at acute KD, y	94	0.93	0.89	0.97	0.006
Incomplete KD	85	1.31	0.99	1.73	0.056
ESR, 10 mm/h	78	0.95	0.91	0.99	0.03
Women	67	1.33	1.03	1.72	0.03

CAA indicates coronary artery aneurysm; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LAD, left anterior descending artery; LCX, left circumflex artery; LMCA, left main coronary artery; and RCA, right coronary artery.

conclude that CAA architecture was an important feature to include for risk stratification, we did not find any association between CAA shape (saccular versus fusiform) and any of the cardiac complications considered in this study, despite this finding being reported in previous studies. This could be associated with the fact that almost half of all imaging reports did not indicate the shape of the CAAs and, as such, the number of missing data were substantial to identify a pattern. The development and utilization of better methods to characterize CAA lesions would be an important next step to further refine risk stratification models.

Outcome Comparisons With Previous Studies

In a 10- to 21-year follow-up study by Kato et al⁴ of 146 patients with KD and CAAs, 90% of patients showed normalization of luminal dimensions within the first 2 years from onset; however, none of the large or giant CAAs, defined as having an absolute diameter of at least 8 mm, showed normalization of luminal dimension. A study from the United States by Friedman et al¹⁸ found an overall CAA proportion of normalization of luminal dimensions of 75%, which they believed was higher than those reported in previous cohorts attributable to more aggressive treatment. Similar to Kato et al, they also found that the probability of normalization of luminal dimensions was inversely proportional to CAA Z score at diagnosis.¹⁸ This was in line with our findings, with >80% of small to medium CAAs and ≈50% of large CAAs achieving luminal diameter normalization. Friedman et al also reported that major adverse cardiovascular events occurred exclusively in large CAAs, which was similar to our findings, where all complications occurred in patients with large CAAs, with the exception of 1 patient with medium CAAs who had CAAs in all 4 branches. In our study, the rate of CAA normalization was similar to Friedman et al and larger than Kato et al (55%–60%), which speaks to potentially more aggressive management in the current era. However, the rate of luminal narrowing for large CAAs with Z score ≥10 at ≈20% was similar to the data from Kato et al⁴ (despite the different definitions of large CAAs), indicating a need for more aggressive management and/or novel approaches in this patient population.

Limitations

This study used echocardiography reports rather than an imaging core laboratory; thus, differences in methods of measurement by participating cardiologists may have contributed to data variability. A secondary analysis of the Pediatric Heart Network's randomized Kawasaki disease trial has previously shown moderately good agreement (interclass

correlation between 0.60 and 0.75 for all segments other than the circumflex) between coronary artery segment dimensions measured at local centers versus core laboratory assessment in this context.¹⁹ Regardless of the method of interpretation, echocardiography is inferior to advanced imaging modalities (eg, computed tomography, magnetic resonance imaging, or invasive angiography) in estimating coronary artery diameter, particularly the distal coronary artery tree, although it is still the standard of care for most patients. Not all patients had such advanced imaging studies (1% of patients with small CAAs, 5% to 8% of patients with medium CAAs, and ≈50% of patients with large CAAs divided roughly equally between angiography and magnetic resonance imaging). In terms of coronary artery branch anatomy, assessment based on reports was required to obtain features, which is subject to interpretation error. Another source of variation is that outcomes were often detected at the time of imaging rather than when they actually occurred, particularly when asymptomatic. Last, our study design was retrospective, and there was no auditing of data at centers, so we cannot exclude the possibility of selection bias in cases submitted, although this would be unlikely.

CONCLUSIONS

In this large, multi-institutional international study conducted in patients with KD who had CAAs, we report that the risks of luminal narrowing, thrombosis, and major adverse cardiovascular complications were nearly completely confined to those with maximum CAA Z scores ≥10. We can also propose that CAAs with Z scores ≥20 should now be considered a separate risk strata because of their distinctly greater risk profile. The presence of complex CAAs, as well as the involvement of LAD and RCA branches, increases an individual's risk for CAA-related complications, and these factors should be taken into account on an individual basis when considering surveillance and management strategies. Future studies could focus on rheology to investigate patient-specific hemodynamic factors, which could increase the risk of complications and assess the effectiveness of more aggressive thromboprophylactic regimens, including triple therapy, in patients with CAAs with Z scores ≥20.

APPENDIX

The members of the International Kawasaki Disease Registry include: Carolyn A. Altman MD—Texas Children's Hospital, Baylor College of Medicine, Houston, TX; Brett R. Anderson MD—Columbia University, College of Physicians and Surgeons, New

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Disclosures

None.

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