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JCS GUIDELINES

JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease

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Table of Contents

Abbreviations

2DE	two-dimensional echocardiography
ACEI	angiotensin converting enzyme inhibitor
ACS	acute coronary syndrome
AMI	acute myocardial infarction
AP	angina pectoris
APV	average peak velocity
ARB	angiotensin II receptor blocker
baPWV	brachial-ankle pulse wave velocity
BCG	Bacille de Calmette et Guérin
BMS	bare metal stent
BNP	brain natriuretic peptide
CAA	coronary artery aneurysm(s)

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Refer to **Appendix 1** for the details of members.
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CABG	coronary artery bypass grafting
CAG	coronary angiography
CAL	coronary artery lesion(s)
cAMP	cyclic adenosine monophosphate
CCU	coronary care unit
CFR	coronary flow reserve
cIMT	carotid artery intima-media thickness
CK	creatine kinase
CT	computed tomography
CTA	computed tomography angiography
CTO	chronic total occlusion
Cx	circumflex
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DL	dilated lesion
DOAC	direct oral anticoagulant
FFR	fractional flow reserve
FMD	flow-mediated dilation
gAN	giant aneurysm
GEA	gastroepiploic artery
HDL-C	high-density lipoprotein cholesterol
H-FABP	heart-type fatty acid binding protein
ICT	intracoronary thrombolysis
iFR	instantaneous wave-free ratio
IHD	ischemic heart disease
ITA	internal thoracic artery
IVIG	intravenous immunoglobulin
IVUS	intravascular ultrasound
KD	Kawasaki disease
LAD	left anterior descending artery
LCA	left coronary artery
LDL-C	low-density lipoprotein cholesterol
LMT	left main trunk
LS	localized stenosis
mAN	medium aneurysm
MDCT	multi detector row computed tomography
MI	myocardial infarction
MLC	myosin light chain
MLD	minimum lumen diameter
MMP	matrix metaroproteinase
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
OCT	optical coherence tomography
oxLDL	oxidative low-density lipoprotein
PCI	percutaneous coronary intervention
PET	positron emission tomography
POBA	percutaneous old balloon angioplasty
PTCRA	percutaneous transluminal coronary rotational ablation
PT-INR	international normalized ratio of prothrombin time
PWV	pulse wave velocity
RA	radial artery
RAS	renin-angiotensin system
RCA	right coronary artery
RITA	right internal thoracic artery
SVG	saphenous vein graft
TC	total cholesterol
TG	triglyceride
t-PA	tissue plasminogen activator

Introduction to the Revised Guidelines

Table 1. Class of Recommendation

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of a procedure or treatment
Class IIa	The procedure or treatment is likely to be useful and effective
Class IIb	The procedure or treatment is not very well established
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and may in some cases be harmful

Table 2. Levels of Evidence

Level A	Proven from multiple randomized interventions or meta-analyses
Level B	Proven in a single randomized clinical trial or a clinical trial that is not a large, randomized intervention
Level C	Consensus in an expert or small clinical trial (including retrospective studies and registration)

More than 50 years have passed since Kawasaki disease (KD) was first reported.[1] According to a nationwide survey, the number of patients with KD who became adults was 136,960 in 2014 (45.9% of the total number of those with a history), and 15,000 adult patients with coronary sequelae (including regression cases) are presumed to exist. Even if the KD coronary artery lesion (CAL) is a small or regressed aneurysm, the tissue is not normal, and most people diagnosed with coronary artery sequelae have a risk of coronary life event. This guideline is for the remote management of cases with such KD heart sequelae. Seven years have passed since the last revision of this guideline in 2013, and various changes have been made to the definition and management of cardiovascular sequelae of KD. In particular, since the AHA's KD guideline[2] announced in 2017 introduced the Z-score of coronary artery diameter as a standard for remote management, established the evaluation of coronary aneurysms according to individual physique, and the stratification of management by Z-score became clearer. In Japan, the Z-score can be calculated from the coronary artery diameter in children,[3] and classification by Z-score has become possible, in addition to classification based on the absolute value of the coronary artery diameter. So, Z-score classification was also adopted in this guideline. In the classification based on absolute values, the lower limit values of medium and large aneurysms were combined as

"above". In other words, an medium aneurysm was ≥4 mm and <8 mm, and a giant aneurysm (gAN) was ≥8 mm. However, in children over 5 years old, the discrepancy between this absolute value standard and the Z-score cannot be ignored. Therefore, it is recommended to give priority to the judgment based on the Z-score for those over 5 years old. In addition, it has been reported that when the coronary artery diameter in the acute phase exceeds 6 mm, the appearance of stenotic lesions is significantly increased in the remote phase,[4,5] and there are many experts who support this. However, as a result of discussion, it was judged that the evidence was still in sufficient, and though it was mentioned in the text, it was not to put on the table (**Table 7**, **Table 18**). Furthermore, in recognition of the importance of follow-up and management for each period from childhood to adulthood, there is a newly reorganized item of "Follow-up according to life stage".

Table 1 and **Table 2** show the class classification and evidence level. Unfortunately, the evidence in children is generally still poor, so we have omitted any that do not have evidence in children. However, we list the class and evidence level when there is evidence from adults regarding findings that are not yet sufficiently evidenced in children, and those that are agreed at the expert level to be important. For the convenience of the reader, the chapter summary is given at the beginning of each chapter, and the evidence required in the future at the end of the chapter. In addition, there are many "unapproved and off-label drugs" in the pediatric field, although treatment under insurance is permitted. In their use, procedures such as the necessity of applying to an ethics committee are left to the policy of each facility, and this guideline clearly states where it is an "unapproved/off-label" drug for children.

We hope that these guidelines will assist readers in diagnosing and following-up patients with KD cardiovascular sequelae.

I. Epidemiology, Genetic Background, and Severity Assessment of Kawasaki Disease (KD)

1. Current Epidemiology

- The number of KD patients has continued to increase despite a decline in the pediatric population.
- Incomplete KD, which does not completely satisfy the diagnostic criteria of KD, has been increasing. It recently accounted for approximately 20% of new onset.
- Intravenous immunoglobulin (IVIG) therapy is performed in 93.5%, and the refractory rate is 17.8%. KD cardiac sequelae are observed in 2.3%.

1.1 Nationwide Survey of KD (2015–16) and Comparison With International Epidemiology (Figure 1)

1.1.1 Numbers of Patients

According to the 24th nationwide survey (2015–16), the number of patients newly diagnosed with KD was 16,323 in 2015, and 15,272 in 2016, yielding a total of 31,595 patients, consisting of 18,060 male and 13,535 female patients,[6] which was almost equal to that of the 23rd survey (31,675) in 2013–14. The mean prevalence during the 2-year survey period was 319.6 patients/100,000 children in the 0–4 years age group (357.2 in males and 280.2 in females), which was a little more than the 305.3 of the 23rd survey (341.3 in males and 267.5 in females).

1.1.2 Yearly Changes in Numbers of Patients

Figure 1[7] shows the changes over time in the number of patients newly diagnosed with KD each year. In addition to nationwide increases in 1979, 1982, and 1986, the number of patients has shown a tendency of annual increment since 1995 to 2015, except in 2016. The mean prevalence in 2015 was 330.2 patients/100,000 children aged 0–4 years (371.2 in males and 287.3 in females), which was the highest to date. It then slightly decreased to 309.0 patients in 2016 (343.2 in males and 273.2 in females). The actual number of patients in 2016 was the same as in 1982; in contrast, the mean prevalence in 2016 was 1.58-fold more than in 1982, reflecting the consistently declining birthrate in Japan.

1.1.3 Seasonal Changes in the Numbers of Patients

The seasonable changing pattern in the number of new cases in the 24th survey was similar to the results of past surveys. That is, the number of new cases was low in the fall (i.e., September and October) and was high in spring (March–May) and summer (June–August).

1.1.4 Age and Regional Distribution

Patients under 3 years of age accounted for 64.1% (65.1% in male, and 62.7% in female). The incidence rate in corresponding ages showed a monomodal distribution and was highest in both boys and girls aged 9–11 months in 2015 as well as in 2016. The sexual difference in the prevalence was mostly (1.51 for boys vs. 1.0 for girls) in infants aged 6–8 months.

The actual number of patients in the 2 years of the survey was highest in Tokyo (3,729) followed by Kanagawa, Aichi, and Osaka. The prevalence was highest in Saitama, Niigata, and Tokushima, and least in Iwate, Toyama, Miyazaki, and Okinawa.

1.1.5 Global and Racial Distribution

KD has been reported from more than 60 countries and regions so far. The prevalence among 100,000 children aged 0–4 years was 71.9–110.0 in China, 170.9–194.9 in Korea, 18.1–21.3 in the USA, and 49.4 in Hawaii. The prevalence in terms of each race in Hawaiian offspring was remarkable: 114.8 for Asian, 304.3 for Japanese, 73.9 for Filipinos, 52.4 for native Hawaiians, and 19.9 for whites.[8]

1.2 Clinical Features

The most frequent day of illness prompting the first visit to hospital was 4th day after onset of symptoms (25.1%), and 64.3% of those patients saw a physician within 4 days from the onset. As for the presence or absence of 6 major symptoms, the symptoms of KD were typical in 77.8%, atypical in 1.6%, and incomplete in 20.6% of cases. Characteristics of the results of the 24th survey were as follows: a modest increase was noted in the number of patients with atypical KD, and the rate of atypical KD was relatively

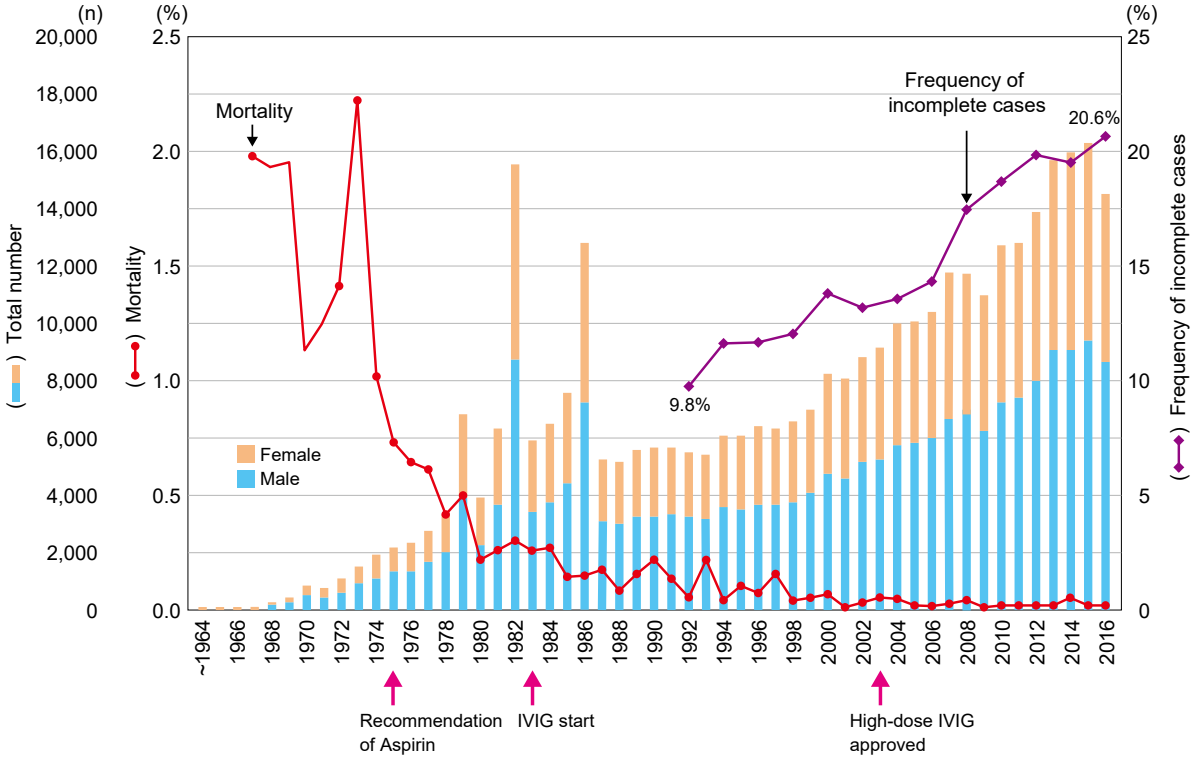

Figure 1. Transition of the total number of cases, mortality, and frequency of incomplete cases. (Source: Prepared based on Division of Public Health, Center for Community Medicine, Jichi Medical University.[7])

high among infants aged less than 2 years as well as in school-aged children. Those with recurrent KD comprised 4.2% of the patients, and the recurrence rate in boys and girls increased in accordance with their age till 5 and 7 years of age, respectively. Among the reported cases, 2.1% had siblings with a past history of KD and 1.2% of them had one of their parents with a past history of KD.

During the 2 years of the 24th survey, 2 infants (1 boy, 1 girl) reportedly died, yielding a mortality rate of 0.01%. Both of them had been complicated with coronary aneurysms; and 1 passed away in the acute phase.

1.3 Treatment

1.3.1 Initial Treatment

Initial treatment with IVIG was given in 93.5% of the patients, but 17.8% of them were refractory. The first dose of IVIG was most frequently administered on the 5th day of illness. It was remarkable that 74.8% of 2-year-old patients, or younger, received IVIG within 5 days of illness or earlier. Combination therapy with initial IVIG and steroids was administered to 13.0% of the patients; and steroid pulse therapy was given to 14.7% of those with steroids combination therapy. The dose of the initial IVIG was 1,900–2,099 mg/kg of body weight in 97.9% of the patients, and the duration of the infusion was 1 day in 97.5%.

1.3.2 Additional Therapy

Additional therapy following first-line therapy was additional IVIG in 19.6%, steroids in 6.9%, infliximab in 1.4%, immunosuppressants in 1.3%, and plasmapheresis in 0.5%. Among the patients who were refractory to the initial IVIG, the reported second-line therapy was IVIG in 90.6%, steroids in 28.9%, infliximab in 7.3%, immunosuppressants in 5.4%, and plasmapheresis in 2.5%.

1.4 Cardiovascular Complications and Sequelae

1.4.1 Acute Phase

Cardiovascular complications were reported in 7.9% (9.0% of boys and 6.4% of girls) of patients, which was approximately 40% reduction in comparison with that reported in the 15th survey. More precisely, complications were: coronary dilation in 5.6%, valvular lesions in 1.54%, coronary aneurysms in 0.82%, giant coronary aneurysms in 0.13%, coronary stenosis in 0.02%, and acute myocardial infarction (AMI) in 0.0%.

1.4.2 Sequelae (Figure 2)[7]

Cardiovascular sequelae developed in 2.3% (2.7% of boys and 1.7 of girls) of patients. More precisely, the cardiovascular sequelae were: coronary dilatation in 1.3%, coronary aneurysms in 0.64%, valvular lesions in 0.36%, giant coronary aneurysms in 0.13%, coronary stenosis in 0.02%, and myocardial infarction (MI) in 0.02%. These sequelae, except for valvular lesions, occurred more often in boys; in addition, the complication rates of giant coronary aneurysms, coronary aneurysms, and coronary dilation were most prevalent in atypical KD.

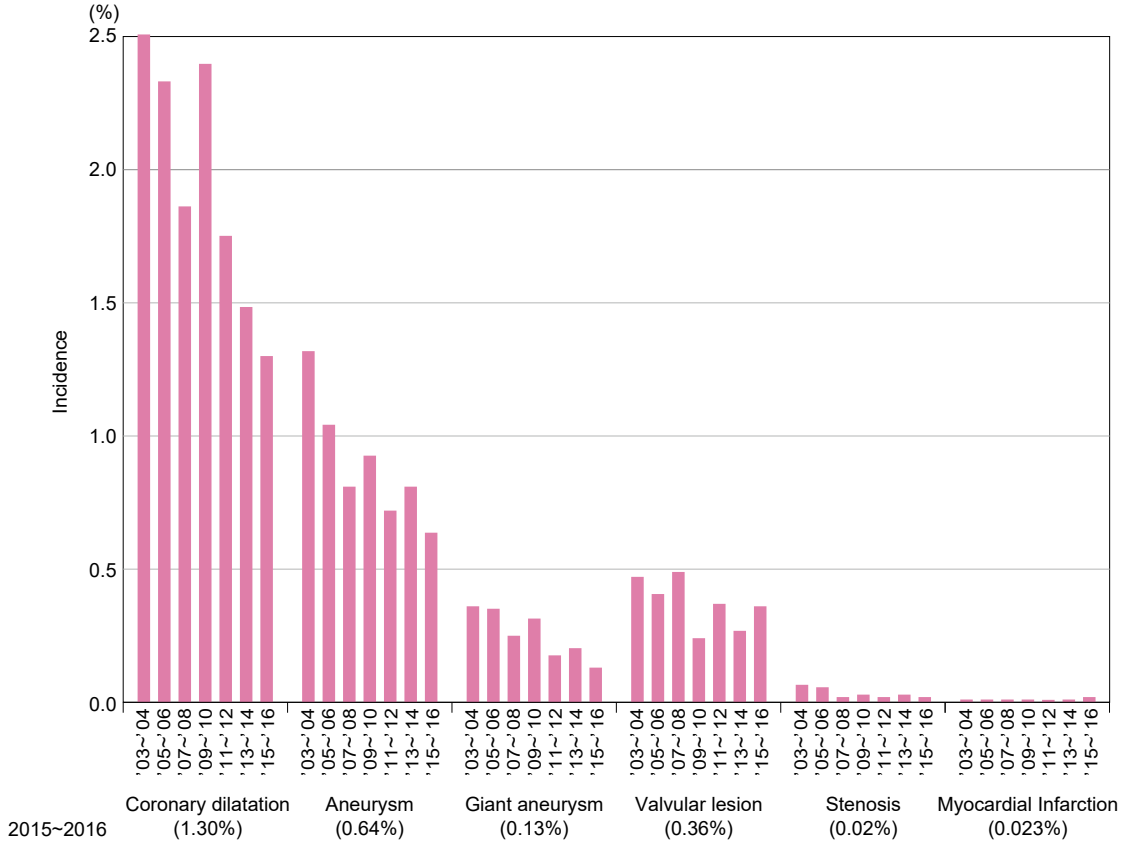

Figure 2. Annual Frequency of Cardiac Sequelae. (Source: Prepared based on Division of Public Health, Center for Community Medicine, Jichi Medical University.[7])

2. Genetic Background of KD

- Among susceptibility loci ever reported, association signals near genes *ITPKC*, *CASP3*, *BLK*, *CD40*, *FCGR2A* identified in genome-wide studies have higher replicability and have been validated in several different ethnicities (Class IIb, Level C).
- Through bioinformatics study, many susceptibility variants for KD identified in genome-wide association studies have been predicted to have functional significance in B-lineage cells (Class IIb, Level C).
- Genotype combination of *ITPKC* and *CASP3* loci have been associated with disease severity in Japan and Taiwan (Class IIa, Level C).

2.1 Epidemiological Findings Suggesting Involvement of Genetic Factors in the Pathogenesis of KD

The number of patients newly affected with KD in 1 year among 100,000 children younger than 5 years old is highest in Japan (330.2 in 2015),[9] followed by South Korea (194.9 in 2014)[10] and Taiwan (66.24 in 2006).[11] The incidence in East Asian nations is markedly higher than in other regions.[4] In the USA, KD is most prevalent among those with Japanese ancestry, and the other Asian populations also have a higher incidence than African and European Americans.[12] Thus the difference in incidence rates, which is up to 10–20-fold, might be genetic in origin. As with the other polygenic diseases, familial aggregation of KD is also known.[13,14] Therefore, the inter-ethnic and inter-individual differences in liability for KD is recognized as attributable to genetic factors.

2.2 Susceptibility Genes for KD

Previously, many candidate genes have been studied in genetic association studies. However, few findings of a positive association from these studies have been validated or replicated or reached a broad consensus. In the gene regions of *ITPKC*,[15] *CASP3*,[16] *BLK*,[17,18] *CD40*,[17,18] and *FCGR2A*[19] significant association of variants with susceptibility to KD were found in studies with a genome-wide design. These association signals were replicable in different ethnicities, and the genes have been recognized as principle susceptibility genes for KD. On the other hand, associations of the variants in the *HLA* class 2 gene region, which are robust and replicable in the Japanese population,[17] were not in most other ethnicities. It is suggested that, in this chromosomal region, there might be ethnic or geographic heterogeneity of the genes or variants relevant to KD. Identification of variants commonly associated with KD and other inflammatory diseases with distinct mechanisms

Table 3. Susceptibility Genes for Kawasaki Disease Identified in Genome-Wide Studies

Genes and chromosomal locations	Function of gene products	Reports of association					
		Susceptibility		Unresponsive to IVIG		Coronary artery lesion	
		Significant association	No significant association	Significant association	No significant association	Significant association	No significant association
FCGR2A (1q23)	Receptor for IgG Fc portion	J[17,36*], T[19], C[19,37–40] K[19,36,41], E etc.[19], Am (E, Af, As, H)[42]	E[43,44], J[45]	–	–	C[38], J[45]	E[43,44]
CASP3 (4q34–35)	Protease involved in progression of cellular apoptosis	J[16,30], E[16], C[39,46,47]	T[48]	J[30**]	C[46,48]	J[30**]	C[39,46], T[48]
HLA class 2 (6p21.3)	Antigen presentation to helper T-cells	J[17], C[39]	C[40], T[49], K[50]	–	–	–	–
BLK (8p23–22)	Src family tyosine kinase involved in B-cell receptor signaling	J[17], T[18,51], C[39,40,52,53], K[41,51,54]	–	–	–	–	–
ITPKC (19q13.2)	Kinase for inositol tris-phosphate molecule	J[15,19,30], K[55], T[56,57], C[58]	T[51,52], C[39,47,61]	J[30**]	–	J[15,30**], T[31**,56], K[55]	–
CD40 (20q12-q13.2)	Receptor for CD40LG	J[17], T[18,62], C[40,63]	C[39,52]	–	–	T[62]	C[63]

*Male-specific association. **Association of genotype combinations of *ITPKC* and *CASP3*. Af, African; Am, American; As, Asian; C, Chinese; E, European; H, Hispanic; IVIG, intravenous immunoglobulin; J, Japanese; K, Korean; T, Taiwanese.

such as inflammatory bowel diseases (*FCGR2A* gene for ulcerative colitis[20]) and autoimmune diseases (*BLK* and *CD40* genes for systemic lupus erythematosus,[21] rheumatoid arthritis,[22] etc.) introduced new viewpoints on the pathogenesis of KD. The importance of B cells has been suggested by a bioinformatics study in which responsible variants of the susceptibility gene loci for various autoimmune disorders identified in genome-wide association studies were predicted by using publicly available information. In that study, accumulation of the responsible variants for KD near the enhancer regions specific to B-lineage cells was shown.[23] Whereas no robust association of the variants in *ITPKC* and *CASP3* gene loci with conditions other than KD has been reported, indicating involvement of these gene products with some unique mechanism of KD inflammation.

2.3 Genes Relevant to More Severe Manifestation of KD

For the established susceptibility genes for KD, the association of the variants with risks for resistance to IVIG treatment as well as for coronary artery lesion (CAL) formation have also been investigated, and some positive association results have been reported (**Table 3**). Genome-wide association studies for variants that confer risk for CAL have been carried out by several research groups outside Japan;[24–29] however, validation in other populations has not been conducted. In Japan, associations between genotype combinations of *ITPKC* and *CASP3* susceptibility variants with risks for IVIG unresponsiveness and CAL formation are reported.[30] Similar genotype combinations of *ITPKC* and *CASP3* genes are also associated with CAL in Taiwan.[31]

2.4 Advancement of Pathophysiological and Clinical Research by Genetic Findings

Unfortunately, information about susceptibility genes has not helped researchers to elucidate substances or microbes triggering the onset of KD. Analyses of the phenotypes of *Itpkc* knockout mice revealed that bone marrow macrophages of these animals express Nlrp3 and secrete interleukin (IL)-1β more than those from wildtype animals, indicating involvement of innate immunity activation in the disease pathogenesis and the possibility of targeting IL-1β for treatment of KD.[32] The association between variants of *ITPKC* and *CASP3* and more severe clinical course highlighted the Ca^{2+}/NFAT pathway in which both gene products play significant roles, as well as cyclosporine, an immunosuppressant that specifically inhibits signal transduction. To date, aiming to affirm safety and tolerability, a clinical study of cyclosporine when orally administered as third-line treatment for refractory cases of KD[33] and an investigator-initiated clinical trial comparing the standard IVIG regimen with that of IVIG plus cyclosporine as the initial therapy for the patients who were expected to become resistant to IVIG by risk scoring system[34,35] have been carried out.

Evidence Required in the Future

The clinical manifestation of KD varies from fulminant cases represented by those with Kawasaki shock syndrome to atypical or incomplete cases that are sometimes difficult to diagnose. The mechanism of the broad range of symptoms and clinical course, which potentially reflects the heterogeneity of the pathogenesis as well as of the pathophysiology, is poorly understood. To elucidate the genetic factors relevant to such heterogeneity, which is expected to provide important clues, a collaborative study in Japan (the Japan Kawasaki Disease Genome Consortium) has been collecting patients' DNA samples and their clinical information. Optimization of the treatment of patients who are expected to be unresponsive to the standard IVIG treatment is the most urgent issue in the clinical practice of KD and future carefully designed pharmacogenomics studies with participants of clinical trials are warranted.

3. Severity Assessment of KD

- The severity assessment in the acute phase includes initial assessment of severity of symptoms and then coronary sequelae 1 month after onset. Assessment related to the prognosis of coronary arteries is the most important from a long-term perspective (Class IIa, Level B).
- The scoring system in the acute phase is widely used in Japan and relied on to predict the possibility of treatment resistance and results that affect the coronary prognosis associated with the severity of symptoms (Class I, Level B).
- For coronary artery sequelae, severity assessment evaluated by Z-score is the standard method, and +2.5 or higher is defined as a long-term significant CAL (sequelae) (Class IIa, Level B).
- The conventional measurement value evaluation is limited to the evaluation under 5 years of age, and there is no standard for evaluation with the actual measurement value over 5 years of age, but the definition of a giant aneurysm (gAN) is ≥8 mm inside diameter (Class IIa, Level C).
- Among moderate aneurysms, it is reported that the development of stenotic lesions and acute coronary syndromes (ACSs) in young patients because of coronary aneurysms are possible when the inner diameter is ≥6 mm. This is important in the long-term management of patients with lesions ≥6 mm (Class IIb, Level B).

3.1 Severity Assessment (Acute Phase)

In the acute phase of KD, various clinical findings and abnormalities of laboratory examinations appear. Though there is a report that cases that fulfil 6 principle signs are more frequently resistant to IVIG treatment than those that fulfil 5 of 6 principle signs,[64] pediatricians do not always consider that the number of principle signs and severity of the disease are correlated.

There are few cases of severe heart failure, unconsciousness, or multi-organ failure that is life-threatening, or cases of "Kawasaki shock syndrome".[65] However, the presence and severity of CAL are the most important factors for evaluating severity in each case.

For predicting the possibility of CAL and judging the examinations and treatment, a couple of scoring system have been studied. To determine the indication of coronary angiography (CAG), Asai and Kusakawa's score[66] was devised in the 1970 s when the accuracy and prevalence of echocardiography was low. In the 1980s, along with the advancement of CAL evaluation by echocardiography, Nakano's score[67] and Iwasa's score[68] were devised. Those scores predict the coronary artery prognosis based on the patient's background such as age and sex and the results of early blood tests. To judge the therapeutic indication of IVIG, which are produced from blood, Harada[69] studied characteristics of cases with CAL and devised a scoring system as part of the work of the Research Committee in the Ministry of Welfare. All these score systems have been used for predicting coronary prognosis, and also for evaluating the severity of KD.

IVIG treatment is well-recognized for its efficacy and safety, and it has been performed in almost 90% of patients, but the problem of refractory cases has been discussed for a long time, and predicting it has been an important issue.

Table 4. Scoring Systems to Predict Nonresponse to IVIG

	Threshold	Points
Kobayashi score (≥5 points; sensitivity 76%, specificity 80%)		
Na	≤133 mmol/L	2
AST	≥100 IU/L	2
Day of starting treatment (or diagnosis)	Day 4 of illness or earlier	2
Neutrophils	≥80%	2
CRP	≥10 mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤12 months	1
Egami score (≥3 points; sensitivity 76%, specificity 80%)		
ALT	≥80 IU/L	2
Day of starting treatment (or diagnosis)	Day 4 of illness or earlier	1
CRP	≥8 mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤6 months	1
Sano score (≥2 points; sensitivity 77%, specificity 86%)		
AST	≥200 IU/L	1
Total bilirubin	≥0.9 mg/dL	1
CRP	≥7 mg/dL	1

AST, aspartate aminotransferase; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; Na, sodium. (Source: Prepared based on Kobayashi T, et al. 2016,[70] Kobayashi T, et al. 2012,[71] Egami K, et al. 2006,[72] Ogawa S, et al. 2012,[73] Sano T, et al. 2007,[74] Okada K, et al. 2009[75])

To this end, various IVIG resistance (refractory) prediction scores, such as the Kobayashi (Gunma) score,[70,71] the Egami (Kurume) score,[72,73] and the Sano (Osaka) score,[74,75] were devised (**Table 4**). Intensive treatment such as steroid combination, including pulse therapy as initial treatment or additional treatment, is usually indicated when a case is assumed to be at high risk of IVIG resistance (refractory). These scoring systems are disseminated and are thought to contribute to the continuous reduction of CAL occurrence.[76] IVIG resistance is a characteristic of severe cases and is also related to the prognosis of the coronary artery. It is a major advance that prediction has become possible.

However, there are reports in other countries that these predicted scores have been judged as unsuitable for practical use.[77] It is thought that differences in the timing of medical treatment, the facilities, and the testing methods affect the efficacy, but the scoring systems appear to be suitable in the current situation at least in Japan.[78]

3.2 Severity Assessment of CAL (Acute Phase)

In the mid-1970 s, when attention was paid to the presence of CAL in KD, evaluation of coronary artery diameter by echocardiography had low accuracy. Severity assessment by tomographic echocardiography two-dimensional echocardiography (2DE) was summarized with reference to the definitive diagnosis by CAG.

From that time, the report in 1983 from the Ministry of Health and Welfare group meeting (Kamiya group)[79] has become the only standard in Japan for the evaluation with actual measurement values, and has been quoted for a long time. However, as the accumulation of normal measured values was insufficient, in this guideline evaluation with the Z-score is strongly recommended.

Table 5. Classification of Coronary Artery Lesion (CAL) in Kawasaki Disease

(a) Definition of CAL in the acute phase (<30 days from onset)	Usually, coronary artery inner diameter should be evaluated using the Z-score measured by echocardiography; • Small aneurysm (sAN) +2.5 ≤ Z-score <+5 • Medium aneurysm (mAN) +5.0 ≤ Z-score <+10.0 • Giant aneurysm (gAN) +10.0 ≤ Z-score Notes (1) If it is difficult to evaluate by Z-score, evaluating by absolute value of inner diameter may be used in patients under 5 years old • sAN: 3 mm ≤ Inner diameter < 4 mm • mAN: 4 mm ≤ Inner diameter < 8 mm • gAN: 8 mm ≤ inner diameter Evaluation by Z-score is strongly recommended for age 5 years and older. (It is overestimated if defined by absolute value.) • The absolute value of a gAn is defined as an inner diameter ≥8 mm even at age 5 or older. (2) Even if the definition of an aneurysm is satisfied during the course, if it does not fulfil the definition of an aneurysm at the onset of 1 month, it will be defined as 'transient dilation'
(b) Severity classification of CAL after 1 month from onset	Severity classification based on changes in CAL after 1 month from the onset according to findings obtained by echocardiography and selective coronary angiography I. No dilation change: no change in the dilation of coronary arteries including the acute phase II. Transient dilation (in the acute phase): mild transient dilation that normalizes by 1 month after onset III. Regression: complicated with CAL beyond 1 month from onset, and bilateral coronary artery findings completely normalize during follow-up, and did not fall into group V IV. Remaining coronary aneurysms: coronary aneurysms on one or both sides on coronary angiography but do not fall into group V V. Coronary artery stenotic lesion: coronary angiography shows a stenotic lesion in the coronary artery. (i) Without ischemic findings in various tests (ii) With ischemic findings in various tests
Notes	(1) The definitions of coronary aneurysm size after the first month of onset are treated according to (a). (2) In the AHA statement, Z-score ≤ +2.0 and < +2.5, which is classified as 'dilation only', was not taken into account in this table because no treatment or management will be necessary in the long-term course (3) For patients with moderate or higher valvular disorders, heart failure, arrhythmia, etc. will be added to each severity classification

Concerning the absolute measurement value, the Kamiya group described that "dilated lesion (DL) is defined as a change when the coronary artery diameter is 3 mm or larger in 5 years old or younger patient by echocardiogram". However, this criterion is inadequate by Z-score evaluation of the diameter with the mean body size of 5-year-old children. If the absolute measurement value is used, the definition of DL is more adequate as diameter ≥3 mm in patient younger than 5 years old (not including 5-year-olds). Another description that "DL is also diagnosed when that lesion shows enlargement ≥1.5-fold of the surrounding coronary arteries by coronary angiogram" has been deleted from this guideline because it has not been evaluated recently. Nor is perivascular wall brightness[80] or loss of tapering of the coronary artery inner diameter contributing to the diagnosis.[81,82]
(Refer to section 4: Diagnosis and Treatment of Incomplete KD)

3.2.1 Classification of CAL

The Kamiya report classified CAL by the findings of CAG. CAL that is 4-fold larger than the diameter of the surrounding coronary artery is called a giant or large aneurysm (gAN), CAL that 1.5-fold larger than and 4-fold smaller than is called a medium aneurysm (mAN), CAL that is ≤1.5-fold less is called a small aneurysm or dilatation (sAN or Dil), and CAL that is extremely small but with enlargement of the coronary artery bifurcation may be expressed as coronary web (web). The echocardiographic classification of gAN, mAN, and sAN (or Dil) modeled on the angiographic grade.

From the late 1990 s, studies have been conducted in the USA and Japan to determine the normal value of coronary artery inner diameter in children by echocardiography.[83–85] In Japan, the Z-score project was completed with high reliability based on sufficient number of samples and research methods.[3] Recently it becomes widely available via the homepage of the Japanese Society of Kawasaki Disease[86] or as a calculator application for smartphones or tablets.[87] In this revision of the guideline, the severity of CAL, the conventional criteria of which have been debated because precise criteria have been unclear until now, will be categorized clearly by Z-score. And it is expected that more exact comparison of treatment outcome or prognosis will be possible (**Table 5**). It is also expected that outcomes can be compared more precisely with those in other countries through the method of creating the Z-score.

Attention is drawn to the American Heart Association (AHA) statement in 2017, which defines a case of Z-score ≥+2.0 or more and < +2.5 as 'dilation only'.[2] In the Japanese situation, most of those cases are called 'transient dilation', and if it persists, long-term observation is not necessary because it does not have significant problems (**Table 5**).

Although KD is treated in most hospitals in Japan, not all facilities currently use the Z-score in daily practice. Therefore, in this guideline coronary artery assessment is basically performed by Z-score as the "Severity classification of CAL 2020", but the absolute measurement value that is generally compatible with the Z-score is described (**Table 5**).

3.3 Severity Assessment of CAL (Long-Term Changes)

From the viewpoint of long-term management, it is necessary to assess the severity of CAL with the temporal changes of CAL. On this point, the definition of CAL after 1 month from onset in **Table 5** has the following 5 categories: I. No dilation group; II. Transient dilation group in the acute phase; III. Regression group; IV. Remaining coronary

aneurysm group; V. Coronary stenosis lesion group. Group V is subdivided by whether CAL is complicated by ischemia or not.

In addition, valvular disorders, heart failure, and arrhythmias that are rarely seen as cardiac complications are factors that increase severity and should be paid attention.

There are several studies on the relationship between the diameter of CAL and clinical significance. It has been considered that gANs with an inner diameter ≥8 mm have a high prevalence of thrombotic occlusion and are likely to cause MI. In recent years, there has been discussion about the possibility of predicting whether mANs will regress or develop ischemia based on the severity detected in the acute phase. Tsuda et al[4,88] classified CAL by inner diameter of 4–6 mm (small), 6–8 mm (medium), and ≥8 mm (giant), and followed 60–120 cases in each group for 15 years. The 4–6 mm (small) group did not develop stenotic lesions, the 58% of the medium group developed stenosis up to 15 years, and a small aneurysm in older children did not show any cardiac events in 30 years.[89]

Furthermore, an 11-year follow-up by computed tomography (CT) of 37 coronary aneurysms in 18 patients in Taiwan indicated that the cutoff value that could most accurately predict the regression of coronary aneurysms was an inner diameter of 5.6 mm.[90] Therefore, the experts support the indication of anticoagulation not only for gANs but also for mANs with an inner diameter ≥6 mm.

4. Diagnosis and Treatment of Incomplete KD

- Because the redness of the Bacille Calmette-Guèrin (BCG) inoculation can be regarded as a principal sign according to the revision of the Japanese diagnostic guidelines in 2019 (6th edition), it is expected that some cases diagnosed as incomplete KD (iKD) according to the 5th edition will be newly diagnosed as complete cases.
- In the 6th revised edition of Japanese diagnostic guidelines, cases showing 4 principal signs without coronary artery complication and cases showing 3 principal signs with coronary artery complications are defined as iKD.
- As the reference items are categorized by the significance of the diagnosis, it is expected to contribute to the diagnosis of iKD when the principle signs are not fulfilled.

4.1 Japanese Diagnostic Guidelines of KD (6th Revised Edition) (Table 6)

The diagnostic guidelines were revised in May 2019.[91] The principal clinical features are as follows.

1. Fever
2. Bilateral bulbar conjunctival injection
3. Changes in the lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
4. Rash (including redness at the site of BCG inoculation)
5. Changes in the peripheral extremities: (Initial stage) reddening of palms and soles, edema; (Convalescent stage) periungual desquamation
6. Nonsuppurative cervical lymphadenopathy

Changes from the 5th revision include that the count of febrile days is not essential, and that redness of the BCG inoculation site is particularly characteristic of KD, so the skin finding previously expressed as "polymorphous exanthema" is revised as "Rash (including redness at the site of BCG inoculation)". As for the criteria for the diagnosis, if 5 of the 6 principal clinical features are recognized then KD is diagnosed only by symptoms (counted as "complete A" in the nationwide survey). If no more than 4 of the 6 principal clinical features are recognized, KD is diagnosed when a CAL found on echocardiogram (counted as "complete B" in the national survey).[92]

However, even if the main symptoms are 4 or less, the risk of complications should be considered when CAL have already started and the signs are improved by diagnosis of iKD and treatment for KD. The 5th revised edition was unclear about the diagnosis in cases with fewer signs. In the 6th revised edition, diagnosis is more clearly based on the number of principal signs and the presence of CAL, if the number of principal signs is less than 4.

This clarifies the strategy of diagnosing and treating iKD without hesitation. At the same time, we recommended that differential diagnoses are sufficiently considered, referring to the disease list that may be associated with coronary artery enlargement and diseases similar in signs to KD. Furthermore, even if the principal signs are less than 2 and the coronary artery is beginning to enlarge, it is not prohibited to start KD treatment until the 7th day from the onset at the latest, although we should be very cautious about the differential diagnosis.

The definition of CAL is described as Z-score is ≥ +2.5, and it is recommended to give priority to using this definition. However, definition by the measurement value of ≥3.0 mm in patients younger than 5 years old, and that of ≥4.0 mm in patients older than 5years old is still used in a considerable number of the hospitals.

On the other hand, "perivascular brightness" and "lack of peripheral tapering" are not supported as distinctly abnormal findings of CAL in KD, based on recent reports[81,93] that state a universally precise method is unclear in every echocardiography machine and it is not objective. Therefore, those findings are not significant for the definition of CAL.

Regarding "Other significant demographic, clinical, echocardiographic, and laboratory features", various supportive symptoms or laboratory data for the diagnosis of KD have been included. The 6th revised edition arranges them into 4 categories, 35 years after the previous description in the 4th revised edition of 1984.

In the first group, particularly specific items are collected (**Table 6**). When the number of principal signs is not fulfilled for diagnosing complete KD, the presence of these items suggests a high possibility of KD. However, neither the critical cutoff line nor the required number of items has been clarified, and those issues will need to be studied in the future.

In the second group, if there are signs that suggest a life-threatening case, it is recommended to consult an experienced hospital where pediatric intensive care is possible.

In the third group, there are risk factors that relate to nonresponsiveness to IVIG treatment.

In the fourth group, other nonspecific, but possible findings in KD are summarized.

4.2 Epidemiology and Characteristics of Incomplete KD

The recent 24th Nationwide Surveillance[6] revealed that among a total of 31,595 patients, the proportion of the

Table 6. Diagnostic Guidelines for Kawasaki Disease (6th Revised Edition): The Japanese Society of Kawasaki Disease and the Japan Kawasaki Disease Research Center, Research on Rare and Intractable Diseases, The Ministry of Health, Labour and Welfare

Kawasaki disease (KD) is a disease of unknown etiology, most frequently affecting infants and young children under 5 years of age. The clinical features can be classified into 2 categories: principal features and other significant demographic, clinical, echocardiographic, and laboratory features.

Principal clinical features

1. Fever
2. Bilateral bulbar conjunctival injection
3. Changes to the lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
4. Rash (including redness at the site of Bacille Calmette-Guèrin (BCG) inoculation)
5. Changes in the peripheral extremities:
   (Initial stage) reddening of palms and soles, edema
   (Convalescent stage) periungual desquamation
6. Nonsuppurative cervical lymphadenopathy

Definitions of complete and incomplete Kawasaki disease

- Complete KD is defined as the presence of at least 5 of 6 clinical features
- Complete KD is also defined as the presence of 4 clinical features, the exclusion of other febrile illnesses, and coronary artery dilation (Z-score of internal coronary artery diameter ≥2.5 SD units or absolute diameter ≥3 mm (<5 years old) or ≥4 mm (≥5 years old)
- Incomplete KD is defined as the presence of 3 of 6 clinical features with coronary artery dilation and the exclusion of other febrile illnesses
- Incomplete KD is also defined as the presence of 3 or 4 principle clinical features without coronary artery dilation but with features from the list of "Other significant clinical features"
- Incomplete KD may be considered in the presence of ≤2 principle clinical features after excluding other diagnoses

Other significant demographic, clinical, echocardiographic, and laboratory features

I. KD may be suspected in the presence of fewer than 4 principle clinical features when the following findings are observed.
   (1) Elevation of hepatic transaminases early in the course the disease
   (2) Increased leukocytes in urine sediment of an infant
   (3) Thrombocytosis in the convalescent phase
   (4) Elevation of brain natriuretic peptide (BNP) or NT-proBNP
   (5) Mitral valve regurgitation or pericardial effusion on echocardiography
   (6) Enlargement of the gallbladder (hydrops of gallbladder)
   (7) Hypoalbuminemia or hyponatremia

II. If a KD patient manifests the following findings, the patient should be considered for admission to a critical care unit.
   (1) Hemodynamically significant myocarditis
   (2) Hypotension (shock)
   (3) Paralytic ileus
   (4) Decreased level of consciousness

III. Risk scores to predict intravenous immunoglobulin (IVIG) nonresponsiveness may be applied to guide patient management. The following features are elements of the risk scores for predicting IVIG resistance.
   (1) Leukocytosis with left shift
   (2) Thrombocytopenia
   (3) Hypoalbuminemia
   (4) Hyponatremia
   (5) Hyperbilirubinemia (jaundice)
   (6) Elevation of C-reactive protein
   (7) Age <1 year

IV. Other nonspecific findings that may be observed in KD and should not exclude the diagnosis.
   (1) Irritability
   (2) Cardiovascular: abnormal extra heart sounds, ECG changes, aneurysm of peripheral arteries other than coronary (axillary etc.)
   (3) Gastrointestinal: abdominal pain, vomiting, diarrhea
   (4) Hematologic: increased erythrocyte sedimentation rate, anemia
   (5) Dermatologic: micropustular rash, transverse grooves across the finger nails
   (6) Respiratory: cough, rhinorrhea, retropharyngeal edema, infiltrate on chest X-ray
   (7) Rheumatologic: pain, swelling
   (8) Neurologic: cerebrospinal fluid pleocytosis, seizures, facial nerve palsy, paralysis of the extremities

Notes

(1) Mortality in the acute phase: <0.1%.
(2) Recurrence rate: 3–4%; proportion of siblings' cases, 1–2%.
(3) Nonsuppurative cervical lymphadenopathy (multiple hypoechoic, enlarged nodes observed on ultrasound) is less frequently encountered (approximately 65%) compared with other principal clinical features during the acute phase. Nonsuppurative cervical lymphadenopathy is observed in approximately 90% of older children and often can be the first clinical feature of KD with fever.

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(Adapted from Kobayashi T, Ayusawa M, Suzuki H, et al.[91])

cases diagnosed as complete A, complete B, and iKD was 77.8%, 1.6%, 20.6%, respectively. There was no significant sex difference in all proportions. As shown in **Figure 1**, the proportion of iKD is gradually increasing. As for the onset age of iKD, the proportion of children who are ≤2 years old and children who are ≥6 years is greater. The proportion of cases in which the number of principal signs was 4, 3, 2, 1 or unknown, was 70.5%, 23.3%, 5.4%, 0.7% and 0.2%, respectively.

Several characteristics of the principal signs are known empirically. BCG redness in an infant, or nonpurulent cervical lymphadenopathy in older children and showing multicystic formation of lymph nodes on ultrasonography is particularly characteristic for the diagnosis of iKD. The

findings in the first group of "Other significant demographic, clinical, echocardiographic, and laboratory features" are also important for the diagnosis of iKD.

Careful attention must be paid to the fact that iKD is not a milder case of KD. CAL in iKD cases is never fewer than in the complete KD cases.[94–96] Sudo et al reported that cases of non-responsive to IVIG are fewer among iKD cases than complete KD; however, the initial treatment in iKD was later and the incidence of the CAL complication was higher than those in complete KD.[94] A recent meta-analysis[97] stated that iKD has a higher risk of complicating CAL than complete KD cases with the odds ratio of 1.45, and the 95% CI of 1.16 to 1.81.

Earlier start of IVIG is necessary when the principal signs are less than 4, or even when there are 3 if other diseases are ruled out sufficiently, and the patient is required to be afebrile before the 10th day of illness. In the case of expected unresponsiveness to standard IVIG treatment, enhanced therapy with IVIG is recommended to start until the 7th day of illness.

II. Pathology of Cardiovascular Sequelae and Coronary Hemodynamics: Long-Term Prognosis

1. Histopathology of Coronary Artery Lesions (CAL)

1.1 Acute-Phase CAL

- More than 50 years have passed since the discovery of Kawasaki disease (KD), and it is estimated that the number of cases of adults with cardiac sequelae will reach 10,000–20,000.
- KD coronary arteritis becomes pan-vasculitis around the 10th day of onset, forms DLs around the 12th day of disease, and inflammation subsides around the 40th day.
- Coronary artery abnormalities in the early stage of KD are DLs. Coronary artery sequelae are defined at 30 days after onset, based on coronary diagnostic imaging. Dilated CAL tend to shrink after the acute phase.
- Histopathologically, the lumen of the dilated lesion (DL) is reduced because of circumferential thickening of the smooth muscle cells that have migrated to the intima and proliferated, and active remodeling occurs even in the remote phase.
- There is still no evidence on the long-term prognosis in patients with a history of KD without aneurysm formation.

Coronary arteritis in KD begins as cellular infiltration of the tunica intima and tunica adventitia 6–8 days after the onset of disease. On about day 10 of disease, neutrophil, lymphocyte and macrophage infiltration into the arterial wall from the luminal and adventitial sides begins, leading immediately to inflammation of all layers of the artery. The inflammation spreads around the artery, and the internal elastic lamina, smooth muscle cells of the media and other structural components of the artery become severely damaged; the artery then begins to dilate. When the damage is severe, aneurysms develop approximately 12 days after onset of KD. The inflammatory cell infiltration persists until about the 25th day of disease, after which the inflammatory cells gradually decrease in number and are almost completely gone by about the 40th day of the disease.[98,99] These findings show that treatment to prevent development of CAL should be completed by the 10th day after the onset of KD.

1.2 Remote-Phase CAL

CAL in the remote phase can be divided into 2 histological types: severe dilation (i.e., aneurysm) and mild dilation that can be thought of as transient dilation or regression of a small to medium-sized aneurysm.

1.2.1 Coronary Artery With Residual Aneurysm

When a medium or large-sized aneurysm forms, it is common for the wall of the aneurysm to show laminar calcification, and an organized thrombus can form on the inside. Moreover, in most cases the lumen is plugged with a fresh thrombus, which is related to the cause of death. In addition, the portions of the artery proximal and distal to the coronary aneurysm have centripetal intimal thickening, and in some cases it can be surmised that death occurred because of luminal stenosis caused by that intimal thickening.[100,101]

On the other hand, sometimes lesions are seen that can be interpreted as recanalized vessels resulting from partial thrombolysis and restoration of blood flow after thrombotic occlusion. There can be multiple channels of recanalization within an aneurysm, and migrated smooth muscle cells surround the blood vessels. These recanalized vessels can have a structure that closely resembles a normal artery.[102]

1.2.2 Coronary Artery With No Residual Aneurysm

So far, none of the patients without aneurysms has had severe cardiac sequelae of KD that were directly related to the cause of death. However, in most of the patients the coronary arteries show a mild tendency to dilation, full circumferential thickening of the intima, etc. It is thought that these changes correspond to those of arteries that dilated during the acute inflammatory stage and then underwent regression during the convalescent stage.[103] Accordingly, in most patients with no residual aneurysm in the remote phase, it can be readily surmised that coronary arteritis had been present in the past.[104] Conversely, it should also be emphasized that this group includes patients in whom any changes that can be presumed to be scars from arteritis cannot be demonstrated.

2. Coronary Hemodynamics in Patients With Coronary Sequelae

- A characteristic of the CAL in KD is that it is a multivessel disease that presents complex hemodynamics with a mixture of expanding lesions and stenotic lesions. The failure of endothelial function in the aneurysm, as well as regressed vessels, is continuing.

2.1 Coronary Circulation in Coronary Sequelae

CAL in KD is a multivessel disease with complex hemody-

Advance Publication

namics caused by the mixture of enlarged lesions and stenotic lesions. In addition, vascular endothelial dysfunction in both CAL and regressed lesions is continuing.

2.2 Hemodynamics in Coronary Aneurysms

Blood flow in a normal coronary artery is laminar. In a small aneurysm the blood flow waveform pattern is pulsatile laminar flow in all cases, and the average peak velocity (APV), coronary flow reserve (CFR), and shear stress on the coronary artery wall are within the normal range. In the middle-sized coronary aneurysm, the blood flow waveform changes from pulsatile to turbulent mainly because of the increase in the inner diameter of the aneurysm, and the APV, CFR, and shear stress show some abnormal values. Furthermore, all cases of giant coronary aneurysms have a turbulent flow pattern, with ≤APV of 10 cm/s, CFR of ≤1.5, and shear stress of ≤10 dyne/cm^2.[105] Coronary aneurysms are reported to cause energy loss because of the turbulent flow in the aneurysm and behave similarly to stenotic lesions[106] In addition to the tendency of stenosis in flow and out flow of coronary aneurysm,[107] it can be said that the aneurysm itself promotes stenosis hemodynamically. Furthermore, the decrease in blood flow velocity in the aneurysm and increase in vascular diameter because of the aneurysm lead to a significant decrease in shear stress, which, coupled with endothelial cell damage caused by the hemodynamic abnormalities in addition to endothelial cell damage associated with vasculitis, induces significant vascular endothelial cell dysfunction in the aneurysm.[108,109] Dysfunction of the vascular endothelial cells enhances vasoconstriction and attenuates antithrombotic, anti-inflammatory, antifibrotic, antioxidant and anti-arteriosclerotic effects. Thrombus formation is the biggest problem in giant coronary aneurysms developing after KD, and thrombus formation occurs easily because of enhanced platelet aggregation and coagulation, and suppression of the fibrinolytic system.[105] Therefore, an important treatment goal in the remote phase of KD is prevention of thrombus formation.

2.3 Evaluation of Stenotic Lesions

2.3.1 Fractional Flow Reserve (FFR)

FFR is a method of evaluating the pressure difference between the distal and the proximal parts of a stenotic lesion when maximal hyperemia occurs because of papaverine hydrochloride or adenosine triphosphate disodium (ATP). Myocardial ischemia is considered to exist when the pressure difference (pressure ratio), the FFR, is less than 0.75. In adults, FFR 0.75–0.80 is regarded as borderline including myocardial ischemia, and is considered as significant stenosis.[110–113] Therapeutic intervention is adopted when FFR is <0.80.[9] In children, less than 0.75 has been reported as an abnormal value.[114]

2.3.2 CFR

There are 2 methods of measuring coronary blood flow. One is measured by Doppler wire during cardiac catheterization as an invasive method,[114,115] and the other is by positron emission tomography (PET), a relatively noninvasive method, using ^{13}N-ammonia, ^{82}Rb (rubidium) or ^{15}O-water as a flow tracer.[116,117] The rate of increase in blood flow in the coronary artery when maximally hyperemic with papaverine hydrochloride, ATP, etc. is the CFR. In adults, it is not only an indicator of coronary artery stenotic lesions and peripheral vascular resistance,[114–117] but also correlates with prognosis.[118] The standard value for children with CFR is reported to be 2.0 or higher, which is equivalent to adults.[10]

If coronary blood flow is quantified, coronary artery peripheral vascular resistance is calculated from blood pressure. According to reports using PET, peripheral blood vessel resistance in the coronary arteries of patients with KD in the remote phase is higher than that of normal subjects, including not only blood vessels with aneurysm, but also blood vessels with aneurysm regression and blood vessels that appear to be normal.[109,119,120] This is important in discussing the hemodynamics of KD.

Both FFR and CFR are useful for the evaluation of coronary stenotic lesions, but there are sometimes discrepancies in the evaluation of multivessel disease. This is explained by the fact that CFR reflects the pathology of not only the epicardial artery but also peripheral blood vessels, whereas FFR is a method purely for evaluating epicardial artery stenosis.[121] In addition, if the coronary artery peripheral vascular resistance is increased in remote-phase KD, as described above, attention should be paid because FFR may be evaluated higher than the actual stenosis.

Judgment on treatment intervention for KD coronary artery disease that has become a multivessel disease, requires not only morphological evaluation but also multilateral evaluation including evaluation by FFR and CFR.

Evidence Required in the Future

- Evaluation of coronary circulation by FFR and CFR in the remote phase of KD.

3. Long-Term Prognosis

- There are no reports of high risk of long-term coronary event in patients who have no coronary sequelae, including transient dilatation.
- The larger the coronary aneurysm, the less likely it is to regress and the higher the risk of cardiac events in the remote phase (Class I, Level B).
- Remodeling of coronary aneurysms continues for a long time (Class I, Level C).
- Even if the coronary aneurysm regresses, the vascular structure does not normalize, vascular endothelial dysfunction and remodeling continue, and stenosis, occlusion, and sometimes re-expansion may occur (Class I, Level B).

The CAL in KD begin with DLs. Normal vascular tissue is destroyed by pan-vasculitis in the coronary artery, and the coronary artery, which has become fragile, is expanded by its internal pressure. Coronary artery dilatation begins around the 11th day of the disease. Rupture of coronary aneurysms occurs within the first month of onset,[122,123] and rarely occurs thereafter.[124] A case in which coronary artery dilatation continues for more than 1 month after the onset of KD is defined as coronary sequelae of KD. The dilated coronary artery leads to intimal proliferation,[123] and the dilated coronary artery lumen narrows (negative remodeling). About half of the cases of sequelae of coronary arteries are said to regress within 1 year,[125] but the larger the aneurysm, the less likely it will regress, and giant aneurysms (gANs) will hardly regress.[122,126,127] If the aneurysm remains, the

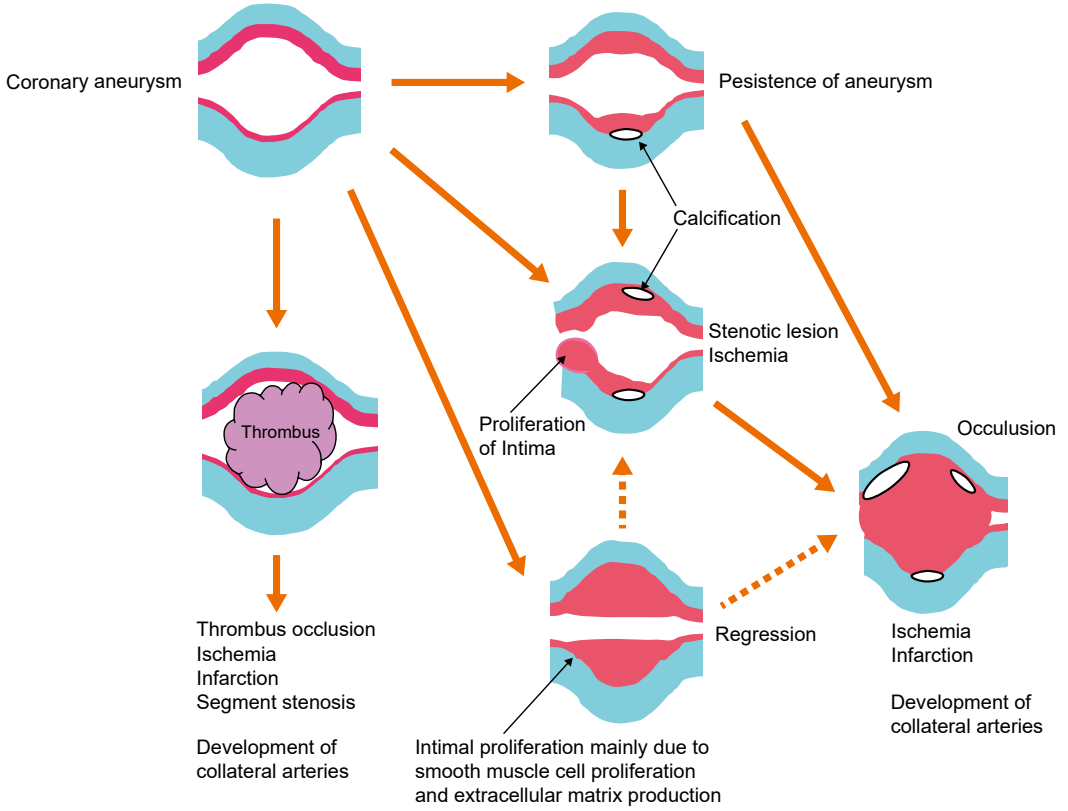

Figure 3. Long-term prognosis of coronary aneurysm.

risk of thrombus formation increases in the aneurysm because of blood flow turbulence, in addition to vascular endothelial dysfunction. Coronary artery thrombotic occlusion and associated acute myocardial infarction (AMI) occur frequently within 2 years of KD onset. On the other hand, coronary artery occlusion and stenosis are also caused by excessive intimal proliferation. Medial vascular smooth muscle cells migrate to the intima in large numbers beyond the inner elastic plate destroyed by the vasculitis, and when transformed, proliferate and produce a large amount of extracellular matrix, resulting in intimal proliferation. Transformed vascular smooth muscle cells actively express growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor β (TGFβ), basic fibroblast growth factor (bFGF), and platelet derived growth factor-A (PDGF-A), even in the remote phase, and induce angiogenesis in the thickened intima, furthering vascular remodeling over a longer period[107,128] (**Figure 3**). Coronary artery stenosis is known to occur particularly at the inflow and outflow of coronary aneurysms,[107,129] and the site has low hemodynamic shear stress. According to Tsuda et al,[4] in 15 years of follow-up an aneurysm less than 6 mm in diameter did not cause a stenosis, compared with 58% for moderate aneurysms from 6 to 8 mm and 74% of gANs greater than 8 mm. In addition, abnormalities in vascular endothelial function continue even in blood vessels that have regressed and appear to be normal on coronary angiography (CAG),[130] and active vascular remodeling continues, sometimes with stenosis or occlusion in the regressed vessels[8] and acute coronary syndrome (ACS).[131] Rarely, reduced coronary aneurysms may re-expand (positive remodeling)[132] In KD, even if myocardial ischemia is caused by coronary artery stenosis/occlusion, it is often clinically asymptomatic,[133] and in such cases, collateral vessels develop into the ischemic region.[107] However, because myocardial ischemia can be a risk of sudden death, it is desirable to detect it early and perform reperfusion therapy if possible. Especially for gANs, Suda et al[126] report that the prognosis for life is 88% at 30 years after onset, but the onset of cardiac events is 59% at 25 years of onset, which means more careful observation is required.

Furthermore, KD coronary artery disease is characterized by highly calcified coronary artery walls. In aneurysms larger than 6 mm in the early stage of disease, the appearance of distant calcification is inevitable.[134] Arterial wall calcification is thought to be induced by osteoblasts derived from the medial smooth muscle cells,[135] but it is not yet clear why excessive calcification occurs in KD.

3.1 Cases Without Coronary Sequelae

Recently, about 98% of children with KD,[136] and 80–85% of the children in generations where intravenous immunoglobulin (IVIG) therapy was not common, were judged to have no coronary artery sequelae. This guideline allows termination of follow-up of patients without coronary artery sequelae after 5 years from onset. However, it has not yet been concluded whether or not patients who are

determined to have no coronary sequelae in the acute phase are at high risk of suffering from coronary artery disease over the long term. Because there are no reports that coronary artery disease risk increases, it is considered that the long-term prognosis for KD cases in which CAL did not occur in the acute phase is the same as that of normal subjects.

Evidence Required in the Future

- Risk of suffering from future coronary artery disease in cases judged to have no coronary sequelae in the acute phase.
- Assessment of cardiac event risk not only by coronary aneurysm diameter but also by coronary aneurysm morphology.

III. Examinations and Diagnosis of Cardiovascular Sequelae

Blood biomarkers, electrocardiography, echocardiography, cardiac catheter coronary angiography (CAG), myocardial perfusion imaging, computed tomography angiography (CTA) and magnetic resonance imaging (MRI) are widely used for testing and diagnosing cardiovascular sequelae. Electrocardiography, echocardiography, and myocardial perfusion imaging are used for exercise and drug-loading tests, which are more clinically significant than tests performed only at rest. **Table 7** summarizes the frequency of each test according to disease severity.

First of all, there is no restriction on life or exercise in the follow-up of patients who have no remaining coronary artery abnormalities in the acute phase. The guideline for follow-up is 1 month, 2 months, 6 months, 1 year after onset, and 5 years after onset (in many facilities, patients have been followed up annually after 1 year). The school life management guidance table is "E allowed (see **Figure 5**)" in principle, and may be "no management required" if 5 years have passed since the onset. It is desirable to write the date of the end of follow-up on the "Kawasaki disease patient card" (**Figure 6**), or to create a new card and give it to the patient and guardian when giving advice on prevention of lifestyle-related diseases. For further follow-up, consult with the guardian (or the patient).

Patients with Kawasaki disease (KD) coronary aneurysms and subsequent stenotic lesions transit from children to adults. There are cases of ischemic heart disease (IHD) and sudden death, and collaboration with physicians, especially cardiologists, has become important.

Electrocardiography and echocardiography are resting examinations, and also the basis of daily medical care. An exercise load test is also used as appropriate. In patients with an actual coronary diameter measurement of ≤4 mm in the acute phase, intimal thickening is absent or minimal, and stenotic lesions are rare.[137] On the other hand, the risk of coronary artery stenosis is high in aneurysms with an acute-phase diameter of ≥6 mm (especially young children with a body surface area of <0.5 mm^2).[4,89,138] In recent years, it has become common to evaluate coronary artery lesion (CAL) using the coronary artery Z-score obtained by correcting the coronary artery diameter with the body surface area based on the standard value. Recent studies[139,140] based on the Z-score showed the regression rate, coronary event rate, and major cardiac events for giant aneurysms (gANs) of ≥10 mm or measured values of ≥8 mm were poor, compared with small aneurysms with Z-score <5.

In addition to CAG, fractional flow reserve (FFR), intravascular ultrasound (IVUS) and optical coherence tomography (OCT), can be used. Especially in older children, the use of myocardial perfusion imaging, CTA, MRI/magnetic resonance angiography (MRA), etc. has become widespread. If there is no need for treatment, the indication of cardiac catheterization is limited.

Electrocardiography, myocardial perfusion imaging,

Table 7. Long-Term Assessment Algorithm

Severity classification			ECG, * echocardiogram	Assessment for inducible ischemia (stress test)	Coronary imaging modalities (CT, MRI, CAG)
I	No dilation		Assess at 1, 2, 6, 12 months, and 5 years (or yearly) until 5 years old	Not necessary	Not necessary
II	Transient dilation				
III	Regression	(Acute phase) small aneurysm	Yearly	Not necessary	Consider at convalescent phase, 1 year from onset, or when the aneurysm regresses Recommended on finishing high school
		(Acute phase) medium/giant aneurysm	Every 6–12 months	Consider every 3–5 years	Consider at convalescent phase, 1 year, then every 3–5 years
IV	Remaining coronary aneurysm	Small aneurysm	Yearly	Consider every 3–5 years	Consider at convalescent phase, 1 year, then every 3–5 years
		Medium aneurysm	Every 6–12 months	Consider every 2–5 years	Consider at convalescent phase, 1 year, then every 2–5 years
		Giant aneurysm	Every 6–12 months	Consider every 1–5 years	Consider at convalescent phase, 1 year, then every 1–5 years
V	Coronary artery stenotic lesion	(i) Without ischemia	Every 6–12 months	Consider yearly	Consider at convalescent phase, 1 year, then every 1–5 years
		(ii) With ischemia	Consider timely	Consider timely	Consider timely

*Exercised ECG is required when necessary. CAG, coronary angiography; CT, computed tomography; MRI, magnetic resonance imaging.

echocardiography, and MR myocardial imaging have exercise- and drug-loading tests, and the detection rate of myocardial ischemia is higher than at rest. These are useful for determining treatment policy, life intensity and exercise restriction.

Regarding safety, first, a guideline has been formulated for radiation exposure of children.[141] Because children are highly sensitive to radiation, cardiac catheterization, myocardial perfusion imaging, and coronary CTA, a study plan that takes into account the total radiation dose has been proposed. For coronary CTA, efforts are being made to reduce exposure dose while maintaining image quality. Second, efforts to reduce adverse events during sedation are necessary, especially when performing MRI on young children, and the need for an appropriate sedation protocol and respiratory circulation monitoring has been proposed.[142]

Evidence has accumulated of vascular stiffness as an assessment of adult cardiovascular event risk for people with KD. Meta-analysis has shown that patients with coronary artery abnormalities have reduced vascular stiffness, compared with controls.[143,144] On the other hand, certain conclusions have not been reached in affected individuals who have no remaining CAL.

1. Blood Examination, Biomarkers and Arteriosclerosis

1.1 Blood Examination

1.1.1 Myocardial Ischemia, Myocardial Infarction (MI)

- Evidence for blood examination and a biomarker, both of myocardial ischemia and MI, in KD patients with long-term follow-up is not established.

a. Markers of Myocardial Cytoplasm

i. Creatine Kinase (CK), Myocardial-Bound Creatine Kinase (CK-MB)

Conventionally, CK is the most common marker used for myocardium necrosis, and has been widely used for diagnosis of MI and prognostic prediction.[145] CK-MB has specificity for the myocardium, and the significance of the evaluation of the myocardium injury is high if the ratio of CK-MB to total CK is considered. In ST-segment elevation MI (STEMI), CK-MB levels begin to rise 3–8 h after the onset, peak at 10–24 h, and returns to normal in 3–6 days. CK and CK-MB have low diagnostic sensitivity in comparison with cardiac troponin, and a stronger tissue disorder is necessary for positive conversion of CK-MB. In the JCS Guideline on Diagnosis and Treatment of Acute Coronary Syndrome, measurement of CK-MB is not recommended for a diagnosis of ACS under conditions of being able to measure cardiac troponin.[146]

ii. Myoglobin

Myoglobin is highly sensitive, and myoglobin levels begin to rise 1–2 h after the onset of MI, peaks at about 10 h, and returns to normal in 24–48 h. It is useful for early diagnosis of MI, and in the service for emergency visit, and also for detection of reperfusion. On the other hand, it has low specificity for the myocardium, so cannot be an independent marker.

iii. Heart-Type Fatty Acid Binding Protein (H-FABP)

H-FABP is a small-molecule protein and abundant in the cytoplasm of cardiac muscle cells. There are fewer skeletal muscle cells than cardiac muscle cells with H-FABP, therefore H-FABP has to some extent a higher specificity for cardiac muscle than myoglobin. Because a negative predicted value is high when using the whole blood for quick qualitative measurement, it is used for early diagnosis and risk stratification of acute MI (AMI). FABP has low sensitivity of diagnosis of MI in the hyper-acute phase compared with high-sensitive troponin.

b. Structural Proteins as Markers of Myocardial Cellular Necrosis

i. Cardiac Troponin: Troponin T, Troponin I (TnT, TnI)

There is approximately 6% TnT in the soluble compartment of the cytoplasm. In STEMI, the evolution of TnT has 2 peaks: the 1st peak is observed 12–18 h after onset during the early phase of cardiac ischemia following the leaking of TnT from cytoplasm, and the 2nd peak occurs 90–120 h after onset following myofibrillar necrosis. These patterns differ from those of TnI, which has 1 peak. TnT is characterized by high sensitivity and specificity for the diagnosis of MI compared with CK, CK-MB, and is used as a first choice for biochemical examination. TnT is also useful for diagnosis of non-STEMI (NSTEMI) and prediction of prognosis[147,148] The ESC/ACC suggest that MI is diagnosed when cardiac troponin transiently increases or decreases beyond 99% of the value for normal subjects.[147] Measurement of high-sensitive cardiac troponin is characterized by high accuracy compared with measurement of conventional Tn, and it is useful to diagnose MI within 2 h after onset in the hyper-acute phase. In the JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome, measurement of cardiac troponin (TnT, TnI) is recommended in order to stratify early risk of ACS in suspected patients with chest symptoms.[146] The measurement of troponin T is recommended for the patients whose onset is unknown, and at that time, the time of arrival to a hospital would be defined as the time of onset.[146]

ii. Myosin Light Chain (MLC)

The level of MLC is affected by the process of myofibrillar necrosis, and elevated at 4–6 h after onset of MI, and reaches the peak 2 to 5 days later, and abnormal value of MLC persists for 7 to 14 days.

Evidence for the biomarker of myocardial ischemia and MI in patients with KD is not established. In JCS Guideline on Diagnosis and Treatment of ACS, it is recommended that measurement of cardiac troponin (TnT, TnI) in order to stratify an early risk of ACS in suspected patients with chest symptom, and the measurement of CK-MB or myoglobin is not recommended for a diagnosis of ACS under the conditions of being able to measure cardiac troponin.[146]

Table 8. Standard of Dyslipidemia in Childhood (Primary and Junior High School Student) Fasting Blood Test

Total cholesterol (TC)	≥220 mg/dL
Low-density lipoprotein cholesterol (LDL-C)	≥140 mg/dL
Triglyceride (TG)	≥140 mg/dL
High-density lipoprotein cholesterol (HDL-C)	<40 mg/dL

Based on Okada T, et al.,[151] TC, LDL-C, and TG are set at the 95th percentile value, and HDL-C is set at the 5th percentile value. (Adapted from The Japan Atherosclerosis Society. 2017.[149])

Table 9. Target Values for Management of Dyslipidemia in Adults

Principle of therapeutic strategy	Risk classification	Target value of lipid management (mg/dL)			
		LDL-C	Non-HDL-C	TG	HDL-C
Primary prevention First, improvement in lifestyle is performed, and then indication for medical treatment will be considered	Low risk	<160	<190	<150	≥40
	Moderate risk	<140	<170		
	High risk	<120	<150		
Secondary prevention Both improvement in lifestyle and initiation of medical treatment are considered	Past history of coronary disease	<100 (<70)*	<130 (<100)*		

*Considered at the onset of familial hypercholesterolemia and acute coronary syndrome. Based on Boers et al.[155] HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride. (Adapted from The Japan Atherosclerosis Society. 2017.[149])

Table 10. Diagnostic Criteria of Metabolic Syndrome of Childhood (6–15 Years Old) (Ministry of Health, Labour and Welfare Research Team, Last Plan in 2006)

Metabolic syndrome is diagnosed when a patient has item 1, and 2 of items 2–4	
1. Abdominal circumference	≥80 cm*
2. Serum lipid ('a or b' or 'a and b')	
a. Triglyceride b. HDL-C	≥120 mg/dL <40 mg/dL
3. Blood pressure ('a or b' or 'a and b')	
a. Systolic BP b. Diastolic BP	≥125 mmHg ≥70 mmHg
4. Fasting blood sugar	≥100 mg/dL

*If the ratio of the abdomen circumference/height is ≥0.5, it is considered that the condition of the patient corresponds to item 1. In primary school students, it is considered that abdominal circumference ≥75 cm corresponds to item 1. HDL-C, high-density lipoprotein cholesterol. (Ohzeki T, et al. 2008.[157])

1.2 Atherosclerosis

- Evidence for a blood examination and a biomarker that can predict the progression of atherosclerosis in KD patients with long-term follow-up is not established.
- Evidence of an association between atherosclerosis and dyslipidemia in KD patients with long-term follow-up is not established.

In the case of atherosclerosis, the diagnosis of dyslipidemia and insulin-resistance is important. Markers of dyslipidemia include total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), and homocysteine attracts attention as an independent risk factor for atherosclerosis. On the other hand, the concept of metabolic syndrome is assumed to be a problem in childhood, and it has been shown that coronary arteriosclerosis progresses when the number of risk factors increases even if the degree of the constituent risk factors was mild. In addition, it is necessary to examine whether a past history of KD or coronary abnormalities can become a risk factor for coronary arteriosclerosis and whether examination will be necessary in future.

In a meta-analysis for KD patients with long-term follow-up, TC and LDL-C levels were significantly high among TC, LDL-C, TG, and systolic pressure, which could become a risk factor for atherosclerosis.[150]

1.2.1 Dyslipidemia (Table 8)

a. Serum TC

As for serum TC in adults, <200 mg/dL is normal, 200–219 mg/dL is borderline, and >220 mg/dL is abnormal. In 2007 the Japanese Arteriosclerosis Society changed the term from "diagnostic criteria of hyperlipidemia" to "the diagnostic criteria of lipid abnormality" and the serum TC level was excluded from the diagnostic criteria because it includes the serum HDL-C level.

b. Serum LDL-C

Oxidative LDL (oxLDL) strongly affects the progression of atherosclerosis. As for serum LDL-C in adults, <120 mg/dL is normal, 120–139 mg/dL is borderline, and >140 mg/dL is abnormal.[149]

c. Serum HDL-C

Serum HDL-C transports excess peripheral cholesterol to the liver in the reverse cholesterol transportation system and has antiatherosclerotic action. The qualitative and quantitative abnormality of the serum HDL-C shows that this defense mechanism for atherosclerosis does not function effectively. The normal level of serum HDL-C in adults is >40 mg/dL, and low HDL-cholesterolemia is diagnosed when serum HDL-C is <40 mg/dL. The Japanese Arteriosclerosis Society publishes a value target for management of dyslipidemia.[149]

Regarding the criteria of dyslipidemia in childhood, there are American findings, but it is unknown whether these equate to Japanese real-life conditions. **Table 8** shows the standard of dyslipidemia in childhood in Japan for 9–16-year-olds from 19 prefectures from 1993 through 1999.[149,151] It is reported that serum HDL-C decreases in the acute phase of KD,[152] and that decreased HDL-C is observed during long-term follow-up of KD patients with CAL.[153]

d. Serum TG

In hypertriglyceridemia, risk factors for atherosclerosis are likely to occur, and hypertriglyceridemia is thought to accelerate atherosclerosis. When serum TG is >150 mg/dL in adults, it is defined as hypertriglyceridemia.[149]

e. Dyslipidemia in KD Patients With Long-Term Follow-up

KD patients (7–20 years after acute illness) and age-matched healthy control subjects were examined for each marker of atherosclerosis, and the levels of TC and apolipoprotein B were significantly higher in KD patients than in healthy subjects. Therefore, small but significant differences in cholesterol and apolipoprotein B levels could suggest increased future risk for atherosclerosis.[154] **Table 9** shows

the target values for management of dyslipidemia in the Japanese adult population.[149] It is necessary for adult KD patients to follow these target values.

1.2.2 Homocysteine

It is reported that homocystinuria is an independent risk factor for atherosclerosis-related diseases such as cerebral infarction and MI.[155] The standard value of plasma homocysteine is 8.2–16.9 μmol/L in men, and 6.4–12.2 μmol/L in women, and the plasma homocysteine level rises after menopause.[156]

1.2.3 Diagnostic Criteria of Metabolic Syndrome of Childhood

Table 10 shows the diagnostic criteria of metabolic syndrome of childhood in Japan as reported by the Public Works for Lifestyle Disease of the Ministry of Health, Labour and Welfare in 2006.[157]

2. Electrocardiography

- Rest electrocardiogram (ECG) is one of the basic follow-up tests during the remote phase of KD with sequelae of the coronary arteries. Ischemic events can be screened by comparing the rest ECG with previous ECG (Class I, Level C)
- Exercise ECG is not very sensitive, but can be easily performed, and has clinical significance because it can be used as a reference for setting exercise intensity in daily life. It is useful in daily medical care (cases of KD with CAL: Class IIa, Level C; cases of suspected ischemic events: Class I, Level C).

2.1 Rest Electrocardiogram

Before intravenous immunoglobulin (IVIG) therapy was established, ECG abnormalities such as PR prolongation, deep Q wave, QT prolongation, relative low potential, ST change, and T wave flattening were observed in the acute phase of KD at a frequency of 43–100%.[158,159] The frequency of arrhythmia was 1–6%, including tachyarrhythmia, atrioventricular block, and branch block.[160–162] Currently, the frequency can be reduced by early treatment, but if ECG abnormalities are observed, follow-up during the remote phase is necessary. A correlation between QT dispersion and coronary prognosis has been reported.[163–166] In patients with coronary artery aneurysms (CAA), abnormal Q-waves and ST-T changes consistent with an infarcted site are observed at the onset of MI, which is useful for regular follow-up of patients with CAL.

2.2 Holter Electrocardiogram

It is recommended to perform Holter ECG if arrhythmia is observed in the acute phase or the patient complains of chest pain or palpitation. In addition, there is the advantage that it can be used for infants who cannot exercise to examine for the appearance of arrhythmia, ST-T change and Q wave.

2.3 Exercise Electrocardiogram

Exercise ECG is clinically meaningful in children because it is simple and relatively safe to perform. Check the ECG at rest, and carefully evaluate if there is any suggestion of myocardial ischemia. A simple exercise ECG while jumping at an arbitrary tempo has been reported for young children.[167] Older children can be double-mastered (3 min), but children may not be fully loaded because of their high exercise tolerance. In the lower grades of elementary school, treadmill tests and ergometer tests are generally available. For detection of myocardial ischemia in KD patients with coronary aneurysms, the sensitivity of exercise ECG is not always good,[168,169] and combined use with an imaging test is recommended.[2]

2.4 Other Electrocardiogram Examinations

Drug-loading body surface ECG mapping, magnetocardiograms, and signal-averaged ECG have been studied, but none of them are widely used in current daily practice.

Rarely, there are cases of dangerous ventricular arrhythmias after KD. In electrophysiological examinations of patients with KD cardiovascular sequelae, abnormalities in sinus function and atrioventricular node function are significantly more common. They do not necessarily correspond to cases of coronary artery stenosis or occlusion, and are thought to involve myocarditis and microcirculation abnormalities of the conduction system.[170]

3. Diagnostic Imaging

- Echocardiography is a minimally invasive examination that is useful for observation of coronary artery morphology and left ventricular wall motion and is one of the basic tests for KD (Class I, Level C). In the assessment of vascular stiffness using vascular echocardiography for cardiovascular event risk assessment, evidence has been accumulated in patients with CAL (Class IIa, Level B).
- Myocardial perfusion imaging is sensitive and useful in detecting myocardial ischemia in patients with coronary artery abnormalities, although there is a risk of radiation exposure and drug load (Class I, Level B).
- CTA can quickly show the shape of the entire coronary artery, and the rate of detecting stenosis is increased, although there is a risk of radiation exposure and the need for heart rate control (Class IIa, Level C).
- MRI requires heart rate control and has a long imaging and sedation time in young children, but it has the advantage of no radiation exposure. MRA can be used to observe the coronary artery morphology under appropriate imaging conditions (Class IIa, Level C).

3.1 Chest X-ray

Pathologically, calcification is observed at the stage of scar formation after 40 days of disease,[171] but chest X-rays can detect it from 1 to 6 years after the disease.[172] It is necessary to check the dorsal and lateral images. It is significant as a screening test for patients with unknown history of KD at the first referral during remote-phase follow-up. When a spherical calcified image matching the coronary artery is observed and coronary artery abnormalities caused by KD are strongly suggested,[173,174] further examination by imaging is required.[172,175,176]

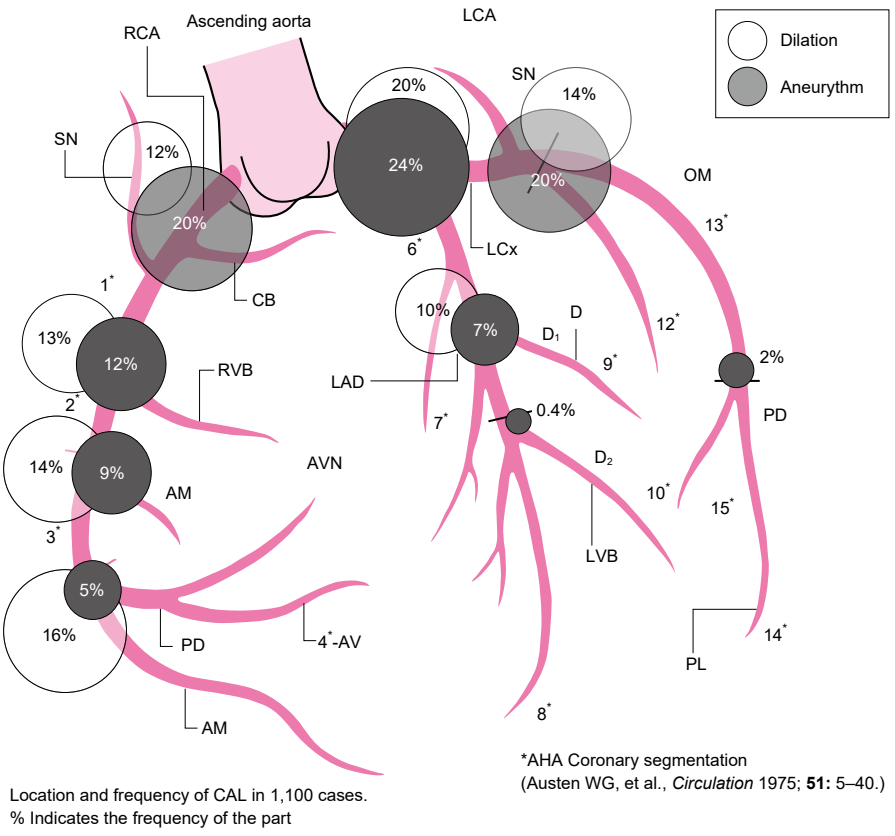

Figure 4. Incidence of coronary artery abnormalities in 3 segments. ○ Incidence of coronary artery dilation; ● incidence of coronary artery aneurysms. AM, Acute marginal branch; AV, atrioventricular branch; AVN, atrioventricular node branch; CB, conus branch; D, diagonal branch; LAD, left anterior descending artery; LCA, left coronary artery; LVB, left ventricular branch; OM, obtuse marginal branch; PD, posterior descending branch; PL, posterior lateral branch; RVB, right ventricular branch; RCA, right coronary artery; SN, sinoatrial nodal branch. (Modified from Suzuki et al. *Pediatr Cardiol* 1986; **7:** 3–9.[138])

3.2 Echocardiography

3.2.1 Resting Echocardiography

Echocardiography is a basic test for KD because it is less invasive and can be performed repeatedly. It is useful for the evaluation of coronary artery expansion over time[88,177,178] and the presence of thrombus in coronary aneurysm.[179] The standard method of visualizing and measuring the coronary arteries has been proposed by Fuse et al.[180] It is important to observe all areas where coronary lesions are likely to occur (**Figure 4**[138]). It is also important to change the posture from the supine position, the left position, and the right position within the range where cooperation can be obtained.

For the diagnosis of coronary artery dilation and aneurysm, Z score is used in addition to absolute diameter for the normal value of inner diameter.[3] The clinical significance of evaluation in the remote phase using the Z-score was also reported in Japan. In both Japan and the USA, compared with small aneurysms of less than 5 mm, the outcome was poor in gANs of Z-score ≥10 or measured values of ≥8 mm.[139,140]

Mitral regurgitation often accompanies the acute phase of KD, in which case echocardiographic follow-up is necessary. Cases of valve replacement have been reported.[181]

3.2.2 Load Echocardiography

Left ventricular wall motion is evaluated in real time with exercise,[182] dobutamine,[183,184] or dipyridamole load.[185] Stress echocardiography, especially with dobutamine loading, has been established as a diagnostic method for IHD. It is useful as a minimally invasive diagnostic method for ischemia and it is a follow-up method in KD.

3.2.3 Vascular Echocardiography Examination as a Risk Indicator for Cardiovascular Disease Events

There are several reports of the significance of flow-mediated dilation (FMD), pulse wave velocity (PWV), and carotid artery intima-media thickness (cIMT) as surrogate markers for adult cardiovascular events in the late stage of KD,[186,187] and systematic reviews have also been reported.[143,144] In patients with coronary artery abnormalities, vascular stiffness is impaired, and these tests are meaningful. On the other hand, results in patients without coronary artery abnormalities are under discussion.

3.3 Nuclear Medicine Examination

Stress myocardial single photon emission computed tomography (CT) is important as a diagnostic method for coronary stenotic lesions after KD, and drug load is used

particularly in infants and lower primary school children who have difficult with exercising sufficiently.[188–192] Myocardial ischemia may sometimes be detected without stenotic lesions in the coronary arteries. If false-positives are negative, myocardial ischemia may be caused by coronary microcirculatory disturbance.[193] With the ECG synchronized acquisition method,[194] it is possible to study cardiac functions such as left ventricular contractility and dilatability, left ventricular wall motion,[195] and myocardial viability.[196,197] However, it is difficult to use in infants with a ventricular volume of ≤50 mL. Myocardial fatty acid metabolism imaging (^{123}I-β-methyl-p-iodophenylpentadecanoic acid),[198] myocardial sympathetic nerve function imaging (^{123}I-MIBG)[199,200] and PET[119–202] have also been clinically applied.

In children, technetium myocardial blood flow products (Tc-99 m sestamibi, Tc-99 m tetrofosmin) are recommended for myocardial SPECT[141,203] instead of thallium chloride (^{201}Tl) in order to reduce exposure. The ^{201}Tl redistribution image was established for predicting cardiac accidents[188] and viability evaluation,[205] but it is expected the patient will receive an exposure dose approximately 8–10-fold higher than that of Tc myocardial perfusion products. Therefore, it is not currently recommended.[206] The physical half-life is 6 h for technecium myocardial perfusion and 73 h for thallium chloride.

3.3.1 Technetium Myocardial Perfusion Imaging

The recommended dose is based on the consensus guidelines for proper implementation of pediatric nuclear medicine examinations.[141] If the calculated dose is below the minimum dose, the minimum dose should be administered and the maximum dose should not exceed the adult dose.

The following points for obtaining a good image should be noted when creating a protocol. (1) Do not hesitate to re-image when there is too much body movement during imaging. (2) The maximum load is continued for 1 min after administration under load. (3) Eating and drinking dairy products after administration of technetium myocardial blood flow preparation, and imaging at least 30 min after administration will assist in reducing liver accumulation. (4) Reduction of artifacts in the vicinity of liver accumulation with the backstroke position (Monzen position) where the left upper limb is raised during imaging.[207] (5) Reduction of artifacts in the vicinity of intestinal tract by soda drinking (stomach fullness) immediately before imaging.

3.3.2 Drug-Loading Method in Myocardial Perfusion Imaging

Dipyridamole has been used for some time, but adenosine has been approved as a nuclear medicine. For adenosine, 0.12 mg/kg/min (0.14 mg/kg/min in overseas results)[208] should be used for 6 min of continuous intravenous administration. With adenosine loading, there are complications such as induction of asthma attack and transient flushing, but as the half-life appears short, symptoms disappear after discontinuation of administration.[209]

3.4 CTA

Advances in instrumentation and analysis technology, including 320-multi detector row CT (MDCT), which has become widespread in recent years, have improved spatial resolution, and improved the accuracy of stenotic lesion assessment,[210] and CTA can partially replace CAG. Compared with CAG, it is performed by injecting contrast medium from the peripheral vein, so it is less invasive, and compared with MRA, the entire coronary artery branch can be observed and the image resolution is high. There are reports that it is more useful for evaluating collateral circulation associated with complete obstruction.[211] The imaging time is short,[212] which is advantageous for infants who need sedation. On the other hand, there are disadvantages such as radiation exposure, the use of contrast media, and the need for β-blockers for heart rate regulation.

In recent years, efforts have been made to reduce exposure while ensuring image quality. It has been reported that the effective dose can be reduced to 1/5 of the conventional one using 320-MDCT.[213] Dual-source CT (DSCT) has been used to reduce the effective dose to 1 mSv or less.[214,215] Intravenous β-blockers, which have short half-lives, for heart rate control are available in Japan.[216] When this test is used for children, techniques such as low-voltage imaging and ECG synchronization should be done at each facility to reduce exposure. A standard protocol should be prepared for the amount and administration method of β-blockers.

It has been reported that the CT calcium score calculated by measuring the calcification area from the CT value of the coronary artery wall during CTA examination is useful for predicting coronary prognosis.[217]

3.5 MRI

The role of cardiac MRI is evaluating coronary artery morphology, myocardial properties, cardiac function, and wall motion. Evaluation of these items has been established in adults. In the remote phase of KD, the main purpose is to evaluate coronary artery morphology. Evaluation of myocardial properties by myocardial MRI techniques[218–221] such as stress perfusion and late gadolinium enhancement, and cardiac function and wall motion evaluation[222] by CineMR in IHD of adults has been established with accumulated evidence. However, the recommended class and evidence level are not listed in **Table 11** of this guideline because the applicability to KD is still slight. It has been reported that a comprehensive assessment by cardiac MRI including myocardial MRI techniques was useful for children with coronary aneurysms.[223]

The visualization of the coronary arteries in KD can be evaluated at 86% or more arteries in the proximal region and 60% or more arteries at all sites compared with CAG.[220,223–226] It is necessary to be careful as it may appear discontinuous at 90% or more of stenosis because of the limits of image resolution. Spiral BB (2D black blood spiral k-space order Turbo Field Echo "TFE") imaging that clearly depicts the blood vessel lumen, blood vessel wall, and thrombus and VISA-BB (volume isotropic Turbo Spin Echo "TSE" acquisition) imaging that can observe blood vessel morphology in any direction. Although it is reported to be useful for morphological evaluation, only a limited number of facilities can take such images with sufficient quality.[227]

MRI has no radiation exposure and MRA does not use contrast media. MRI/MRA can clearly show wall thrombus and vascular wall properties, as well as the lumens even with circumferential calcification.[227] On the other hand, there are the disadvantages of a long examination and sedation time for young children, and image resolution is not high enough to evaluate the degree of advanced stenosis, and skill is required for setting the imaging conditions

Table 11. Examinations: Class of Recommendation and Level of Evidence

Examinations and patient's coronary artery status	COR	LOE
Stress ECG		
No CAAs and no symptoms	IIb	C
With CAAs without any symptoms	IIa	C
With ischemic symptoms	I	C
Echocardiography (rest)		
No CAAs and no symptoms	I	C
With CAAs without any symptoms	I	C
With ischemic symptoms	I	C
Vascular stiffness tests by echocardiography		
No CAAs and no symptoms	IIb	B
With CAAs without any symptoms	IIa	B
Stress cardiac echocardiography		
No CAAs and no symptoms	IIb	C
With CAAs without any symptoms	IIa	C
With ischemic symptoms	I	C
NM scintigraphic stress imaging		
No CAAs and no symptoms	IIb	C
Regressed CAAs without any symptoms	IIa	C
With CAAs without any symptoms	I	B
With ischemic symptoms	I	B
CTA		
No CAAs and no symptoms	IIb	C
Regressed CAAs without any symptoms	IIa	C
With CAAs without any symptoms	IIa	C
With ischemic symptoms	IIa	C
MRA		
No CAAs and no symptoms	IIb	C
With CAAs without any symptoms	IIa	C
With ischemic symptoms	IIa	C
Coronary angiography		
No CAAs and no symptoms	III	C
With CAAs without any symptoms	IIa	C
With ischemic symptoms	I	A

COR, class of recommendation; LOE, level of evidence;CAA, coronary artery aneurysms; CTA, computed tomography angiography; MRA, Magnetic Resonance Angiography; NM, Nuclear Medicine.

compared with CTA. It is said that sufficient image quality can be obtained with imaging equivalent to that of adults in children aged 8 years or older without sedation.

Screening for the presence of implantable medical devices should be done before the MRI examination. Although gadolinium contrast agents are less risky than iodinated contrast agents, caution is also required. Nephrogenic systemic fibrosis (NSF) has been reported as a rare but serious complication.[228] Although the effects of gadolinium retention in the brain have been discussed, conclusions have not yet been reached.[229]

3.6 PET

The use of ^{15}O-water PET was investigated for use in KD, and it was reported that even in cases without CAL, myocardial flow reserve (MFR) in stress perfusion was decreased and coronary vascular resistance was increased.[119,201] In 2012, PET using ^{13}N-ammonia was accepted for health insurance. By this method, the absolute value of myocardial blood flow was obtained with higher image quality and lower exposure than myocardial blood flow scintigraphy. In 2015, there was a report that evaluated improvement of chronic inflammation in a giant coronary aneurysm using ^{18}F with a PET/CT combined scanner.[230]

4. Cardiac Catheterization

4.1 CAG

- Patients with evidence of inducible myocardial ischemia on testing should undergo invasive CAG (Class I, Level A).
- Patients who have percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should undergo invasive CAG within the first year (Class IIb, Level C).
- Patients with moderate to giant coronary aneurysms in the acute phase should undergo invasive CAG at regular intervals (Class IIa, Level C).
- Patients suggested to have significant coronary stenosis by noninvasive imaging such as coronary magnetic resonance or coronary CT should undergo invasive CAG even without apparent inducible myocardial ischemia (Class IIa, Level C).
- Patients suggested to have intracoronary thrombus by noninvasive imaging such as echocardiography should undergo intracoronary thrombolysis (ICT) in addition to invasive CAG (Class IIb, Level C).

CAG, which is the most invasive of the imaging examinations of KD, enables detailed image evaluation of the coronary artery lumen, and is the gold standard for evaluating the degree of stenosis, prognostic prediction, and therapeutic indications of coronary artery disease.[113,231–233] However, through advances in other noninvasive imaging modalities such as coronary MRI and coronary CT, the number of tests required for confirmation and follow-up of coronary artery disease after KD has decreased in recent years.

In addition, simple CAG does not directly evaluate the functional severity of coronary stenosis or the physiological abnormalities of CAL. Therefore, recently CAG is not performed alone but is performed with intracoronary pressure measurement using a pressure-sensor guidewire

or coronary blood flow velocity measurement (e.g., FFR, instantaneous wave-free ratio [iFR]) using a Doppler guidewire to evaluate the functional severity of coronary artery stenosis,[1,4] before, during, and after PCI, and before and after CABG.

4.1.1 Evaluation Before and After PCI and CABG for Patients With Myocardial Ischemia

For patients with myocardial ischemia on various stress tests, CAG is performed preoperatively to determine the indications for PCI, and to ensure safe and effective PCI, and is also necessary to determine the effectiveness during PCI and for postoperative evaluation and follow-up after PCI.[190,234–236] In particular, PCI for coronary artery stenosis caused by KD has a high restenosis rate, and early postoperative CAG after PCI is important because there have been cases of stenosis occurring soon after PCI.[237,238]

4.1.2 Level of Coronary Artery Disease and Follow-up

Similar to the AHA severity classification,[2] the "Severity classification of cardiovascular lesions in Kawasaki disease" in this guideline is based on diagnostic imaging, including echocardiograms, in the acute phase, and no longer measures the size of coronary aneurysms on CAG. However, even if other diagnostic imaging techniques are used, not only the size of the CAA, but also the form, position, number, etc. in detail, should be examined to determine the modalities of subsequent follow-up, the interval, and treatment methods.

In addition, if the aneurysm has regressed because of intimal thickening and the lumen appears normal on CAG, follow-up can be discontinued empirically. However, decreased endothelial function is reported, even a long time, 10 years, after onset,[130,239] and an actual case of ACS is reported in patients with regressed CAA.[240] Therefore, it is necessary not only to evaluate the lumen by CAG, but also to continue to evaluate the coronary wall structure by coronary artery MRI and CT.

On the other hand, coronary artery stenosis in the remote phase of KD frequently occurs at the inflow and outflow of the aneurysm.[133,241] CAG with multiple cross-sections is necessary to evaluate such stenosis. Significant stenosis has an inner diameter of ≤25% in the main coronary artery branch and an inner diameter of ≤50% in the main trunk of the left coronary artery (LCA). In the case of significant stenosis, it is desirable to perform various image inspections at intervals of 6 months to several years depending on the rate of stenosis progression in individual cases, even without symptoms of myocardial ischemia.[133,241]

Especially in KD, the rate of detection of myocardial ischemia by various conventional tests is low, and sudden death may occur as the first symptom of myocardial ischemia;[133,241,242] therefore PCI is considered in cases of stenosis ≥75% of left anterior descending coronary artery even without any myocardial ischemic findings.[236]

Approximately 16% of patients with CAL develop complete occlusion, but it may be clinically asymptomatic and is not uncommonly found for the first time by routine follow-up coronary imaging.[133] In cases of coronary occlusion, collateral circulation is always observed. The development of collateral circulation that is often marked enough to result in negative ischemic findings is one of the characteristics of coronary occlusion caused by KD. However, there are cases of myocardial ischemia and symptoms appearing as the patient grows up, and careful follow-up is necessary.

Even if it appears to be a normal coronary artery, occlusion of a thin branch that is not noticed on antegrade contrast image may be revealed by collateral circulation from the contralateral branch and it is necessary to take enough time to examine the coronary angiogram until the venous phase.[243]

In addition, it is desirable to perform CAG when stenotic lesions are suspected on coronary artery MRI or CT in children.

4.1.3 ICT

During echocardiographic follow-up of medium to large CAA, asymptomatic patients may have intra-aneurysmal thrombi, and cardiac catheterization and CAG may be performed for thrombolysis. Some blood clots are difficult to interpret because there may be blurred contrast or contrast defect. Even in such cases, there are cases in which the contrast defect disappears with ICT, and it has been reported that it is desirable to try ICT as soon as coronary thrombus is recognized.[244–246] However, in a recent recommendation for adult AMI, standard thrombolytic therapy is not the ICT, but intravenous thrombolysis[146] and children are considered to be applicable.

4.1.4 Disadvantages of CAG

The disadvantages of CAG include complications caused by an invasive procedure, unnecessary increase in PCI, and associated medical costs. In general, mortality as a complication of CAG in adults is ≤0.2%, and complications such as cerebrovascular disorder, MI, hemorrhage are ≤0.5%.[247]

Of course, as with X-ray CT, efforts should be made to reduce as much as possible the radiation exposure to children in their developing stages.[248,249]

Care should be taken when performing catheterization of patients with KD who have giant CAA and are taking warfarin, because vascular damage such as femoral artery puncture hematoma and pseudoaneurysm may occur.[250]

4.2 Cardiac Function Tests

4.2.1 Left Ventriculography

- Patients whose left ventricular (LV) function cannot be assessed by noninvasive examination should undergo left ventriculography (Class IIa, Level C).
- Patients who need evaluation of LV contractility should undergo left ventriculography together with CAG (Class IIa, Level C).

In IHD, the number of compromised coronary artery branches and left ventricular (LV) function are important factors affecting long-term prognosis.[251] Cardiac function is evaluated by measuring LV pressure, cardiac output, LV volume, LV ejection fraction, and so on. Left ventriculography (LVG) is the gold standard for determining LV function, particularly local dysfunction, and the presence of wall motion is evidence of viable myocardium.

Traditionally, LVG was the standard method for evaluating LV contractility. However, recent advances in noninvasive diagnostic imaging techniques have made this possible without using LVG. In particular, the remarkable progress in echocardiography has made it possible to evaluate not only local contractility but also local diastolic function in 3D at the bedside,[252,253] and LVG is no longer performed just for the purpose of evaluating cardiac function.

Advance Publication

On the other hand, the advantage of LVG is that, unlike echocardiography, it can record good images with high reproducibility in almost all patients. If the risk of complications from LVG is expected to be low, LV angiography may be performed together with CAG. Left ventriculography is useful in patients who only have unclear echocardiographic images.

Evidence Required in the Future

- To what extent can noninvasive imaging be an alternative to CAG in younger patients?
- At what intervals and in what patients with coronary sequelae should diagnostic imaging and myocardial ischemic local testing be performed?
- What to do when an asymptomatic patient is suspected to have a thrombus in a coronary aneurysm on routine echocardiography?

5. Summary of Examinations and Diagnosis

Table 11 summarizes the recommendations and levels of evidence for testing methods in the remote phase of KD. In addition, **Table 7** summarizes the standard for the frequency of testing. See also the JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases[233] and the American Heart Association's Kawasaki Disease Management Statement.[2]

IV. Treatment of Cardiovascular Sequelae

In Kawasaki disease (KD) patients with cardiovascular sequelae, management of ischemic heart disease (IHD) is important to improve symptoms and prevent or treat cardiovascular events. IHD is a state of insufficient oxygen supply to the myocardium caused by stenosis or obstruction of the coronary arteries, and it is roughly divided into angina pectoris (AP) and myocardial infarction (MI). The former consists of stable AP (exertional angina and coronary spastic angina) and unstable AP (UAP), and the latter includes acute MI (AMI) and old MI (OMI). UAP and AMI are together termed "acute coronary syndrome (ACS)". In adults it is classified as ACS without persistent ST-segment elevation and ST-elevation AMI on the basis of ECG findings, and the guidelines of the Japanese Circulation Society for each disease were published separately, but they have been combined into a new guideline.[146]

Myocardial ischemia in KD is caused by thrombotic obstruction in coronary artery aneurysms (CAA) and luminal stenosis of the inflow or outflow of the CAA because of intimal thickening;[129] these conditions are subject to medical or nonmedical treatment. In the following sections, we describe direct medical treatment for myocardial ischemia including antiplatelet drugs, anticoagulants, coronary vasodilators, antianginal drugs, and thrombolytic agents, and indirect treatment for vascular lesions such as angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and statins. Nonmedical treatment, or invasive treatment, consists of catheter therapy and coronary bypass operation; the catheter therapy includes balloon angioplasty, stent implantation, and rotablator.

Clinical research on IHD in children with KD and other causes has been either retrospective or in a small number of subjects, even if prospective, in most cases, and therefore empirical therapies have been performed with reference to evidence for adults in Japan as well as in Western countries.[2,254] However, it is unclear whether the findings of IHD caused by atherosclerosis in older-aged adults can be extrapolated to children and young adults with KD and remodeling from coronary arteritis. Furthermore, many medical agents for adults are unapproved or off-label for children, and therefore high-quality clinical research is required for acquiring insurance approval. Registry studies of KD patients with CAA have started domestically and internationally.

In the present guideline, it is clearly stated that some medical agents and devices are unproved or off-label in Japan, and processes required for their use, such as deliberation by ethics committees, depend on the policy of each institution.

1. Pharmacotherapy

1.1 Medical Treatment of Myocardial Ischemia

The object of medical treatment for myocardial ischemia is divided into increasing oxygen supply and decreasing oxygen demand in the myocardium.[255] Medications increasing oxygen supply are the antithrombotic drugs to suppress thromboembolism, thrombolytic agents to resolve thromboembolism, nitrates to dilate the coronary arteries, calcium antagonists to prevent spasm of the coronary arteries, and others. Antithrombotic drugs are roughly classified as antiplatelet drugs and anticoagulants; antiplatelets are used for arterial thrombus in ACSs and atherothrombosis, and anticoagulants for deep vein thrombosis and thrombosis in the left atrium with atrial fibrillation. Medications decreasing oxygen demand are β-blockers, calcium antagonists, and renin-angiotensin system (RAS) inhibitors to reduce heart rate and afterload.

In KD patients with CAA, aspirin and other antiplatelet drugs are basic therapy, and anticoagulants are mainly added to those with large CAA and a past history of MI.[2,256] Thrombolytic agents are administered to KD patients for prevention of MI by resolution of thrombus and improvement of cardiac function through recanalization of obstructed coronary arteries. Nitrates, β-blockers, and calcium antagonists may be also effective for AP in KD patients by increasing coronary artery supply and decreasing oxygen demand. RAS inhibitors and antihyperlipidemic agents such as statins are described in the next section because they act on vascular lesions.

1.2. Medical Treatment of Coronary Artery Lesions (CAL)

- Statins are used to prevent cardiovascular events in patients with CAL (Class IIb, Level C).
- ACEI or ARB is used to prevent coronary artery stenosis in patients with CAL (Class IIb, Level C).

1.2.1 Statins

Statins, which are reported to have multifaceted pharmaco-

logical actions such as anti-inflammatory action, antioxidant action, blood coagulation inhibition, and thrombolysis promotion, as well as decreasing the cholesterol level, are expected to improve vascular endothelial function.[257–260] In a KD vasculitis model induced by *Lactobacilius casei cell* wall extract, atorvastatin suppressed T cell activity and proliferation, TNF-α production, and matrix metaroproteinase (MMP)-9 activation.[261] Therefore, statin is expected to exert a restorative effect on coronary artery damage. American Heart Association Guidelines of Kawasaki Disease[6] recommended that empirical statin therapy be considered in patients with aneurysm for the non-lipid-lowering (pleiotropic) effects (Class IIb, Level C). Currently, clinical trials to investigate the safety and usefulness of atorvastatin in patients with KD associated with CAA are being conducted in Japan and the USA.

1.2.2 ARB, ACEI

Significant coronary artery stenosis is often observed at the proximal and distal sites of the aneurysm or at the inter-aneurysmal site in a multiple aneurysm lesion. This stenosis is formed by thickening around the intima as part of the vascular reconstruction, which is largely caused by the action of the RAS localized in the vascular wall. Angiotensin II (AngII), via angiotensin II-1 type receptor (AT1R), induces hypertrophy of vascular smooth muscle cells, promotion of extracellular matrix production, increased oxidative stress, increased production of adhesion molecules and growth factors, or increased cytokines/chemokines expression.[2,262] There is a report that ARB (candesartan 0.2–0.3 mg/kg/day, started within several days after aneurysm formation) might be effective in preventing coronary stenosis by intimal over-thickening.[263]

Evidence Required in the Future

- Safety and efficacy (regression of CAA and prevention of ACS) of statins, ACEI, or ARB in KD patients with aneurysms.

1.3 Antiplatelets and Anticoagulants (Table 12)

- During the acute febrile phase, a moderate dose of aspirin, 30–50 mg/kg/day, three times daily, is administered orally, then reduced to a low dose, 3–5 mg/kg/day once a day after defervescence, which is continued for 2–3 months after the onset (Class I, Level C).
- Oral administration of low-dose aspirin is continued for patients with persistent CAA (Class I, Level C).
- Antiplatelet drugs such as clopidogrel, ticlopidine, and dipyridamole are used in combination with low-dose aspirin for patients with medium or large CAA (Class IIa, Level C).
- Warfarin is used in combination with low-dose aspirin for patients with large CAA, past history of MI, and thrombosis in the CAA. The dose is adjusted for the international normalized ratio of prothrombin time (PT-INR) target range of 2.0–2.5 (Class IIa, Level C).

1.3.1 Antiplatelets

The number of platelets in the acute phase of KD tends to decrease immediately after onset, is smaller in more severe cases, and then increases in the recovery phase. Based on study of platelet aggregation and platelet-derived microparticles,[264,265] the number of platelets generally normalizes after 31–40 days of illness, and platelet activation continues for as long as 2 or 3 months after the onset. Accordingly, antiplatelet drugs are administered in this period for all patients, and continued for patients with persistent CAA to prevent thrombosis and IHD.

a. Aspirin

Aspirin inhibits cyclooxygenase-1 (COX-1) by acetylation and suppresses production of thromboxane A_2 to promote platelet aggregation, and thereby has an antiplatelet effect. Aspirin has high-level evidence for IHD in adults,[3,4] and is covered by insurance for children with KD including cardiovascular sequelae. Because aspirin is an established standard therapy for acute treatment, oral administration of moderate-dose aspirin (30–50 mg/kg/day, three times daily) should be started if KD is diagnosed and fever is present. After defervescence, aspirin is reduced to a low dose (3–5 mg/kg/day, once a day PO), and continued until 2–3 months after onset even if CAA is absent and until regression if CAA is present.

According to the package leaflet, a past history of hypersensitivity, digestive ulcer, bleeding tendency, aspirin asthma, and other conditions are contraindications; severe liver dysfunction requires careful administration, but is not contraindication. Because a relationship with Reye syndrome has been suggested, it is desirable stop aspirin if the patient is suffering from varicella or influenza. Inhibition of COX-1 persists during the cellular life span of platelets, 8–10 days, after discontinuation of aspirin, and the effect remains for more than several days until newly produced platelets are in the majority.[266] Hence changing to another antiplatelet is usually unnecessary.

b. Dipyridamole

Dipyridamole has an antiplatelet effect by increasing the cyclic adenosine monophosphate (cAMP) concentration mainly via inhibition of phosphodiesterase. CAL of KD is not described in the package leaflet, but administration is applicable for insurance reimbursement, and the dose, 2–5 mg/kg/day, is orally administered three times daily. Single use of dipyridamole is not recommended for IHD in adults, because the clinical effect has not been proved.[146,266] Worsening of angina symptoms needs to be considered, because the coronary steal phenomenon may occur by dilatation of a normal coronary artery and reduction of blood flow of a stenotic coronary artery.

c. Ticlopidine, Clopidogrel

Ticlopidine and clopidogrel inhibit the adenosine diphosphate receptor ($P2Y_{12}$) coupled by inhibitory G-protein, and increase the concentration of cAMP through suppression of adenylate cyclase, inducing an antiplatelet effect. Neither of these drugs is covered by insurance for children; clopidogrel is applicable for adults with IHD after percutaneous transluminal coronary angioplasty, and ticlopidine for those with thromboembolism who undergo cardiovascular surgery or extracorporeal blood circulation. Because adverse events are fewer compared with ticlopidine and a combination effect with aspirin has been demonstrated, clopidogrel is preferred in adults. For children, ticlopidine is orally administered, 2–5 mg/kg/day, 2–3 times daily, and clopidogrel, 0.2–1.0 mg/kg/day, once a day. It is reported that 0.2 mg/kg/day is enough for an effect of clopidogrel in infants, 0–24 months of age.[267] Adverse effects such as thrombotic thrombocytopenic purpura, agranulocytosis, and severe liver dysfunction may appear early, and accord-

Table 12. Administration of Antiplatelet and Anticoagulant Drugs in Kawasaki Disease

Drug	Main indication	General usage and dosage	Main contraindication, care with administration, and adverse effects
Antiplatelet drugs			
Aspirin	Cardiac sequelae of KD: angina pectoris, myocardial infarction, prevention of thromboembolism after coronary artery operation	3–5 mg/kg/day, once daily, oral administration; 30–50 mg/kg/day, 3 times daily, for acute KD, divided oral administration Adults: 81 mg tablet (100 mg for enteric coated tablet), once a day, oral administration	*Contraindications*: hypersensitivity, gastric ulcer, bleeding tendency, aspirin asthma, etc. *Care with administration*: liver/kidney dysfunction, cardiac dysfunction etc. *Adverse effects*: shock, bleeding, toxic epidermal necrolysis, cytopenia, asthma attack, liver dysfunction, gastric ulcer, and others. Cease administration if patient has varicella or influenza
Flurbiprofen	No indication for KD or cardiac diseases	3–5 mg/kg/day, 3 times daily, divided oral administration* Adults: 40 mg/dose, 3 times daily, oral administration	*Contraindications and care with administration*: gastric ulcer, severe liver/kidney dysfunction, cardiac dysfunction, hypertension, hypersensitivity, aspirin asthma etc. *Adverse effects*: shock, acute renal failure, gastric and intestinal bleeding, aplastic anemia, asthma attack, toxic epidermal necrolysis etc.
Dipyridamole	Angina pectoris, myocardial infarction	2–5 mg/kg/day, 3 times daily, divided oral administration* Adults: 25 mg/dose, 3 times daily, oral administration	*Contraindications*: hypersensitivity, combined use with adenosine, hypotension etc. *Care with administration*: hypotension, severe cardiac disease etc. *Adverse effects*: shock, bleeding, toxic epidermal necrolysis, cytopenia, asthma attack, liver dysfunction, gastric ulcer etc. The effect is decreased by xanthine derivatives and increased by adenosine
Ticlopidine	Treatment of thromboembolism or improvement of blood flow disturbance with cardiovascular surgery or extracorporeal blood circulation	2–5 mg/kg/day, 2–3 times daily, divided oral administration* Adults: 200–300 mg/day, 2–3 times daily, divided oral administration	*Contraindications and careful administration*: Bleeding, severe liver dysfunction, leucopenia, hypersensitivity, hypertension etc. *Adverse effects*: because thrombotic thrombocytopenic purpura, agranulocytosis, and severe liver dysfunction may appear early, blood tests should be performed once per 2 weeks during the 2 months after the start of administration. Other main adverse effects are cytopenia, bleeding, toxic epidermal necrolysis, gastric ulcer, renal failure, interstitial pneumonia, and lupus-like symptoms
Clopidogrel	Ischemic heart disease after percutaneous transluminal coronary angioplasty	0.2–1.0 mg/kg/day, once daily, oral administration* Adults: 300 mg, once daily, oral administration on the starting date, followed by 75 mg oral maintenance dose, once daily	*Contraindications*: bleeding, hypersensitivity, combined use with selexipag etc. *Care with administration*: bleeding tendency, severe liver/kidney dysfunction, hypertension etc. *Adverse effects*: Because thrombotic thrombocytopenic purpura, agranulocytosis, and severe liver dysfunction may appear early, blood tests should be performed once per 2 weeks during 2 months after the start of administration. Other main adverse effects are bleeding, toxic epidermal necrolysis, gastric ulcer, liver dysfunction, interstitial pneumonia, and cytopenia
Anticoagulant drugs			
Warfarin potassium	Treatment and prevention of thromboembolism such as myocardial infarction and venous thrombosis	0.16 mg/kg/day, less than 12 months of age; 0.04–0.10 mg/kg/day, 1 year old to less than 15 years old, once daily, oral administration; dosage is adjusted to the target range of PT-INR 2.0–2.5* Adults: 1–5 mg/day, once daily, oral administration	*Contraindications*: bleeding, severe liver/kidney dysfunction, immediately after operation on the central nervous system, hypersensitivity, pregnancy etc. *Care with administration*: hepatitis, diarrhea, heart failure, sepsis, hypotension, neonates, malignancy etc. *Adverse effects*: hemorrhagic complications, dermal necrosis, liver dysfunction, hypersensitivity, etc. Warfarin is likely to be influenced by diet (e.g. the effect is decreased by fermented soybeans and green juice, and increased by poor eating), and interacts with many drugs
Heparin sodium (unfractionated heparin)	Treatment and prevention of thromboembolism such as myocardial infarction and venous thrombosis	10–20 units/kg/h, continuous intravenous infusion (bolus dose of 50 mg/kg may be infused intravenously at the start); dosage is adjusted to the target range of 1.5–2.5 fold APTT or ACT* Adults: diluted as 10–30 units/mL, intravenous infusion at the start, 1.5 mL/min, followed by continuous infusion, 1.0 mL/min; or 5,000–10,000 units, intravenous administration, every 4–8 h	Relative contraindications or care with administration: bleeding, severe liver/kidney dysfunction, immediately after operation or trauma to the central nervous system, hypersensitivity, heparin-induced thrombocytopenia etc. Adverse events: shock, bleeding, thrombocytopenia, liver dysfunction, hypersensitivity etc. Be aware of interactions with anticoagulants, thrombolytic agents, and antiplatelets

*Pediatric usage and dosages are not described in the product information leaflet, but dipyridamole is applicable for insurance reimbursement with regard to cardiac sequelae of Kawasaki disease. ACT, activated clotting time; APTT, activated partial thromboplastin time; PT-INR, Prothrombin time international normalized ratio.

ingly blood tests should be performed about once every 2 weeks during the 2 months after the start of drug administration.

d. Other Drugs

The following antiplatelet drugs are not covered by insurance for adults with IHD or for children. Flurbiprofen, an inhibitor of COX-1, is empirically used for acute KD patients with liver dysfunction,[268] but it has not been proved by enough evidence whether there is less liver dysfunction with flurbiprofen than with aspirin. Cilostazol, an inhibitor of phosphodiesterase, needs to be used carefully in patients with significant coronary stenosis because it increases heart rate.[146] Prasugrel[269] and ticagrelor,[270] new $P2Y_{12}$ inhibitors, are reported to be used for children with sickle cell disease.

1.3.2 Anticoagulants

a. Warfarin Potassium

Warfarin has a chemical structure similar to vitamin K, and inhibits production of vitamin K-dependent coagulation factors in the liver, resulting in its anticoagulant effect. Warfarin is covered by insurance for thromboembolism including MI and venous thrombosis in children as well as adults. The dose for children (0.16 mg/kg/day in younger than 12 months of age and 0.04–0.10 mg/kg/day in ≥1 year age and <15 year old) is orally administered once a day. Because the susceptibility to warfarin is individually different and can change in the same individual, the dose has to be regularly adjusted using PT-INR. Administration to pregnant women is contraindicated because of the risk of teratogenicity and tendency for bleeding. The effect of warfarin is susceptible to dietary and drug interactions; its effect is decreased by fermented soybeans (natto), green juice, and formula milk fortified with vitamin K, and increased by breast feeding and reduced feeding. When any drugs are used in combination with warfarin, they should be adjusted by referring to the package leaflet and the proper use information.[271]

The indication of warfarin for KD is giant aneurysm (gAN), past history of MI, and thrombosis in CAA; the dose is adjusted to the PT-INR target range of 2.0–2.5, considering age, the high risk of bleeding in infants, and clinical condition.[256,272] Even if the CAA is classified as medium aneurysm (mAN) based on the acute diameter, cardiac events are high in infants with a body surface area <0.5 m^2, with CAA ≥6 mm,[89] and therefore the indication of warfarin should be decided by referring to the Z-score of the CAA diameter. A retrospective study of KD patients with gAN in Japan showed that the incidence of MI was significantly less in the combination therapy group treated with aspirin and warfarin than in the aspirin alone group,[273] and the freedom from cardiac events was relatively good (92.5% at 1 year and 91% at 10 years) in patients receiving the warfarin and aspirin combination therapy.[274]

Because most MI (87.1%) occur within 18 months after the onset in patients with gAN,[122] anticoagulation therapy should be managed strictly during this period. If a gAN persists, there is no point of view on the appropriate period of warfarin administration,[256] although it was reported to be at least 5 years.[275] Warfarin cannot prevent MI perfectly,[122,140] and has the problem of a high incidence of bleeding,[276] so the long-term indication should be decided by taking both risks and benefits into consideration.

b. Heparin Sodium (Unfractionated Heparin)

Heparin sodium activates antithrombin III, and inhibits thrombin, IXa–XIIa factors, and kallikrein, and thereby suppresses blood coagulation. Treatment and prevention of thromboembolism is covered by insurance in adults, but not children. For children, the intravenous maintenance dose, 10–20 units/kg/h, is infused continuously with or without a bolus intravenous administration of 50 mg/kg over 10 min.[256] In some institutions, the dose is started lower, 5–8 units/kg/h, and increased appropriately taking the risk of bleeding into consideration. The present guideline recommends the target value of activated partial thromboplastin time (APTT) as 1.5–2.5-fold that of control, which corresponds to approximately 46–70 s (≈50–60 s twice),[256] with reference to the Japanese guideline for adults.[266,277] Bleeding including potential, severe liver or kidney dysfunction, immediately after operation or trauma of the central nervous system, hypersensitivity, and past history of heparin-induced thrombocytopenia are relative contraindications.

c. Other Drugs

As heparins or heparinoids, heparin calcium, subcutaneous injection formulation, low-molecular heparin to inhibit Xa factor by combination with antithrombin III, danaparoid, fondaparinux, and others are available, but none of them are covered by insurance in children. As recently developed direct oral anticoagulants (DOAC), 4 drugs, dabigatran, rivaroxaban, apixaban, and edoxaban, are used mainly for atrial fibrillation in adults. Although none of them is not covered by insurance in children, clinical trials of rivaroxaban are ongoing for children with deep vein thrombosis and after Fontan operation. A clinical trial of DOAC for KD is expected.

Evidence Required in the Future

- Indication of the combined therapy with aspirin and other antiplatelets.
- Comparison of DOAC for large CAA on warfarin therapy.

1.4. Coronary Vasodilators and Antianginal Drugs (Table 13)

- Beta-blockers, Calcium antagonists, or nitrates to prevent ACS in patients with CAL (Class IIb, Level C).

1.4.1 β-Blockers

Beta-blocker is administered to prevent reinfarction after MI, sudden death, and long-term mortality. Beta-blocker reduces myocardial oxygen demand, which induces antianginal effects, increased diastolic coronary blood flow, reduced ischemia, and reduced cardiac events. However, in patients with coronary spasm, β-blocker may exacerbate coronary spasm by increasing α-receptor activity because of the β-receptor blockade. The usefulness of carvedilol, an antioxidant and α- and β-blocker, has been studied in adults and children with heart failure. β-receptor selective metoprolol and bisoprolol have also been shown to be effective in patients with KD.[275,278] The American Heart Association guidelines on KD[2] recommend empirical treatment with β-blockers be considered for patients with gAN (Class IIb; Level C).

1.4.2 Calcium Antagonists

In KD patients, MI, which may be considered to be associ-

Table 13. Indications, Dosage, Administration, and Precautions for Coronary Vasodilators and Antianginal Drugs in Kawasaki Disease

Drug name	Indications	General dosage and administration	Major contraindications, care with administrations, and adverse drug reactions
β-blockers			
Carvedilol	Chronic heart failure caused by essential hypertension, renal parenchymal hypertension, angina pectoris, ischemic heart disease extension type cardiomyopathy, or tachycardic atrial fibrillation	Starting dose is 0.05 mg/kg twice daily. If tolerated, patients may have their dose increased to 0.1–0.4 mg/kg twice daily* Adult dosage and administration: angina pectoris: 20 mg once daily; chronic heart failure: starting dose is 1.25 mg twice daily. If tolerated, patients may have their dose increased to 2.5–10 mg twice daily	*Major contraindications*: bronchial asthma, diabetes acidosis, serious bradycardia, cardiogenic shock, noncompensated heart failure, right heart failure caused by pulmonary hypertension, pregnancy *Care with administration*: hypoglycemia, diabetes mellitus, or severe hepatic or renal failure *Adverse drug reactions*: serias bradycardia, complete AV block, shock, cardiac failure, hepatic injury, acute renal failure, toxic epidermal necrolysis, anaphylaxis
Metoprolol	Angina pectoris, tachycardic arrhythmia, chronic heart failure caused by essential hypertension	1–2 mg/kg/day, divided 2 or 3 times* Adult dosage and administration: angina pectoris or tachycardiac arrhythmia: 60–120 mg/day divided 2 or 3 times	*Major contraindications*: hypersensitivity, diabetic acidosis, serious bradycardia, cardiogenic shock, right heart failure because of pulmonary hypertension, congestive heart failure, pregnancy *Careful administration*: bronchial asthma, hypoglycemia, diabetes mellitus, severe hepatic or renal failure, bradycardia, variant angina pectoris *Adverse drug reactions*: cardiogenic shock, congestive heart failure, AV block, sick sinus syndrome, bronchial asthma, hepatic injury
Calcium-channel blockers			
Nifedipine	Essential hypertension, renal parenchymal hypertension, angina pectoris, variant angina pectoris (CR tablet only)	1–2 mg/kg/day, divided 2 or 3 times (CR tablet: once or twice)* Adult dosage and administration: 10 mg, three times daily L tablet: 20 mg twice daily for angina pectoris CR tablet: 40–60 mg once daily for angina pectoris	*Major contraindications*: hypersensitivity, cardiogenic shock, or pregnancy *Care with administration*: subaortic or submitral valve stenosis, serious hypotension, serious hepatic or renal dysfunction, congestive heart failure *Adverse drug reactions*: erythroderma, agranulocytosis, thrombocytopenia, hepatic injury, disturbance of consciousness
Amlodipine	Hypertension, angina pectoris	2.5 mg once daily for 6 years old or older (not applicable for 5 years old or younger: 0.06–0.3 mg/kg/day once daily*)	*Major contraindications*: hypersensitivity, pregnancy *Care with administration*: serious hypotension, hepatic injury, serious renal dysfunction *Adverse drug reactions*: fulminant hepatitis, hepatic injury, agranulocytosis, leukopenia, AV block, rhabdomyolysis
Diltiazem	Essential hypertension, angina pectoris, variant angina pectoris	1.5 mg/kg/day divided 3 times* Adult dosage and administration: 30 mg three times daily (patients may have their dose increased to 60 mg three times daily)	*Major contraindications*: serious congestive heart failure, 2nd-degree or more AV block, sick sinus syndrome, hypersensitivity, pregnancy *Care with administration*: congestive heart failure, serious bradycardia, severe hypotension, serious hepatic injury *Adverse drug reactions*: complete AV block, serious bradycardia, congestive heart failure, erythroderma, hepatic injury
Nitrates			
Isosorbide dinitrate	Angina pectoris, myocardial infarction (except for acute phase), other ischemic cardiac disease	Oral: 0.5–1 mg/kg/day divided 3–4 times Other dosage forms: weight conversion with reference to adult dosage* Adult dosage and administration: per oral or sublinguinal: 5–10 mg three or four times daily Tape: 40 mg every 24–48 h Spray: 1.25 mg once into oral cavity	*Major contraindications*: serious hypotension, cardiogenic shock, angle-closure glaucoma, brain injury, severe anemia, hypersensitivity, concomitant use of PDE5 antagonist *Care with administration*: pulmonary arterial hypertension, hypertrophic obstructive cardiomyopathy *Adverse drug reactions*: hypotension, headache, palpation, vertigo, rash
Nitroglycerin	Angina pectoris, myocardial infarction, cardiac asthma	0.1–0.15 mg once sublinguinally* Adult dosage and administration: 0.3–0.6 mg once subliguinally. If ineffective, add same dosage	*Major contraindications*: serious hypotension, cardiogenic shock, angle-closure glaucoma, brain injury, severe anemia, hypersensitivity, concomitant use of PDE5 antagonist *Care with administration*: pulmonary arterial hypertension, hypertrophic obstructive cardiomyopathy *Adverse drug reactions*: hypotension, headache, palpation, vertigo, rush

*Pediatric usage and dosages are not described in the product information leaflet. However, carvedilol and nifedipine are reimbursed for chronic heart failure and hypertension, respectively, in children. CR, control released; L, long acting.

ated with coronary spasm, can develop at rest or during sleep.[279] In adults, long-acting Ca antagonist (amlodipine) can reduce coronary events in patients with AP and myocardial ischemia after MI. However, their use is limited to patients with congestive heart failure or absence of atrioventricular block.

1.4.3 Nitrates

In an examination of dilatability by nitrate (isosorbide nitrate) on coronary angiography (CAG) in the convalescent phase of KD, the dilatability at both the aneurysm (7–8%) and site of regressed aneurysm (11–14%) was impaired compared with normal site (16–19%). At impaired sites, which have poor endothelial cell dysfunction, an expansion effect on acute ischemia cannot be expected.[280] Sublingual or oral administration should be considered for AMI. Do not use nitrate excursively because long-term use can induce tolerance.

Evidence Required in the Future

- Myocardial protective effect of β-blocker for KD patients with gAN.

1.5 Thrombolytic Therapy and Reperfusion Therapy

- In addition to ECG and ultrasonic cardiography (UCG), brain natriuretic peptide (BNP) (or N-terminal pro-BNP [NT-proBNP]) and troponin (TnT or TnI) measurements are mandatory for the diagnosis and assessment of severity of ACS (Class I, Level C).
- Reperfusion therapy both within 12 h from the onset and within 2 h of the hospital visit is recommended for AMI with ST-elevation or with complete left bundle branch block. Although primary percutaneous coronary intervention (PCI) is ideal in patients with suitable body size for catheter intervention, thrombolytic therapy is recommended in cases of ACS in small children complicated by KD (Class I, Level C).

The most major cause of death in KD complicated by coronary sequelae is myocardial ischemia by newly developed thrombi at the site of coronary stenosis located at the inlet or outlet of an aneurysm.[122] The risk of thrombotic occlusion is the highest in patients with so-called "giant" aneurysms (i.e., Z-score ≥10 or diameter ≥8 mm). Although asymptomatic coronary artery occlusion could be found incidentally, AMI and death are most frequent within 1–2 years from the onset of KD.[281,282] Vascular occlusion during the remote phase of KD is believed to be caused by mixed effects of vascular endothelial malfunction, congestion of coronary blood flow, and abnormality in coagulation of the fibrinogenolysis system.[275,283] There is no research with high-level evidence concerning thrombolytic therapy for the coronary sequelae of KD; consequently, the recommendation is based on the evidence in the field of atheromatous IHD in adults.

The pathophysiology of myocardial ischemia has been classified into MI and AP, based on the presence or absence of myocardial necrosis. However, the presence of myocardial necrosis can be confirmed only after serial measurement of myocardial biomarkers, which is not necessarily practical in the clinical situation requiring urgent diagnosis and treatment. Here, the definition of ACS is derived from the JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome:[146] ACS is the clinical spectrum of unstable IHD, in which myocardial ischemia/necrosis is caused by rapid narrowing/obstruction of the coronary artery as a consequence of thrombogenesis.[146] Similar to ACS in adults, its diagnosis and severity in patients with KD is judged by abnormal ST-T changes on ECG, focal myocardial dyskinesis on echocardiography, elevation of myocardial biomarkers, and increased BNP or NT-proBNP. Because the sensitivity of creatine kinase (CK) and its myocardial-bound fraction (CK-MB) as biomarkers for myocardial necrosis is low, TnT and TnI are recommended for that purpose.

To improve the prognosis of ACS, adequate coronary reperfusion (TIMI3) is mandatory irrespective of whether by systemic thrombolysis or PCI. The ACC/AHA/SCAI (Society for Cardiovascular Angiography and Interventions) guideline[283a] recommend that thrombolytic therapy should be performed within 12 h from the onset of AMI. In Japan, primary PCI without preceding thrombolytic therapy is usually performed, especially for cases within 90 min of hospital arrival. However, there is not enough evidence on whether thrombolysis or primary PCI should be adopted in children with coronary aneurysms complicating KD. It is partly because there are few patients with ACS complicating KD in comparison with atheromatous ACS, and primary PCI for pediatric patients can only be per-

Table 14. Thrombolytic Therapy for Thrombotic Coronary Occlusion in Kawasaki Disease*

Indication		Within 12 h of onset of ACS Asymptomatic coronary thrombosis		
Drugs		3rd-generation	Monteplase	Recombinant modified t-PA
		2nd-generation	Alteplase	Recombinant t-PA
		1 st-generation	Urokinase	
Administration		Systemic IV infusion Intracoronary thrombolysis should be considered in cases of modest effect		
Doses	IV or DIV	Monteplase	27.5×10^3 U/kg	IV injection for 2–3 min
		Alteplase	$290–435\times10^3$ U/kg (0.5–0.75 mg/kg)	IV injection of 10% of the total dose for 1–2 min, DIV of the remaining 90% for 60 min
		Urokinase	$10–16\times10^3$ U/Kg	DIV for 30–60 min
	Intracoronary	Urokinase	4×10^3 U/kg	Intracoronary infusion for 10 min; repeatable no more than 4 times

*Safety and effectiveness are not established in children. Alteplase (Activacin®, Grtpa®); Monteplase (Cleactor®). ACS, acute coronary syndrome; DIV, dripping intravenous infusion; IV, intravenous injection; t-PA, tissue plasminogen activator.

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formed at a limited number of facilities. Moreover, in cases of gAN it is often difficult to pass a catheter through the stenosis/occlusion site, even by experienced interventionists. Consequently, whether PCI is adopted or not should be decided prudently and systemic thrombolytic therapy is often selected for children for the following reasons. Firstly, ACS as a KD sequela is mainly caused by thrombotic occlusion of coronary aneurysm, and secondly, bleeding complications are less common in children than in adults. In addition, PCI in children is usually more difficult than in adults because of their smaller body size.

The effectiveness of thrombolytic therapy in patients with AMI manifested by ST-elevation or accompanied by complete left bundle branch block (CLBBB) has been established. In fact, the sooner thrombolytic therapy is initiated within 12 h from the onset, the less deaths and complications occur. When primary PCI cannot be performed within 12 h from the onset of ACS and within 2 h of hospital arrival, systemic thrombolysis is recommended.[146] If PCI can be performed within 3–24 h after thrombolysis, PCI could be further performed with the expectation of greater efficacy. Nonetheless, in cases of recurrent cardiac arrest or with a long period of resuscitation after AMI, thrombolysis is a relative contraindication because of the risk for serious bleeding.

Urokinase, tissue plasminogen activator (t-PA), or modified t-PA are usually administered for thrombolysis (**Table 14**). Urokinase has little tissue affinity and activates the fibrinolytic system. In contrast, t-PA has potent tissue affinity and modified t-PA has a long biological half-life. Therefore, the last 2 drugs can reduce the total dosage and thus can be administered in a rapid single infusion. However, the indication for thrombolysis should be carefully judged when additional PCI such as stent insertion is required. Repeat administration of t-PA might be avoided in these circumstances.

Evidence Required in the Future

- Indication for thrombolytic therapy caused by ACS in cases of gAN, as well as the indication and selection of patients for primary PCI.

1.6 Initial Medical Treatment of Acute Myocardial Infarction

- Primary PCI is recommended for the early phase of AMI, if possible; when it is difficult to perform, systemic thrombolysis with intravenous infusion of urokinase or t-PA should be done (Class I, Level C).
- When the effectiveness of systemic thrombolysis is insufficient, intracoronary thrombolysis (ICT) should be taken into consideration (Class I, Level C).
- Circulatory collapse because of acute heart failure may require continuous dripping intravenous infusion (DIV) of diuretics, dopamine, dobutamine, and/or phosphodiesterase inhibitor (Class I, Level B).
- Carperitide and nicorandil may be effective in AMI in children as well as in adulthood, although their safety and effectiveness have not been established in children (Class IIb, Level C).

Vigorous crying and vomiting often can be the first symptoms of AMI or AP in infants and toddlers. Children may not be able to properly describe severe chest pain. Therefore, chest X-ray, 12-lead ECG, echocardiography, and blood sampling for laboratory tests should be performed when children with a past history of KD, especially those with coronary sequelae, develop those suspicious signs and symptoms of coronary ischemia. Significant ST-T changes may not be present on ECG in the early phase of MI; hence, it is important to record serial ECGs.

The treatment strategy of AMI complicating KD is to reperfuse the ischemic myocardium as soon as possible, which is quite similar to treatment for ACS in adulthood. However, primary PCI is quite often impossible in cases of MI in early childhood. Moreover, transfer to facilities where PCI can be performed is usually time-consuming. Therefore, systemic thrombolytic therapy by intravenous infusion of urokinase or t-PA may be frequently required instead of primary PCI.[256] There has been no large-scale clinical research of thrombolytic therapy in only patients with KD. In adult patients with AMI manifested by ST-T elevation, systemic thrombolysis is recommend when primary PCI is unable to be performed within 12 h from the onset of AMI and within 2 h from hospital arrival. The effectiveness of intravenous heparin infusion for ACS was established before the advent of reperfusion; heparin infusion under APTT monitoring during primary PCI may be recommended even after urokinase or t-PA infusion.[146] According to a nation-wide survey in 2004–09 concerning of patients with ACS complicating KD conducted by the Ministry of Health, Labor and Welfare, systemic thrombolysis was performed for those patients with asymptomatic intracoronary thrombosis, and ICT was performed in 5 of these patients with STEMI. It is noteworthy that ICT within several hours from the onset of AMI was effective in patients with coronary aneurysms of no more than 10 mm diameter.[284] Based on evidence established in atheromatous ACS, it would be acceptable to perform PCI in school-age children, or older, with a past history of KD complicated by ACS.[2]

Standard medical therapies for AMI are as follows: oxygen administration, secure IV line, administration of analgesics and sedatives, maintenance of circulatory stability (against cardiogenic shock), therapies focusing on anti-heart failure and antiarrhythmia. Both analgesics and sedatives are critical, because persistent chest pain will provoke increased myocardial oxygen demand. Diuretics, dopamine, dobutamine, and/or phosphodiesterase inhibitors will be carefully administered against acute heart failure, cardiogenic shock, systemic hypotension, and circulatory instability; in these cases, physicians should always be careful not to increase cardiac afterload.[146,285] Carperitide (natriuretic peptide) and nicorandil are valuable supportive therapies, but there is not established evidence in terms of pediatric ACS and acute myocardial ischemia complicating KD. Carperitide is known to have pharmacological effects of vascular dilatation and diuresis, to improve cardiac sympathetic nerve activity, and to prevent left ventricular remodeling by suppression of the renin-angiotensin-aldosterone system. Nicorandil reportedly demonstrates improvements the microcirculation and cardiac function in chronic heart failure.[146]

Evidence Required in the Future

- Indication and effectiveness of thrombolytic therapy for ACS caused by coronary aneurysms, especially, the ideal therapy for ACS in every age group.

2. Nonpharmacological Therapy

2.1 Catheter-Based Therapy (Table 15)

- PCI for AMI is recommended to be performed by a skillful coronary interventionist, where emergency CABG is possible (Class I, Level C).
- The indication for elective PCI is the existence of myocardial ischemia.
- Percutaneous transluminal coronary rotational ablation (PTCRA) is a suitable procedure for localized stenosis (LS) with calcification (Class IIa, Level C).
- The diameters of reference vessels and the femoral artery in children are small, which is the limiting factor in the size of the guiding catheter and the selection of device.
- The management of gANs and severe coronary artery calcification, which are characteristics of CAL caused by KD should be considered carefully.

In IHD caused by atherosclerosis, PCI is indispensable for coronary revascularization as well as CABG.[286–288] However, the age of coronary revascularization in patients with CAL caused by KD ranges from children to adults. In this population, the goal is to maintain quality of life (QOL) for a long life. It is speculated that the prevalence of coronary revascularization in this population is less than 1%.[289,290] In small children, the diameters of reference vessels and the femoral artery are small, and the size of the guiding catheter suitable for use with a larger balloon or burr is limited by the diameter of the femoral artery.[291] The culprit lesions are complicated with gANs and severe calcification, and their morphology varies with each lesion. Therefore, the role of PCI in this population has not been established and the level of evidence is low.

2.1.1 Emergency PCI

The purpose of emergency PCI is reduction of myocardial ischemia, decrease in myocardial infarct size, prevention of death from acute cardiac event and improvement of long-term prognosis.[282,292] The indication of PCI for AMI is within 12 h after the onset of AMI. Revascularization is needed as soon as possible[146] (Class I, Level C).

a. Thrombolysis

Thrombolysis should be performed in either small children who cannot undergo PCI or in the situation of early PCI unable to be performed. (please see **IV-1.5**)

b. Primary PCI

PCI should be performed by a skillful coronary interventionist. It should be performed in the institution which emergency CABG is possible, because it is needed to manage the cardiogenic shock that can often occur.

i. Aspiration Therapy

Thrombotic occlusion in a gAN is the cause of AMI in KD. The revascularization is often impossible by aspiration therapy alone, because of the massive thrombus in the gAN. In the addition, percutaneous old balloon angioplasty (POBA) and antithrombotic therapy such as argatroban are needed[293] (Class IIa, Level C).

ii. POBA

POBA is often useful, when revascularization by thrombolytic therapy alone is unsuccesful[131] (Class IIb, Level C).

Table 15. Catheter-Based Therapy: Class of Recommendation (COR) and Level of Evidence (LOE)

	COR	LOE
Emergency PCI		
Thrombolysis (childhood)	I	C
Thrombolysis (after adolescence)	IIa	C
Thrombus aspiration	IIa	C
POBA	IIa	C
Stent implantation (BMS)	–	–
Stent implantation (DES)	–	–
Intravascular imaging	IIa	C
Elective PCI		
POBA (regional stenosis without calcification)	IIa	C
PTCRA (regional stenosis with calcification)	IIa	C
Stent implantation (BMS)	–	–
Stent implantation (DES)	–	–
Anastomotic stenosis after CABG	I	C
Intravascular imaging	IIa	C
Myocardial ischemia evaluation (FFR iFR)	IIa	C

BMS, bare-metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; POBA, percutaneous old balloon angioplasty.

iii. Stent Implantation

The long-term results of stenting are unknown, although the early results after the procedure are good.[294,295] It is difficult to accurately evaluate the diameter of the culprit lesion, because of massive thrombus and the existence of aneurysms. Careful evaluation of the coronary artery wall by either intravascular ultrasound (IVUS) or optical coherence tomography (OCT) is needed. There are often some complications such as new appearance of aneurysm, or fracture and malapposition of the stent in the late period.[296–298] Stent implantation is desirable to avoid rather than to save a life. "Stent-less primary PCI" is better in this population.

2.1.2 Elective PCI

The purpose of elective PCI is to improve the symptoms and myocardial ischemia, and to prevent a future cardiac event.

The indication for elective PCI is a LS >75% with the symptoms of myocardial ischemia. It is desirable to detect myocardial viability by several modalities,[190,236] such as radioisotope stressed myocardial perfusion imaging, fractional flow reserve (FFR),[299] instantaneous wave-free ratio (iFR),[113] two-dimensional echocardiography (2DE), computed tomography (CT), magnetic resonance angiography (MRA), positron emission tomography (PET), treadmill test (TM), and coronary flow reserve (CFR).[291]

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a. POBA

It is effective for LS without calcification or aneurysm less than a few years after the onset of KD.[190,234,300–303] It is not effective for LS with severe calcification many years after the onset of KD. The evidence level is low because of the small number of reports. Because the extracellular matrix is rich and edematous during the intimal thickening in LS of the early period after KD, an effective minimum lumen diameter (MLD) with balloon angioplasty of about 8 atm is possible to get. Although there are good results immediately after POBA in cases of aneurysm, asymptomatic occlusion within 1 year has been reported. Most of the patients with a good indication are small children. Because there is not a commercially available guiding catheter for small children, each institution will need to design one for each patient. POBA should be performed carefully in the small patient with LS in the proximal site of the left anterior descending artery (LAD), because the inflated balloon can affect the left main trunk (LMT) (Class IIb, Level C).

b. PTCRA

Coronary artery calcification increases with aging after the onset of KD. PTCRA is suitable for LS with calcification.[302,304–306] The burr rotates at high speed to grind the arteriosclerotic lesion into small fragments. It should be performed by a skillful interventionist. The length of the culprit lesion is short in most cases. The incidence of complications such as perforation and peripheral thromboembolism is less compared with that in IHD caused by atherosclerosis. It is desirable that the indication of body size is adolescents and young adults. A MLD >2.25 mm cannot be insured, because the size of burr ranges from 1.25 to 2.25 mm. Because the size of the guiding catheter is >6Fr, PTCRA is limited by the diameter of the femoral artery in children.[291] With a larger MLD, upgrading to a larger burr is needed. Because the larger burr cannot be insured, asymptomatic occlusion and restenosis often occur in the late period.[26] The 1 year restenosis rate after the procedure is 10–30%. It is reported that there is no restenosis after re-PTCRA for 15 years; however, there has not been a long-term result more than 15 years.[304,306] Post-dilatation with a balloon >10 atm should be avoid, because it can cause new appearance of aneurysms in the late period. Therefore, some physicians do not use balloon dilatation[307] (Class IIa, Level C).

c. Stenting

Although there are good results in some case reports of stent implantation, such as bare-metal stent (BMS) and drug-eluting stent (DES), there are no long-term results.[126,308–314] Dual antiplatelet therapy (DAPT) is recommended after implantation of DES. Despite stenting, LS with calcification caused by KD can progress after the procedure with aging. As complications in the late period, restenosis, new appearance aneurysms, and fracture and malapposition of the stent have been reported.[296,297,312,313] Stenting should be carefully considered, because the long-term outcome remains unknown. It seems that "Stent-less PCI" is better.

d. Percutaneous Balloon Angioplasty of the Anastomotic Site of the Graft

POBA of the anastomotic site performed a few months after surgery can help prevent graft occlusion. The patency of internal thoracic artery (ITA) grafts in small children has been problematic, possibly because of anastomotic stenosis caused by the progressive intimal thickening that develops soon after the operation. When the vessel diameters are small, postoperative stenosis at the anastomotic site decreases the residual lumen of the ITA graft[315] (Class I, Level C).

e. Chronic Total Occlusion (CTO)

Although CTO is often detected, collateral arteries develop well in such cases. Some successful early results in cases of CTO have been reported;[316–318] however, some adverse effects occurred in the late period of more than 1 year, because most of the patients had undergone stent implantation. The indication for CTO must be considered from the viewpoints of effectiveness, adverse effects and invasiveness of the procedure. The indication for segmental stenosis also remains unknown.[297]

2.1.3 Intravascular Imaging and Functional Myocardial Ischemic Evaluation

These modalities are useful for the diagnosis, indication and selection of the procedure, and evaluation before and after the procedure. Intravascular imaging comprises IVUS and OCT, both of which can assist with measuring the minimal lumen area and evaluating the characteristics of the coronary wall.[307] OCT has higher resolution and lower extent in the visual points, compared with IVUS. In adults of IHD, a PCI-guided physiological ischemic myocardial evaluation such as FFR is recommended for determining the indication, when ischemia cannot be detected by the usual modalities in patients with severe coronary stenosis[113,299] (Class IIa, Level C).

2.1.4 Selection of PCI or CABG

In stable IHD, PCI for 1-vessel disease is recommended, whereas CABG is recommended for multivessel disease or the left main lesion, depending on the SYNTAX score or complication with diabetes mellitus. However, it should be selected in this population, considering the following points: the morphology of the stenosis, age, body size, sex, adherence with medication, life plan, and long-term outcome, cost and risk.[238,291] The target of revascularization by PCI is the affected native coronary artery, and the graft is a new route to provide myocardial blood flow.[291] Although PCI for LS with gANs may improve myocardial ischemia, the existence of the gAN retains the possibility of thrombotic occlusion. There is a fundamental difference between PCI and CABG. The optimal timing for each procedure may be slightly different from the viewpoints of effect and complications.

Evidence Required in the Future

- Long-term results and outcome in patients who undergo emergency PCI.
- Long-term results and outcome in patients who undergo PTCRA.
- Long-term results and outcome in patients who undergo stenting.

2.2 Surgical Treatment (Table 16)

- In-situ left or right ITA (RITA) bypass grafting for the target branch in the left anterior descending and left circumflex (Cx) artery regions, which causes clinical ischemic symptom, or significant stenosis detected by FFR or scintigraphy (Class I, Level B).

Table 16. Indications for Surgical Treatment in Kawasaki Disease	
Coronary artery bypass grafting (CABG)	When severe stenosis in the proximal portion of a coronary artery causes myocardial ischemia, CABG should be considered. The in-situ left or right internal thoracic artery is the best conduit in CABG. For the right coronary artery, right gastroepiploic artery can be the option of choice. Saphenous vein graft should be avoided as far as possible. Fractional flow reserve or scintigraphy is helpful to determine the severity of stenosis and the presence or absence of ischemia, and to improve the outcome of CABG. The primary indications for CABG are: 1. Significant stenosis of the left main trunk 2. Multivessel disease 3. Stenosis in the proximal portion of the left anterior descending artery 4. Jeopardized collaterals Factors that should be taken into account for decision-making of CABG are: 1. History of myocardial infarction or identified myocardial ischemia, even for 1-vessel disease 2. Recanalization or collateral may influence patency of the bypass graft 3. CABG can be safely performed in young children aged 1 year. However, if the patient is young, graft patency rate can be less optimal. Deferral of CABG can be considered only when medical therapy is effective
Mitral regurgitation	Mitral valve repair or replacement can be indicated for severe ischemic mitral regurgitation
Severe left ventricular dysfunction	Left ventricular assist device or heart transplantation considered
Other complications	Cardiac tamponade, ventricular aneurysm, peripheral artery aneurysm or stenosis can be indications for surgical treatment

Modified from guideline for diagnosis and treatment of complications of Kawasaki disease, published in 1985.

- In-situ ITA bypass grafting for the target branch in the right coronary artery (RCA) regions, which causes clinical ischemic symptom, or significant stenosis detected by FFR or scintigraphy (Class IIa, Level B).
- Bypass grafting for patients with the LMT disease, 2-vessel or 3-vessel disease (Class I, Level B).
- CABG is the preferred modality of treatment for patients with a history of MI, poor left ventricular function, or coronary lesions unsuitable for PCI (Class I, Level B).
- Conventional on-pump CABG operation should be firstly considered (Class I, Level B).

2.2.1 Indications for CABG

Efficacy of CABG performed at the appropriate timing usually persists for a long time and provides favorable long-term survival. Kitamura and colleagues reported the 25-year outcomes of patients with KD complicated with coronary artery stenosis ≥75% and clinical symptoms of ischemia or ischemic findings on ECG or scintigraphy after exercise or drug stress test.[319] Tsuda and colleagues reported that of KD patients who underwent CABG younger than 12 years old, 59% had 1-vessel disease, 30% had 2-vessel disease, and 8% had 3-vessel disease.[320] Therefore, CABG should be considered even for 1-vesssel disease, especially in young patients, because the efficacy of PCI has not been proved. Moreover, for the same reason, CABG should be considered first for patients with ACS.[321]

Severity of the native coronary stenosis is the important predictive factor of long-term patency of bypass grafts. Especially, when the target has only stenosis of ≤50%, the bypass graft is frequently occluded. In addition, string sign is also frequently seen when the stenosis is 75%.[320] Therefore, preoperative evaluation of the severity of stenosis is crucial. Currently, visual assessment of stenosis is not considered reliable,[322] and FFR is the most popular and reliable modality of evaluating severity of stenosis in the adult population. Although FFR is not widely performed in children, its usefulness for child patients should be established in the future. Measuring the FFR can improve graft patency, even with fewer bypass grafts, and consequently, recurrence of angina and excessive consumption of grafts can be avoided.[323–325] Ogawa and colleagues reported that FFR and CFR were reliable tests for KD patients, similar to common adult patients. In addition, they report that the cutoff values in adult patients, which were 2.0 for CFR and 0.75 for FFR, were applicable to KD children.[114] Not only the CAL, but also findings on scintigraphy should be considered to achieve successful CABG.

2.2.2 Graft Patency and Conduit Choice

For child patients, who will grow, in-situ arterial grafts provide excellent graft patency. Wakisaka and colleagues reported that the patency rates of saphenous vein grafts (SVG) at 1, 10, 25 years were 84.4%, 57.2%, and 51.5%, respectively.[326] As atherosclerotic change of venous grafts progresses over the years, their use should be avoided if possible. The patency rates of ITA to LAD and the ITA to non-LAD are significantly higher compared with venous grafts.[320,326] The patency rate of the ITA was 87% at 20 years while that of the SVG was 44% at 20 years and gastroepiploic artery (GEA) at 5 years was 86%.[319] Even for non-LAD targets, the patency rates at 20 years of the ITA/GEA and SVG were 87% and 44%, respectively.[319] For patients aged more than 10 years, graft patency is higher than for patients aged less than 10 years. Kitamura and colleagues reported that the rates of ITA in patients aged more than and less than 10 years were 93% and 86%, respectively, at 10 years after operation. The rates for SVG in patients aged more than and less than 10 years were 58% and 25% at 10 years.[319]

In an observational study of 114 patients for 25 years, 4 ITA grafts presented the string sign in the short term and restored graft lumen as progression of native coronary stenosis in the late follow-up period.[1] Tsuda and colleagues reported that the graft patency rate of the ITA in patients younger than 12 years was 87% at 20 years after operation.[320] It has been proved that the ITA has growth potential,[327,328] while the SVG does not. Therefore, the anastomotic site or the target branch with a SVG can

Table 17. Summary of Treatment Options: Severity Classification, Class of Recommendation (COR) and Level of Evidence (LOE)

	Severity classification	COR	LOE
Aspirin	IV, V	I	C
	III	IIb	C
	I, II	III	C
Other antiplatelet drugs	IV, V	IIa	C
	III	IIb	C
	I, II	III	C
Anticoagulants	IV, V	IIa	C
	III	IIb	C
	I, II	III	C
Coronary vasodilator Antianginal drugs	V	IIa	C
	IV	IIb	C
	I, II, III	III	C
Statins Angiotensin II receptor blocker Angiotensin-converting enzyme inhibitor	III, IV, V	IIb	C
	I, II	III	C
Percutaneous coronary intervention	Vb	I	C
	Va	IIb	C
	I, II, III, IV	III	C
Coronary artery bypass grafting	Vb	I	B
	Va	IIb	C
	I, II, III, IV	III	C

present deformity.[326,328,329] Consequently, use of ITA grafts is considered safe and reliable for child patients.[330,331] Moreover, because thrombotic occlusion hardly occurs in the ITA graft, anticoagulant or antiplatelet drugs need not be prescribed for selected patients.

2.2.3 Surgical Management and Procedures

Jeong and colleagues[332] reported their experience of 25 CABG patients. Of 5 patients who underwent off-pump CABG, functional graft failure was seen in 9% and the rate of freedom from target vessel revascularization at 10 years was 86.5%; 3 of 40 ITA grafts were occluded.

Several randomized studies of on-pump vs. off-pump CABG for adult patients without KD have been reported. Kobayashi and colleagues reported the advantages of off-pump CABG, such as transfusion and neurological deficit with comparable graft patency.[333] On the other hand, some studies in the USA and Europe where on-pump CABG is prevalent showed that off-pump CABG was associated with less bypass grafts, lower graft patency rate, and higher rates of repeat revascularization or cardiac events.[334–336] It has been widely accepted that off-pump CABG is beneficial for patients with renal failure and chronic obstructive pulmonary disease or aged more than 80 years. Off-pump surgery is not recommended for the following reasons: the risks of stroke, renal and respiratory failure during cardiopulmonary bypass are extremely low, the ITA and target branch are quite small and the procedures are technically demanding, and very long term patency after operation is mandatory.

2.2.4 Clinical Outcomes of CABG

Indications for PCI or CABG should be decided by heart team conference, considering the specific characteristics of patients with KD, which are quite different from other patients.

a. Early Results

For patients with KD, CABG is reported to be sufficiently safe, even in children. The mortality rate in previous reports was nearly 0%, even when the patients had a history of MI, emergency, and poor ejection fraction.[319,330,337] In addition, the patency rate of the ITA graft is quite high. Even if anastomotic stenosis is seen on early postoperative angiography, percutaneous balloon angioplasty is reportedly effective to achieve long-term patency.[338,339]

b. Late Results

Kitamura and colleagues[319] examined the surgical outcomes of 114 patients, and reported that the survival rates at 10, 20, and 25 years after CABG were 98%, 95%, and 95%, respectively. They mentioned that the cause of death was mostly cardiac related. The rate of freedom from cardiac events, including death, MI, angina, syncope, ventricular fibrillation, PCI and repeated CABG, at 10, 20, and 25 years were 81%, 67%, and 60%, respectively.[319]

2.2.5 Indications for PCI and CABG

The devices and technique of PCI has been developing. For patients with KD, PCI is reported to be effective.[304] Surveillance in Japan reported by Muta and colleagues[238] described a survival rate after PCI that was similar to that after CABG as the first intervention of the coronary artery in KD. In that report, the repeat revascularization was less frequent after CABG and there was no benefit for patients younger than 12 years.

Dionne and colleagues examined the clinical outcomes in 5 Canadian institutions, and reported that the rates of survival and freedom from repeat revascularization after CABG were 100% and 100%, respectively, while those after PCI were <50%, which was significantly lower than for CABG.[340] Tsuda and colleagues mentioned that for patients younger than 12 years, CABG is considered favorable,[320] whereas PCI is beneficial for treating anastomotic stenosis after CABG.[326]

2.2.6 Surgical Treatment for Coronary Artery Aneurysm

Decreased velocity of blood flow in the aneurysm can cause thrombus formation and MI. Anticoagulant or warfarin is administered to prevent these complications. On the other hand, the wall of aneurysm is usually thickened and calcified. It is true that rupture of aneurysm associated with KD never or hardly occurs. This should be considered separately from aneurysm formation associated with coronary pulmonary artery fistula. Previously, resection or aneurysmorrhaphy combined with CABG, aimed at avoiding thrombus formation or anticoagulant administration, were

reported occasionally.[341] However, safety and efficacy have not been generally accepted. Intimal degeneration or inflammation may be the cause of thrombus formation.[342]

2.2.7 Treatment of Left Ventricular Dysfunction

Mitral valve repair or replacement may be indicated for ischemic mitral regurgitation. Heart transplantation should be considered for patients with severe left ventricular dysfunction.

Evidence Required for the Future

- The impact of management of coronary aneurysm and anticoagulant therapy for survival and prevention of cardiac events.
- Relationship between anticoagulant therapy and the location and the size of CAA.

3. Summary of Treatment Options (Table 17)

V. Follow-up According to Life Stage

Overview

More than half a century has passed since the first report of Kawasaki disease (KD) in 1967. According to the Japanese nationwide survey of KD, the number of adults with a history of KD increased from 33,688 in 1998 to 136,960 in 2014, a 4-fold increase for the recent 15 years, which is close to half of the overall patients with a history of KD.[343,344] Considering the high morbidity rate (17.2–18.7%) of coronary involvement before and during the introductory period of intravenous immunoglobulin (IVIG) therapy, the number of adult patients with coronary involvement, including regressed aneurysms, amounts to 15,000 at present. According to the Japanese registry of all cardiac and vascular disease (J-ROAD) run by the Japanese Circulation Society, the annual number of acute coronary syndrome (ACS) in adults with a history of KD amounts to 92 and that of catheter intervention or bypass surgery for coronary involvement of KD is 60.[345] According to reports from the USA[2] and Japan,[5] KD etiology accounts for 5.0–9.1% among the number of acute myocardial infarctions (AMIs) in adults under 40 years of age, suggesting the importance of KD sequelae in adult cardiology clinics.

Therefore, coronary involvement after KD should be managed from convalescence, school-age, adolescence to the entire adulthood through the transition to adult care, suggesting the importance of management of the disease by life stage, from the viewpoint of lifelong cardiology. However, fundamental and clinical issues of the disease in adults are poorly understood, because of the limited number of reports, which include only retrospective studies and case series. Therefore, long-term management of the disease, including management of school children and adults, pharmacological and nonpharmacological therapy, and planning of pregnancy and delivery is performed at present, in accordance with the natural history of KD with coronary sequelae in childhood and the evidence of ischemic heart disease (IHD) in non-KD adults. However, it should be recognized that the coronary sequelae of KD are distinct from IHD in non-KD atherosclerotic adults with respect to the pathology and that the impact of aging and/or conventional coronary risk factors on the pathobiology of the disease in adulthood is unknown. In addition, there is the issue of missed KD in adult patients with IHD[5] and the transition issue, which is related to the seamlessness of the social system and of the strategy for dealing with social psychological issues.

Evidence Required for the Future

- Can a history of KD without coronary involvement be a risk factor of IHD in lifelong cardiology?
- Can the process of atherogenesis be superimposed on already established Kawasaki coronary sequelae in adulthood?
- What size of coronary dilatation in the convalescence of acute KD is a risk for premature ACS in adulthood?

1. Management at School

- We summarize the management of school life for patients with a history of KD, based on the severity of coronary arterial lesions (CAL).
- We describe the use of both the Ministry of Health and Welfare criteria (1983)[79] and Z-score for the severity criteria of CAL.
- There are no physical limitations (E-allowed*) in patients in severity classification groups I and II (there are no DLs in these groups).
- There are no physical limitations (E-allowed*) in the severity classification III group (regression group). In this group, the dilatations, including aneurysms, have regressed.
- Because patients with severity classification IV have DLs without stenosis, there are basically no physical limitations (E-allowed*), but it is D or E-prohibited* when they have giant aneurysms (gANs) (i.e., Z-score ≥10 or inside diameter ≥8 mm).
- There are physical limitations of various levels in the severity classification V group (with stenotic lesions). They have to follow the instructions of pediatric cardiologists.

*See **Figure 5**

The details of the long-term prognosis in patients with a history of KD is still unclear. There are still few reports of which type of CAL in the early stage of KD will create clinical problems in the mid- and long term.[122,125,137,140,346] Despite the insufficient evidence, the criteria for managing school life of patients with a history of KD is the presence or absence of CAL, and the severity classification in cases of CAL. This severity classification is described in guidelines (2013) given by the Japanese Circulation Society.[272]

Recently, use of the Z-score, which is an evaluation of CAL based on body surface area, was recommended in Japan[3] and by the AHA.[2] Until now, the Ministry of Health and Welfare criteria (1983) have been used in Japan for severity classification of CAL.[79] Both criteria now exist in the clinical setting, but they are not unified. Therefore, we address both criteria in the management of school life of children with a history of KD (**Table 18**). It is important that a family member, a school teacher, or a healthcare worker (chief physician) shares information about the

Table 18. Management of Kawasaki Disease at School

Severity classification of CAL			Z-score classification	Measured value (<5 years old)	School activity management	Long-term follow-up
I	No dilation		<2.5	<3.0 mm	No limitations for life or exercise E Allowed	No management required after 5 years from onset
II	Transient dilation					
III	Regression	(Acute phase) small aneurysm			No limitations for life or exercise E Allowed	(Referral to internal physician)
		(Acute phase) medium/ giant aneurysm				Referral to internal physician
IV	Remaining coronary aneurysm	Small aneurysm	2.5≤Z<5.0	≥3 mm to <4.0 mm	No limitation for life and exercise E Allowed	
		Medium aneurysm	5.0≤Z<10	≥4.0 mm to <8.0 mm		
		Giant aneurysm	≥10	≥8.0 mm	D "E prohibited" is possible when there is no change for >1 year	
V	Coronary artery stenosis	Without ischemia			E prohibited ("D" for giant aneurysm. "E prohibited" is possible when there is no change for >1 year)	
		With ischemia			A–D	

CAL, coronary artery lesions. Refer **Table 5**.

condition of the child(ren). The chief physician writes a detailed summary (**Figure 6**[347]) and instructions for school life management (e.g., instruction table for school life management in 2011 version, **Figure 5A**,**B**[348]). In addition, for more detailed information sharing, it is desirable that the family member, teacher concerned with school life, and the chief physician have discussions when management category D or more is necessary.

1.1 Children Without CAL in the Acute Phase

- Severity classification I or II (patients do not have any dilated lesions (DLs) in the acute phase, including transient dilatation until 1 month after the onset).
- Z-score classification <2.5; actual value <3 mm.

1.1.1 Management Instructions

◦ There are no limits on exercise at school.
◦ The follow-up period for children without any CAL in the acute phase is 5 years. Therefore, the management category in this group is "E-allowed" for these 5 years. After this, they are "No management required".
◦ If the patient enters elementary school before 5 years after onset, we provide an instruction table for school life management. If 5 years have passed before entrance to elementary school, they are "No management required".

1.1.2 Long-Term Follow-up

Children without abnormal findings such as ECG and UCG for 5 years after the onset of KD do not need follow-up.

1.2 Children With Regression (Regressed Group)

- Severity classification III (patients with remaining dilatation or more lesions developing after 1 month of the onset. However, CAL completely normalize during follow-up and a stenotic lesion is absent.)

1.2.1 Management Instructions

◦ There are no limits on exercise at school life (i.e., "E-allowed" for school life management, as in section 1.1.1).

1.2.2 Long-Term Follow-up

Children are recommended to undergo imaging studies such as computed tomography (CT), or magnetic resonance imaging (MRI) at the end of school life.
Even if CAL show regression, this group must have periodic check-ups because CAL with ≥6-mm inside diameter may progress to calcified lesion and/or a stenotic lesion after 10–20 years.

1.3 Children With Children With Aneurysm and Dilatation

- Severity classification IV (patients have had coronary arterial dilatations and aneurysms without a stenotic lesion since 1 month after onset).
  (i) Small aneurysm (sAN); Z score classification (2.5 ≤ Z- score <5), actual value 3 mm to <4 mm
  (ii) Medium aneurysm (mAN); Z score classification (5 ≤ Z <10), actual value >4 to <8 mm
  (iii) gAN; Z score classification (10 ≤ Z), actual value ≥8 mm.

1.3.1 Management Instructions

(i), (ii) sAN and mAN: no limits on exercise at school (i.e., "E-allowed" for school life management as in section 1.1.1).
(iii) gAN: physical limitations are necessary for "D" or "E-prohibited"
If a coronary lesion regresses: same as section 1.2.
If a stenosis lesion develops: same as section 1.4.

1.3.2 Long-Term Follow-up

This group must have periodic check-ups until they finish school (every 6 months to 1 year). After that, they should

[Revised in 2011]

School Life Management Table (for Elementary School Children)

Name M / F Birth date (years) School Grade Class Date

1. Diagnosis (findings)	2. Level of management	3. School sport club activity	4. Next visit	Name of institution:
	Management required: A, B, C, D, E	Name of club ( )	___ years ____ months later	Name of physician: (seal)
	No management required	Allowed (Note:)・Prohibited	or when symptoms develop	

[Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise]

Type of sport	Sport activity	Intensity of exercise		Mild exercise (C, D, E - allowed)	Moderate exercise (D, E - allowed)	Intense exercise (E - allowed)
	Basic exercise*	Warming-up exercise Exercise-play to improve athletic ability	Grade 1-2	Balance exercise-play (play consists of different body postures such as lying down, sitting up/down, and standing up)	Exercise-play using apparatus (grabbing, releasing, rotating, rolling or going through the apparatus)	Exercise-play to change location (crawling, running, jumping, and hopping)
		Warming-up exercise Exercise to improve athletic ability	Grade 3-4	Balance exercise (exercise consists of different body postures such as lying down, sitting up/down, standing up, and hopping)	Exercise using apparatus (grabbing, holding, rotating, and releasing the apparatus, and exercise using a rope)	Strength competition (push or pull the partner, or compete strength), combination of basic movements
		Warming-up exercise Strength-training exercise	Grade 5-6	Exercise to improve flexibility (including stretching), light walking	Exercise to improve techniques (Rhythmic exercise and exercise using a ball, hoop or clubs)	Full-body activities within a given time/course (short-rope jumping, long-rope jumping, long-distance running)
	Athletics	Running and jumping exercise-play	Grade 1-2	Walking in different ways, rubber rope jumping	Hopscotch	Full-strength foot race, straight-course relay race, relay race with low obstacles
		Running and jumping exercise	Grade 3-4	Walking and light standing broad jump	Slow jogging, light jumping (standing long/high jump)	Full-strength foot race, round-course relay race, low hurdle race, high/long jump with short running start
		Athletics	Grade 5-6			Full-strength sprint, hurdle race, high jump with running start, long jump with running start
	Ball sports	Games, ball games, tag (for early grades), games using goals or nets, baseball-type games (for middle grades)	Grade 1-2	Target shooting with ball throwing, bouncing and catching	Target shooting with ball kicking and holding, ball kicking, tag, encampment games	Competition-style exercise
			Grade 3-4	Basic ball handling (passing, catching, kicking, dribbling, shooting, and batting)	Simple games (games with basic exercises with modified rules to fit the place and apparatus used)	
		Ball sports	Grade 5-6			
	Apparatus gymnastics	Exercise-play using apparatus	Grade 1-2	Exercise-play using climbing frames	Exercise-play using monkey bars and wall bars	Exercise-play using mat, horizontal bars and vfaulting horse
		Apparatus gymnastics using mats, vaulting horse or horizontal bars	Grade 3-4 Grade 5-6	Basic exercises Mat exercise (basic movements such as forward roll, backward roll, handstand against wall, and bridging) Vaulting horse (basic movements such as jumping with legs apart) Horizontal bars (basic movements such as forward roll landing)	Basic techniques Mat exercise (e.g., forward/backward rolls, forward/backward rolls with legs apart, handstand against wall, and handstand with support) Vaulting horse (e.g., jumping with legs apart with short running start, jumping with legs folded, and forward roll on the horse) Horizontal bars (e.g., back hip circle with support, forward roll landing with a leg over the bar, front hip circle, and back hip circle)	Combination of gymnastic movements
	Swimming	Play with water	Grade 1-2	Play with water (foot race, playing train in swimming pool)	Floating and diving (e.g., prone float with hands against the wall, and paper-rock-scissors or staring game in water)	Relay race in the pool, bubbling, and bobbing
		Floating and swimming	**Grade 3-4**	**Floating (e.g., prone float, back float, jelly fish float)** Swimming movements (flutter kicks, frog kicks)	**Floating (e.g., kick and float)** Swimming (e.g., repeated bobbing, etc.)	**Crawl stroke and breaststroke with supportive apparatus**
		Swimming	Grade 5-6			Crawl stroke and breaststroke
	Dance	Rhythmic play	Grade 1-2	Pretend play (e.g, birds, bugs, dinosaurs, and animals)	Pretend play (e.g., airplane, fun-park rides)	Rhythmic play (e.g., bouncing, whirling, twisting, and skipping)
		Expression movement	Grade 3-4 Grade 5-6	Improvised expression movement	Light rhythmic dance, folk dance, simple Japanese folk dance	Combination of variable movements (rock and samba dance) Japanese folk dance with strenuous movements
	Outdoor activities such as play in the snow or on the ice, skiing, skating, and waterfront activities			Playing on snow or ice	Waking with ski plates or skates and waterfront activities	Skiing and skating
Cultural activities				Cultural activities without prolonged activities requiring physical strength	Most cultural activities not described in the right column	Playing instruments requiring physical exertion (such as trumpet, trombone, oboe, bassoon, horn), playing or conducting quick rhythmical music, playing in a marching band
School events and other activities				・Follow the above intensity of exercise during athletic festival, during athletic meetings, ball sports competitions, and exercise tests. ・Students other than those in Category "E" should consult with their school physician or their attending physicians in determining whether they will participate in other special school activities such as class trips, camp schools, seaside schools, and training camp. ・Consult school/attending physicians for the distance of running and swimming (refer to the school curriculum guideline)		

Remarks

Definitions Mild exercise: Physician activities that do not increase respiratory rate in average children at the same age.
Intermediate exercise: Physical activities that increase respiratory rate without causing shortness of breath. Players may talk with partners, if any, during exercise.
Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath.

* Basic exercise: including resistance (isometric) exercise.

Figure 5A. School activity management tables. Elementary School students, Junior and Senior High School students. Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise. Exercise intensity: Mild exercise: Physical activities that do not increase respiratory rate in average children at the same age, Intermediate exercise: Physical activities that increase respiratory rate without causing shortness of breath. Players may talk with others during exercise, and Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath. Express the allowed exercise intensity from "A" to "E". Only "E" will be noted as "Allowed" or "Prohibited" for school sport club activities, and will be referred to as "E-allowed" or "E-prohibited". (Adapted from Japanese Society of Kawasaki Disease.[348])

Advance Publication

[Revised in 2011]

School Life Management Table (for Junior and Senior High School Students)

Name M / F Birth date (years) School Grade Class Date

1. Diagnosis (findings)	2. Level of management	3. School sport club activity	4. Next visit	Name of institution:
	Management required: A, B, C, D, E	Name of club ( )	___ years ____ months later	Name of physician: (seal)
	No management required	Allowed (Note:) ・Prohibited	or when symptoms develop	

[Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise]

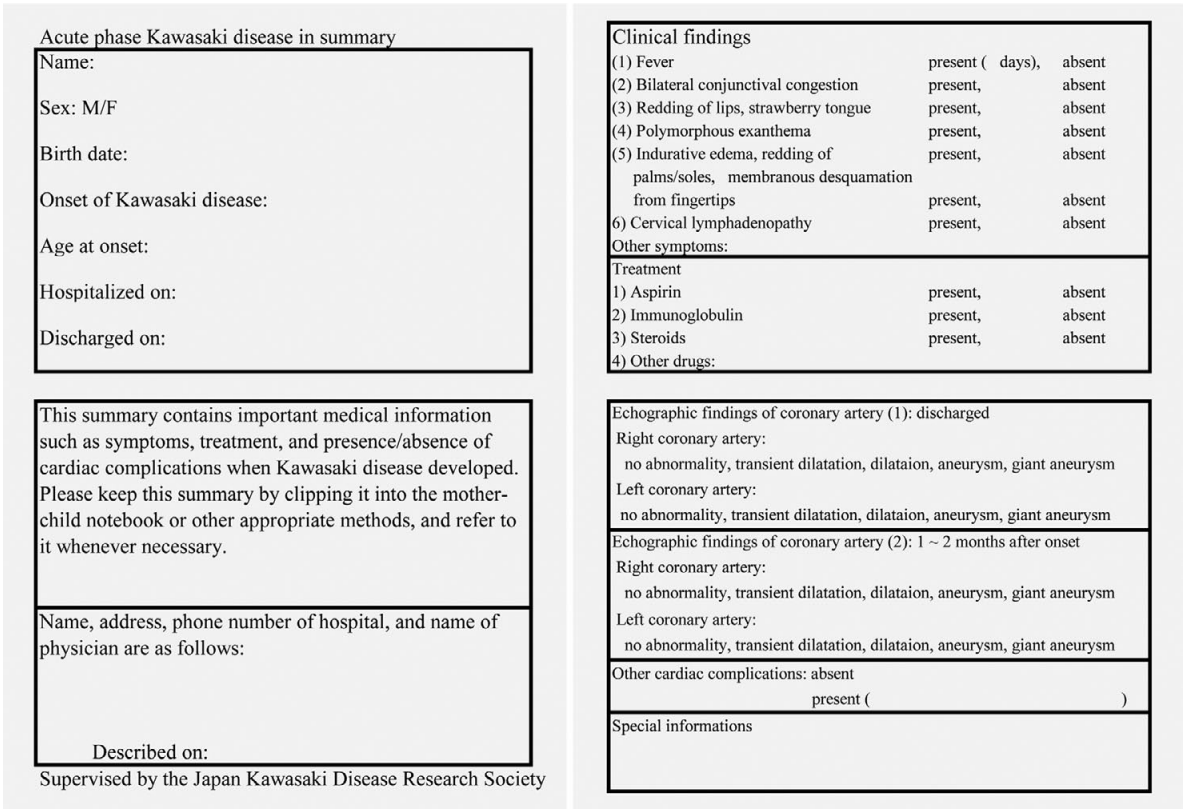
Sport activity \ Intensity of exercise				Mild exercise (C, D, E - allowed)		Moderate exercise (D, E - allowed)		Intense exercise (E - allowed)	
Type of sport	Basic exercise	Warming-up exercise Strength-training exercise		Light exercise or rhythmic movement to communicate with other students Basic movements (throwing, hitting, catching, kicking, jumping)		Exercise to improve flexibility, techniques, high-force movement, and endurance		Exercise with maximum endurance, speed, and muscle strength	
	Apparatus gymnastics	(Mat, vaulting horse, horizontal bar, and balance beam)		Calisthenics, light mat exercise, balance exercise, light jumping		Practice of low-grade technique, running to perform actions such as holding, jumping, and rotation		Performance, competition, combination of actions	
	Athletics	(racing, jumping, throwing)		Basic motion, standing broad jump, light throwing, light jumping (must avoid running)		Jogging, short run and jump		Long-distance running, sprint race, competition, time race	
	Swimming	(freestyle, breaststroke, backstroke, butterfly)		Easy movement in water, float, prone float, kick and float, etc.		Slow swimming		Competition, swimming marathon, time race, start and turn	
	Ball sports	Goal games	Basketball	Slow exercise without running	Basic movements (e.g., passing, shooting, dribbling, feinting, lifting, trapping, throwing, kicking, and handling)	Training with footwork (with no close body contact)	Simple games using basic movements (adjust games according to the time, space and apparatus available to practice collaborative playing, and offensive/defensive components)	Time race, applied practice, simplified game, game, competition	Competition
			Handball						
			Soccer						
			Rugby						
		Net games	Volleyball		Basic movements (e.g., passing, servicing, receiving, tossing, feinting, stroking, and shots)				
			ping-pong						
			Tennis						
			Badminton						
		Baseball-type games	Softball		Basic movements (e.g., pitching, catching, and batting)				
			Baseball						
		golf			Basic movements (light swinging)		Practicing at golf range		
	Martial arts	Judo, kendo, sumo		Etiquette, basic movement (e.g., ukemi, swinging, sabaki)		Practicing simple techniques and forms with modest basic movements		Applied practice, competition	
	Dance	Original dance, folk dance, modern dance		Basic movement (e.g., hand gesture, steps, expressions)		Dance with modest basic movements		Dance recitals	
	Outdoor activity	Play in the snow or on the ice, skiing, skating, camping, climbing, swimming marathon, water-front activities		Playing on water, snow, or ice		Walking with ski plates or skates, slow skiing/skating, hiking on flatlands, playing in the water, etc.		Climbing, swimming marathon, diving, canoeing, boating, surfing, wind surfing, etc.	
Cultural activities				Cultural activities not requiring long-term physical activity		Most cultural activities not described in the right column		Playing instruments requiring physical exertion (such as trumpet, trombone, oboe, bassoon, horn), playing or conducting quick rhythmical music, playing in a marching band	
Cultural activities not requiring long-term physical activity				・Follow the above intensity of exercise during athletic festival, during athletic meetings, ball sports competitions, and exercise tests. ・Students other than those in Category "E" should consult with their school physician or their attending physicians in determining whether they will participate in other special school activities such as class trips, camp schools, seaside schools, and training camp					

Remarks

Definitions Mild exercise: Physician activities that do not increase respiratory rate in average children at the same age
Intermediate exercise: Physical activities that increase respiratory rate without causing shortness of breath. Players may talk with
Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath.

* Basic exercise: including resistance (isometric) exercise

Figure 5B. School activity management tables. Elementary School students, Junior and Senior High School students. Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise. Exercise intensity: Mild exercise: Physical activities that do not increase respiratory rate in average children at the same age, Intermediate exercise: Physical activities that increase respiratory rate without causing shortness of breath. Players may talk with others during exercise, and Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath. Express the allowed exercise intensity from "A" to "E". Only "E" will be noted as "Allowed" or "Prohibited" for school sport club activities, and will be referred to as "E-allowed" or "E-prohibited". (Adapted from Japanese Society of Kawasaki Disease.[348])


Acute phase Kawasaki disease in summary

Name:

Sex: M/F

Birth date:

Onset of Kawasaki disease:

Age at onset:

Hospitalized on:

Discharged on:

This summary contains important medical information such as symptoms, treatment, and presence/absence of cardiac complications when Kawasaki disease developed. Please keep this summary by clipping it into the mother-child notebook or other appropriate methods, and refer to it whenever necessary.

Name, address, phone number of hospital, and name of physician are as follows:

Described on:

Supervised by the Japan Kawasaki Disease Research Society

Clinical findings

(1) Fever	present (days),	absent
(2) Bilateral conjunctival congestion	present,	absent
(3) Redding of lips, strawberry tongue	present,	absent
(4) Polymorphous exanthema	present,	absent
(5) Indurative edema, redding of palms/soles, membranous desquamation from fingertips	present,	absent
6) Cervical lymphadenopathy	present,	absent

Other symptoms:

Treatment

1) Aspirin	present,	absent
2) Immunoglobulin	present,	absent
3) Steroids	present,	absent

4) Other drugs:

Echographic findings of coronary artery (1): discharged
Right coronary artery:
no abnormality, transient dilatation, dilataion, aneurysm, giant aneurysm
Left coronary artery:
no abnormality, transient dilatation, dilataion, aneurysm, giant aneurysm

Echographic findings of coronary artery (2): 1 ~ 2 months after onset
Right coronary artery:
no abnormality, transient dilatation, dilataion, aneurysm, giant aneurysm
Left coronary artery:
no abnormality, transient dilatation, dilataion, aneurysm, giant aneurysm

Other cardiac complications: absent
present ( )

Special informations

Figure 6. A Card for Summary of acute-phase Kawasaki disease. (Adapted from Japanese Society of Kawasaki Disease.[347])

be referred to an internal medicine physician.
The testing and intervals should be taken into consideration case by case.
Because the 2 dimensional echocardiography findings and coronary angiography (CAG) findings may not be always same, it is desirable that the CAG evaluation is done at least once in patients with dilation and aneurysm. Pediatric cardiologists take into consideration the medical treatments in reference to **Table 17**.

1.4 Children With Stenotic Lesions in the Coronary Artery

- Severity classification V (patients with stenotic lesions confirmed by CAG)
- Physical limitations are required and they need instructions about follow-up and school life management from a pediatric cardiologist.

1.4.1 Stenotic Lesion (+), Myocardial Ischemia (–)

- Severity classification V(a) group (patients without ischemic findings on testing)

a. Management Instructions

gAN (−): school life management: "E-prohibited"
gAN (+): school life management: "D or E-prohibited"

- Patients require instruction on the need for medical treatment and adherence to medications.
- When we control international normalized ratio of prothrombin time (PT-INR) in the target range of 2–2.5 with warfarin, it is necessary for patients to pay attention to the side effect of bleeding tendency on aspects of both life and exercise.
- Provide information about both symptoms and the correspondence at ischemia.
- Conduct an evaluation of physical limitations by testing.
- When gANs remain, do not permit participation in athletic activity. The management instruction is "D". When there are no changes for 1 year after onset, it may become "E-prohibited".

1.4.2 Stenotic Lesion (+), Myocardial Ischemia (+)

- Severity classification V(b) (patients with evidence of myocardial ischemia (+) on testing)

a. Management Instructions

- Physical limitation is necessary: "D" or lower.
- No athletic activity: "A" to "D" category, based on evaluation of exercise tolerance and myocardial ischemia.
- Emphasize the importance of medication.
- Category of management instruction may change after results of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

1.4.3 History of Myocardial Infarction (MI)

- Severity classification V(b) (patients with clear ischemic findings on testing)

a. Management Instructions
- Limits on both life activities and exercise: "A" to "E" category on case by case basis based on cardiac function.
- Awareness of side effects such as bleeding tendency with medical treatment.
- No athletic activity is recommended.

1.4.4 Long-Term Follow-up (including 1.4.1–1.4.3)
- Periodic testing until they finish school. Transit patient to an internal medicine physician.
- Pediatric cardiologist will judge both the testing and the interval in reference to **Tables 7** and **11**).

1.5 Children With Lesions Other Than Coronary Artery Aneurysm (CAA) and CAL

1.5.1 Valvular Disease
- Pediatric cardiologists evaluate cardiac function and surgical indication.
- Pediatric cardiologists judge the level of activities of daily life and the limits on exercise based on evaluation of valvular disease.
- If valvular disease is recovered based on echocardiography, patient is "No management required".

1.5.2 Arrhythmia
- Pediatric cardiologists judge the level of activities of daily life and the limits on exercise If there are no problems with cardiac function, and there no sign of myocardial ischemia, follow an arrhythmic management guideline.[349]
- If there are problems with cardiac function, and are any signs of myocardial ischemia, the pediatric cardiologist judges the patient's overall condition.

1.5.3 Aneurysms Excepting the Coronary Arteries
- Pediatric cardiologists evaluate the site and size of aneurysms, and they follow the patient.

1.5.4 Post Cardiac Operation
- After KD patients undergo cardiac operations such as CABG, valvular surgery or heart transplant, it is necessary that pediatric cardiologists follow and manage these patients.

1.5.5 Vaccination
- Vaccines that are affected by antibodies from IVIG treatment are considered for measles, rubella, mumps, and varicella.[350] Patients should preferably receive live vaccines 6 months after IVIG unless there is an outbreak.

1.5.6 Lifestyle for Arteriosclerosis Prevention
- There is the concern that KD becomes an arteriosclerotic risk factor. Therefore, the pediatric cardiologist needs to instruct patients about a lifestyle for arteriosclerosis prevention in the future when they hand a card for summary of acute-phase KD (**Figure 6**).

1.6 Transition to Cardiovascular Physician
- Pediatric cardiologists need to transit patients with coronary artery sequelae to internal medicine physicians specializing in the cardiovascular system.
- It is very important for pediatric cardiologists to explain that the patient has CAL and needs to maintain medication and follow-up. The cardiologists should encourage follow-up to prevent the loss of follow-up (so-called dropout cases).

Evidence Required in the Future
- Long-term prognosis and management based on CAL severity classification, because children with CAL have to spend their school life safely.

2. Management of the Adolescent/Young Adult (AYA) Generation (Transition Medicine)

- Preventing the loss of follow-up (the so-called dropouts) is the most important issue in the management of the AYA generation (Class IIa, Level C).
- In healthcare transition, it is essential to keep in mind a management method that promotes the independence of the AYA generation (Class IIb, Level C).
- A transition checklist based on the growth timeline of each individual in the AYA generation is useful (Class IIa, Level C).

The important background to AYA healthcare transition is the psychological structure unique to this generation; that is, the life events they face, such as attending school, working, living alone, marriage, pregnancy and childbirth. A feature of the AYA generation is that each event is closely related to the loss of follow-up.

2.1 Definition of the Adolescent/Young Adult Generation and Population Background

Adolescents are generally from 12 to 18 years old; young adults are generally in their late teens to early 20s. In terms of age, the lower limit of the AYA generation is 12–15 years old and the upper limit is 24 years old as stated in many sources; some state that the upper limit is 29 or 39 years old.[351] Japan's AYA generation population (14.6%) exceeds that of children under 15 years old (12.2%).[352]

2.2 Adolescent/Young Adult Generation Suffering From Chronic Pediatric Diseases and Requiring Healthcare Transition

With the background of improving the survival rate from chronic diseases, healthcare transition for the AYA generation, which requires special treatment during childhood, has become an important theme.[353] Moreover, not only the AYA generation the midpoint of the time axis from childhood to adulthood, but unique issues such as the maturity of thinking and establishment of identity as adolescents also arise at this time,[354] so appropriate care that can go along with the growth and development of the AYA generation is essential.

The AYA generation accounts for 58% of unscheduled hospitalizations mainly for cardiac events in adults with congenital heart disease, which highlights the importance of the issues of pregnancy, medical insurance, and employment in the background of the AYA generation.[355] Moreover, there are reports that loss of follow-up in the AYA generation suffering from congenital heart disease can lead to a high risk of unplanned hospitalizations.[356,357] In addition, deaths of those in the AYA generation who have congenital heart disease are more likely to occur immediately after the transition to adulthood, which also highlights

this generation's relationship to immaturity.[358] These factors should be used as a reference for the healthcare transition model for coronary sequelae after KD because the disease backgrounds are similar.

2.3 Coronary Sequelae After KD and Healthcare Transition

2.3.1 Number of Patients

The Nationwide Survey on KD states that the total number of registrations exceeds 300,000, with 120,000 registrants being over the age of 20 years.[359] This suggests the importance of managing the AYA generation.

2.3.2 Characteristics of the Clinical Course and Adherence

Even patients with 2-vessel coronary artery disease or severe stenosis often progress asymptomatically. In particular, total occlusion of the right coronary artery (RCA) may be observed for the first time during periodic imaging, and as an asymptomatic cardiac event, it often leads to recanalization after occlusion. This is related to poor adherence and may progress to neglecting medication and even loss of follow-up.

2.3.3 Current Situation of Healthcare Transition

A questionnaire survey conducted by the Managing and Ethics Committee of the Japan Society of KD states that there are about 90% of patients who are in need of healthcare transition for coronary arterial sequelae, and 40% of physicians have had patients with coronary arterial sequelae drop out of follow-up.[360] In a report of cases of lost follow-up for myocardial perfusion imaging of coronary arterial sequelae after KD for patients aged over 15 years old, those with no history of medical check-up for 5 years and defined as lost to follow-up were 43% of the overall, and the frequency was as high as 61% for those under 20 years old at the time of examination.[361] Both of these findings suggest that managing coronary arterial sequelae after KD is essential.

2.3.4 Key Points of Healthcare Transition Management

Preventing loss of follow-up by patients is important, and the 4 points below should be considered.

a. Relationship Between Pediatrician and Adult Physician as a Barrier

Chronic coronary artery disease is a specialized field for cardiologists (adult physicians), and the barrier for disease intervention may be low. If information such as the collateral circulation unique to coronary arterial sequelae of KD is shared, then it is highly likely that cardiologists will be able to achieve the desired intervention for this disease.

Another barrier is the confusion of adult physicians towards the psychological care of the AYA generation who have needed therapeutic interventions since childhood, especially those with a strong dependency relationship with their guardians.[362] It is possible that this background reflects the report[360] of the desire of 72% of pediatricians that responsibility for patients who have transitioned to adulthood should be shared between the cardiologist and pediatrician.

b. Medical System as a Barrier

Creation of a medical summary is the first step to overcoming this barriers. It is useful to create a summary for transition that includes the pediatrician's past examination findings and management plans,[363] in addition to findings from selective CAG through cardiac catheterization, echocardiography,[364,365] coronary CT angiography,[176,216] magnetic resonance angiography (MRA),[225] and myocardial perfusion imaging.[190,197] If the goals and issues of AYA generation management can be recreated through a discussion between the pediatrician and cardiologist based on the summary, it can be shared as an active plan and will become a means to overcoming system barriers.

The healthcare insurance services of the AYA generation is also an issue in the system.

Table 19. Check List for the Transition Period of Kawasaki Disease

1.	Past history, complications, cardiac events, treatment history
2.	Details of examinations for coronary complications
3.	Drug ingredients, effects and side effects
4.	Long-term prognosis
5.	Necessity of lifelong medical care
6.	Necessity of transition
7.	Possible clinical symptoms
8.	Lifestyle management (eating habits, exercise, smoking, drinking, obesity prevention)
9.	Educational advancement, employment
10.	Marriage, pregnancy, birth, heredity
11.	Symptoms requiring emergency care and medical institutions for getting check-up
12.	Social security system (medical benefits system), health insurance (social insurance, national insurance, life insurance)
13.	Development of skills for daily living (negotiation, individual decision-making, problem-solving)

(Adapted from Mitani Y. 2018.[369])

c. Patient–Doctor Relationship in Connection to Healthcare Transition

Pediatricians and adult physicians must consider the patient's growth timeline and know the educational elements the AYA generation needs. In a statement of the American Academy of Pediatrics in 2017, along with the importance of educating the AYA generation on recognizing diseases that continue from early childhood, "fostering independence" is also mentioned.[366] Unilateral interaction between the guardian and physician while ignoring the AYA patient may hinder "fostering independence". In addition, education for children and the AYA generation consistent with their growth timeline towards transition preparation to actual practice is recommended as the Six Core Elements.[362] On the other hand, the AYA generation and their families may be dependent on pediatricians who have long provided their healthcare treatment, and this must also be considered along with "fostering independence." This background should also be recognized in the healthcare transition of patients with coronary arterial sequelae after KD.

d. Transition Checklist

For the AYA generation, it is important to visualize what is needed within the timeline of healthcare transition. A practical plan becomes necessary not only in terms of

Advance Publication

medical content but also educational factors and vocational choices.[367] Recommendations on healthcare transition for congenital heart disease in adults are also useful for the transition of patients with coronary arterial sequelae after KD,[368] and a transition checklist sample for KD based on this is presented in **Table 19**.[369]

3. Management of Adulthood

3.1 Treatment

3.1.1 General Management and Medical Therapy

- Lifelong follow-up of the KD patients without any coronary involvement from disease onset is not recommended (Class IIa, Level C). However, lifelong health education for conventional coronary risk factors is recommended (Class IIa, Level C).
- KD patients with any coronary aneurysms in the convalescent phase, even without ischemic findings, are candidates for transition management to adulthood. Lifelong management (Class IIa, Level B) and medical therapy (specified in the respective chapters) is recommended. Statins may be recommended in such adults for their anti-inflammatory effects (Class IIa, Level C). Dual antiplatelet therapy (DAPT) is appropriately recommended (Class IIb, Level C) and warfarin is recommended for adult patients with gANs, a history of AMI, and concern for thrombotic complication in the aneurysm (Class IIa, Level C). However, bleeding complication should be taken into consideration, especially in the elderly. Lifelong follow-up of patients even with regressed aneurysms is recommended (Class IIa, Level C).
- Any adult patients with severe comorbidities including ischemic findings associated with coronary stenosis, MI, heart failure or severe arrhythmia are categorized as the most severe cases and should be managed in accordance with the natural history of KD in childhood and the guidelines of IHD in non-KD adults (Class IIa, Level C).
- Because missed KD is presumed to account for a large percentage of the adult Kawasaki population, the diagnosis of KD should be made in collaboration between pediatric and adult cardiologists.
- The follow-up schedule should be tailored in accordance with the severity of the coronary involvement and the evidence or guideline of non-Kawasaki adult patients with coronary artery disease.

a. Patients Without Coronary Involvement After Onset of Acute KD

This patient group does not have any coronary involvement in the convalescence phase of acute KD, which accounts for approximately 97% of current de novo KD cases in Japan.[6] This group includes 2 subgroups of patients with and without coronary involvement during the acute illness. Lifelong follow-up is not recommended for these subgroups (Class IIa, Level C). As evidence to support this recommendation, almost all the fatal pediatric cases occurring long after KD onset were associated with coronary involvement at autopsy,[370] and adult cases of ACS with a confirmed history of acute KD did not include any patients without coronary involvement from disease onset.[5] However, because KD patients without coronary involvement from disease onset have subclinical coronary inflammation at autopsy,[371] and because it is unknown whether a history of KD increases the incidence of AMI in adults at the susceptible age for such events, it remains to be determined whether a history of KD without coronary involvement from disease onset could be a lifelong risk for coronary vascular disease. Therefore, education regarding conventional risk factors is recommended even after regular follow-up is discontinued (Class IIa, Level C). Regular follow-up with noninvasive investigation may be tailored in accordance with the request of the patient and the family.

b. Patients With Coronary Involvement at Convalescence and Without Any Ischemic Findings in Adulthood

This group includes 2 subgroups of patients with regressed or persistent aneurysms without ischemic findings, both of which account for the majority of candidates for transition to adult care. Persistent or regressed coronary aneurysms are associated with coronary intimal thickening in autopsy studies.[103] The evidence of endothelial dysfunction,[239,372] chronic inflammation,[373,374] and intravascular ultrasound (IVUS)-derived various intimal lesions in patients with coronary aneurysms,[375] and reports of the adult cases of ACS with persistent or regressed aneurysms as culprit lesions,[5] suggest lifelong follow-up of such patients in accordance with the schedule for long-term follow-up is recommended (Class IIa, Level B). Pharmacological therapy is recommended in accordance with the risk-stratified treatment schedule described in the pharmacological treatment section. Statins may be recommended for the anti-inflammatory effects, especially in adults (Class IIb, Level C).[374] DAPT is recommended in accordance with the risk stratification of the patients (Class IIb, Level C),[11] and add-on warfarin is recommended for patients with gANs, a history of MI, and thrombus formation in the aneurysm, especially in children (Class IIa, Level C).[274] However, the risk for hemorrhagic complication should be considered, especially in the older population. Lifelong follow-up of patients with regressed aneurysms, which account for the largest population of patients with coronary involvement after KD, is recommended (Class IIa, Level C). Pharmacological therapy may be considered individually in such patients.[5]

c. Adults With Ischemic Findings Related to Coronary Stenosis, MI, Cardiac Failure or Severe Arrhythmia

This group includes a subgroup of patients with ischemic findings related to coronary stenosis or MI, which is the most severe subgroup for management of the transition to adult care. Individualized treatment is required for associated conditions in accordance with the natural history of coronary sequelae after KD and guidelines of IHD treatment in non-KD adults. Regular follow-up, noninvasive investigation of the ischemia 3–4 times annually, and related coronary imaging (CAG, multi detector row CT [MDCT], MRI) are recommended.

d. Missed KD Adults With Coronary Aneurysms

In the setting of the adult cardiology clinic, a history of KD may be unclear in many patients with unexplained coronary aneurysms. In fact, presumed KD cases account for more than a half of adult KD patients associated with ACS. In Japan, the diagnosis of acute KD became possible after the release of the first diagnostic instruction around 1970. Follow-up of coronary sequelae from the onset of KD became possible after the first reports of coronary aneurysms by CAG or echocardiography around 1975–80.[376,377] The diagnosis of typical coronary sequelae in

patients with a confirmed history of KD is easily made through collaboration between pediatric and adult cardiologists. In cases of a missed history of KD, aneurysms related to KD may be subjected to a diagnosis of exclusion. As for the etiology of coronary aneurysms in adulthood in general, atherosclerosis (50%), congenital (30%), inflammatory (15%, including KD, Takayasu arteritis, systemic lupus erythematosus), systemic syndromes, including Noonan syndrome and Williams syndrome, genetic disorders, including Marfan syndrome and Ehrlers-Danlos syndrome, and injury (chest injury and therapeutic injury) are described.[378,379] In cases of coronary stenosis without aneurysms or with apparently normal coronary arteries including regressed aneurysms in the absence of a history of KD, the diagnosis of KD may be challenging, although characteristic findings on coronary imaging, including ring-like calcification, recanalized vessels and severe intimal thickening, by CAG, MDCT and IVUS, may be helpful.

Evidence Required in the Future

- Efficacy of antiplatelet therapy, warfarin, or statins in patients with coronary sequelae after KD.
- Negative effect of DAPT or warfarin in the adult population of KD.
- Diagnosing KD in adult patients without a confirmed history of KD.

3.1.2 Nonpharmacotherapy

a. Catheter-Based Therapy

- It is necessary to determine whether or not ACS in young adults is caused by CAL from KD.
- It is desirable to discuss the medical planning for each patient with a skillful coronary interventionist, surgeon and pediatric cardiologist who understand CAL caused by KD (Class I, Level C).

In IHD caused by atherosclerosis, primary PCI is indispensable in the treatment of an emergency ST-elevated MI[146] The mortality of ACS in adults has reduced remarkably since the 1980s, with the development of coronary care unit (CCU) and "door to balloon" system of management. On the other hand, ACS in young adults has increased with changes in lifestyle. Nowadays, patients with a history of KD are middle-aged, because 50 years have passed since the first report of KD. They are asymptomatic until the onset of ACS with aging, and are transferred to the emergency hospital. The prevalence of ACS caused by KD in young adult cases of ACS is speculated to be about 5–10%, which is very low.[306,380]

Specific characteristics such as calcified coronary aneurysms in the proximal portion of the epicoronary arteries or segmental stenosis that implies recanalization strongly suggest CAL caused by KD.[381] A past history in childhood should be asked of patients with coronary artery calcification in proximal lesions that are suspected as regressed coronary aneurysms.[382] Furthermore, it is essential to discriminate between dilation from atherosclerosis and an aneurysm caused of KD.[383] In CAL caused by KD, the lesions of coronary artery calcification are usually localized in the portion which the aneurysms existed previously. In contrast, coronary artery calcification caused by atherosclerosis is diffuse, and not always consistent with aneurysms. The distribution of coronary artery calcification is different in these 2 conditions.[384]

For IHD of adults, the results of PCI are better than those for intracoronary thrombolysis (ICT), and primary stenting with a drug-eluting stent (DES) is usually accepted.[146] However, treatment by PCI in this KD population has not been established. It is desirable to avoid primary stenting, because of the adverse effects such as thrombosis, malapposition, restenosis and new appearance of aneurysms. Either thrombolysis or add-on balloon coronary angioplasty can be considered as the procedure, if the patient cannot be transferred to an emergency hospital where PCI is possible.[306] Intravascular imaging helps to evaluate the state of culprit lesions, such as thrombus or severe stenosis with calcification. It seems that "primary stent free PCI" is better in this population, because they are young.[306,385]

Either intra-aortic balloon pump or percutaneous cardiopulmonary support is needed to prevent death in patients with cardiogenic shock and fatal ventricular arrhythmia. IMPELLA and VA–ECMO (extracorporeal membrane oxygenation) can also be considered.[146] Strict management of respiration and hemodynamics with the use of inotropic agents and anti-arrhythmic agents should be performed in the CCU. The use of angiotensin converting enzyme inhibitor (ACEI), β-blockers and human atrial natriuretic peptide (hANP) help to reduce the occurrence of adverse effects. The indication of cardiac resynchronization therapy for chronic heart failure can be discussed. Either ablation or implantable cardioverter defibrillator would be useful to prevent sudden death from fatal ventricular arrhythmia. Cardiac transplantation and left ventricular assist device are considered in patients with severe heart failure.[386–388]

Medical planning of each patient should be discussed with a skillful coronary interventionist, surgeon and pediatric cardiologist who knows KD (Class I, Level C). The natural outcome remains unknown. Patients with CAL are asymptomatic except for occurrence of ACS, although management for emergency cardiac events is dispensable. PCI should be performed when it is considered to improve both prognosis and QOL. The effectiveness, risk of complications, quality and degree of success of the procedure must be discussed. We select the best procedure for each patient on this basis, derived the accumulation of evidence from the initial and the long-term results.

Evidence Required in the Future

- Long-term outcome in patients who undergo PCI for CAL compared with the natural history of patients with CAL caused by KD.
- Long-term outcome of KD patients after AMI.

b. Surgical Treatment

- Revascularization of the anterior descending artery with bypass grafting using in-situ internal thoracic artery (ITA) to the anterior descending artery (Class I, Level A).
- Bilateral ITA to left anterior descending artery (LAD) and circumflex (Cx) artery (Class I, Level B).
- Use of right ITA (RITA) to RCA in patient with hypoplastic left Cx artery (Class IIa, Level C).
- Use of in-situ right gastroepiploic artery (GEA) to the RCA with stenosis >90% and good run-off (Class IIa, Level C).

KD is the major cause of IHD of adolescent or young adult patients. Indications and strategy of CABG for adult patients with KD are based on the JCS 2018 Guideline on Revascularization of Stable Coronary Artery Disease

Advance Publication

published in 2018.[113] Patients with KD are usually young, have a long life span after CABG and have coronary aneurysm and stenosis in the proximal portion of the coronary arteries. Radial artery (RA) or saphenous vein graft (SVG) can be utilized, especially for adult patients, and sequential and composite grafting are useful in some selected situations. Graft design should be tailored to the characteristics of each patient.

i. Conduit Choice

The in-situ ITA is the best conduit to revascularize the LAD, in terms of improved graft patency and patient survival.[389] Arterial grafts are recommended especially for KD,[390] because the patients are young and have lower operative risks. Many observational studies and meta-analyses have proved that use of a second arterial graft to LCX or RCA provides improved survival in patients with multivessel disease. In the ART trial published in 2019, outcomes after the use of bilateral ITA (BITA) were comparable to those with the use of single ITA in the 10-year follow-up.[391] However, BITA should be primarily considered for patients with KD. Tadokoro and colleagues reported that the 30-year survival rate was as high as 91.0% with primary use of BITA in their 36-year experience of CABG for KD.[392] Although BITA should be principally grafted in the left coronary artery (LCA) region,[393–397] the use of the RCA can be rationalized when the left Cx artery is small or unsuitable for ITA grafting.[398,399]

In adult KD patients, the RA is a useful option.[400] As for the second arterial graft, the patency rates and clinical outcomes of RA+RITA are mostly similar in the previous reports, whereas the use of BITA includes an increased risk of sternal wound infections. The patency rate of the RA is generally considered to be higher than that of SVG. However, an advantage of the RA was not found when the stenosis is not severe,[401] whereas the patency of the SVG is not associated with severity of stenosis. Kitamura and colleagues examined 92 CABG patients with KD and a mean age of 15 years, and reported favorable graft patency of the RA rather than the SVG.[392]

Several long-term follow-up studies describe the clinical advantage of using 3 arterial grafts.[402–407] As the third arterial graft, the GEA is usually considered. The GEA is indicated, exclusively when the target has severe stenosis and/or sufficient flow demand, such as stenosis >80%,[408,409] stenosis >90%,[410] stenosis located at the proximal portion of the RCA,[411] or minimum lumen diameter (MLD) <1.1 mm.[412]

The use of SVG is not recommended for KD patients, even for adult patients. For KD, the rate of SVG patency at 10 years was reported as 57%.[326] For patients more than 10 or 12 years old, the patency rate of the SVG was significantly lower than that of arterial grafts.[289,413]

SVG is usually used as an aorto-coronary bypass graft because it provides high perfusion pressure and has a large luminal diameter. Therefore, the patency of the SVG is not influenced by the severity of stenosis in the target branch.[412,414] In addition, the SVG is applicable to AMI, which is unsuitable for ITA grafting. In contrast, thrombosis, and intimal hyperplasia and stenosis or occlusion of atherosclerosis in the late follow-up period is relatively frequent in the SVG. Redo-CABG is indicated after initial CABG in childhood. Kitamura and colleagues reported that 9 of 114 patients underwent redo-CABG because of graft failure in 7 and new lesion in 2.[319]

ii. Sequential Anastomosis and Composite Graft

Arterial graft provides long-term patency because of its tolerance to high luminal pressure and antithrombotic intimal function. To achieve total arterial grafting to multiple targets, it may be necessary to create one bypass graft to two or more targets. Dion and colleagues reported a high graft patency rate and freedom from repeat revascularization.[415]

Composite graft is a combination of two arterial grafts in a Y- or I-shaped configuration. Composite grafting can be beneficial to minimize aortic manipulation and to maximize the targets of arterial revascularization. The disadvantage of a composite graft is the risk of competitive flow, which is commonly associated with late graft failure. For young KD patients, Tadokoro and colleagues reported that composite graft using an arterial conduit was useful and reliable, according to their experience.[392] Competitive flow in the bypass graft to the LAD should be avoided.[416] Appropriate target selection and graft design are crucial in composite grafting.[417]

iii. Off-Pump vs. On-Pump CABG

It is generally accepted that the advantage of off-pump CABG is avoidance of stroke and renal and respiratory complications, and fewer blood transfusions. Disadvantages may be the quality of suturing or selection of anastomotic sites. In patients with KD, an advantage of off-pump CABG cannot be obtained in most cases.

iv. Surgery for CAA

CAA thrombotic occlusion complicates MI. Contrast-enhanced CT is useful for diagnosis and evaluation of CAA.[176]

Rupture of CAA caused by KD is quite rare,[124] but surgery for extremely large aneurysm may be rationalized.[418]

3.2 Lifestyle and Exercise Guidance

- Adult patients with KD should receive thorough lifestyle and exercise guidance on coronary risk factors that promote adult atherosclerosis.
- The coronary risk factors that promote adult atherosclerosis are generally well known. The coronary risk factors that influence the progression and prognosis of CAL with post-inflammatory arteriosclerosis in adult patients with KD are unknown. In adult KD patients with post-inflammatory arteriosclerosis, there is the possibility that coronary risk factors for atherosclerosis cannot be avoided. Therefore, they need thorough lifestyle and exercise guidance.

3.2.1 Improvement of Lifestyle, Treatment of Coronary Risk Factors

Various guidelines address the removal of the following atherosclerotic risk factors in adult KD patients with post-inflammatory arteriosclerosis.

a. Hypertension

In the Guidelines for the Management of Hypertension 2019 (JSH2019),[419] the blood pressure (BP) level has 4 phases: normal BP defined as <120/80 mmHg; normal high BP is 120–129/<80 mmHg; high BP is 130–139/80–89 mmHg; "hypertension" is >140/90 mmHg.

- Target BP in patients with KD is <130/80 mmHg as well as that of the patients with complications for adulthood.

Table 20. Diagnostic Criteria for Dyslipidemia (Blood Collected From KD Patients in Fasting State)*		
LDL-cholesterol	≥140 mg/dL	Hyper-LDL cholesterolemia
	120–139 mg/dL	Borderline hyper-LDL cholesterolemia**
HDL-cholesterol	<40 mg/dL	Hypo-HDL-cholesterolemia
TG	≥150 mg/dL	Hypertriglyceridemia
Non-HDL-cholesterol	≥170 mg/dL	Hyper-non-HDL-cholesterolemia
	150–169 mg/dL	Borderline hyper-non-HDL-cholesterolemia**

*Fasting over 10 hours. **When borderline hyper-LDL cholesterolemia or borderline hyper-non-HDL cholesterolemia is detected, investigate any high risk condition and consider need of treantment.
• When there is a coronary lesion, including coronary artery aneurysm, the LDL-cholesterol management targets apply to secondary prevention.
• Lipid management targets are according to the risk category similar to general adults as shown in **Table 9**.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride. (Adapted from Japan Atherosclerosis Society. 2017[149])

- If the target BP cannot be achieved, initially nonpharmacologic therapy, including improvement in lifestyle, is provided, and medical therapies are only recommended when the target BP is still not sufficient.
- Medical therapies are used for the treatment of hypertension complicated with heart disease. Particularly, consider ACEI from an early stage when cardiac dysfunction is detected.
- Improvements in lifestyle are as follows:
  (1) Sodium restriction: <6 g/day
  (2) Active intake of vegetables and the fruits. However, we do not recommend aggressive intake of vegetables and fruits because the patients with serious renal failure are at risk of hyperkalemia. Excessive intake of fruits containing a lot of sugar is not recommended for obese or diabetic patients needing caloric restriction.
  (3) Restrict intake of cholesterol and saturated fatty acid.
  (4) Active intake of fish (fish oil) and taking high-purity eicosapentaenoic acid supplement.
  (5) Weight loss: BMI (body weight (Kg) ÷ [height (m)× height (m)]) <25
  (6) Exercise: mainly regular aerobic exercise (walking, fast walking, swimming, aerobics, slow jogging, cycling, bench step motion etc.) with the goal of ≥30 min on at least 3 days per week). When there is cardiac dysfunction, activity is according to the appropriate exercise prescription (see **V. 3.2.2**).
  (7) Sobriety: men drink ≤20–30 mL/day ethanol, and women are ≤10–20 mL/day.
  (8) Smoking cessation, including the prevention of passive smoking.

b. Dyslipidemia
- Dyslipidemia is defined according to the Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017[149] (**Table 20**)

c. Hyperglycemia
- Hyperglycemia is defined according to the Japan Diabetes Society Treatment Guide for Diabetes 2018–2019.[420]
- Glycosuria form is defined any of the following are met: fasting blood sugar >126 mg/dL early in the morning, more than 2 h value 200 mg/dL in 75 gOGTT, more than occasional blood glucose level of 200 mg/dL, > 6.5% HbA1c (NGSP).
- Target value of glycemic control is HbA1C (NGSP) <7.0 (i.e., target value for complications prevention), and andHbA1C (NGSP) <6.0 is the target value for blood glucose normalization if possible.
- Treatment is timely choice of oral hypoglycemics, which are matched with the patient's clinical condition, including DPP-4 inhibitor and biguanide, thiazolidine, sulfonyl urea (SU), glinide, and alpha-glucosidase inhibitor. In addition, use of SGLT2 inhibitor is considered for cases of the low cardiac function with old MI.

d. Smoking
- Smoking is a systemic disease (addiction+smoking-associated diseases), and smoking cessation, including passive smoking, is necessary for all patients with a history of KD.
- Use of electronic cigarettes or heating-type cigarette containing nicotine is contraindicated, as well as normal cigarette smoking.
- Instruction and the regimen of smoking cessation are based on the Guidelines for Smoking Cessation (JCS 2010 revised edition),[421] and the Standard Manual for Smoking Cessation treatment sixth edition.[422]

e. Psychological Stress
- Patients should endeavor to decrease or remove any psychological stress at school or the workplace. They should regulate their daily life and ensure they get enough sleep.

3.2.2 Exercise Guidance
Recently, aggressive cardiac rehabilitation is expected and steadily gives results in adult patients with coronary artery disease caused by atherosclerosis. However, for adult patients with cardiovascular sequelae in KD, most may be comparatively young people with time limitations, and in this group practicing cardiac rehabilitation effectively seems to be rare. In adult KD patients with cardiovascular sequelae with cardiac dysfunction, enforced cardiac rehabilitation and improvement of cardiac rehabilitation centers are expected in the future.

Concrete prescription of cardiac rehabilitation and exercise program are based on the Guidelines for Rehabilitation

Advance Publication

in Patients With Cardiovascular Disease (JCS 2012).[423]

Evidence Required in the Future

National registry study to confirm the effects of cardiac rehabilitation in adult KD patients with cardiovascular sequelae.

3.3 Pregnancy and Delivery

- When female patients with coronary arterial lesions (CAL) caused by KD reach childbearing age, physicians should explain the risks of pregnancy and delivery.
- Patients in NYHA I without myocardial ischemia should be assessed using standard obstetric criteria to determine the method of delivery (Class I, Level C).
- Coronary artery revascularization should be considered before pregnancy in patients with myocardial ischemia.
- Cardiologist who understand the management of CAL caused by KD and obstetricians should collaborate closely to prepare for each patient's individual condition (Class I, Level C).

3.3.1 Problems in Pregnancy and Delivery

Pregnancy induces changes in the hemodynamics and hemostatic system within weeks. A 40–50% increase in cardiac output occurs in normal pregnancy. Pregnancy also induces a series of hemostatic changes, with an increase in the concentration of coagulation factors, fibrinogen, and platelet adhesiveness, as well as diminished fibrinolysis, which leads to hypercoagulability. Pain with labor can greatly affect changes of the sympathetic nervous system. The physiological adaptation for labor and the post-partum period requires 4–6 weeks.[424] Physicians should assess female patients with a history of KD for preservation of cardiac function during pregnancy and labor, the risk of drugs during pregnancy including antithrombotic drugs, optimal methods of delivery, and management of cardiac accidents that may develop during pregnancy or the perinatal period.[425] When female KD patients reach childbearing age, physicians should assess them for CAL, myocardial ischemia or myocardial injury, treat such disorders if present before pregnancy to reduce the risk during delivery, and explain appropriate management during pregnancy and the risk of childbirth to the patient. Pregnant women may undergo cardiac and coronary magnetic resonance (MR) at week 12 of pregnancy or later.[426] Although the number of women with a history of KD and who have given birth is small and evidence is limited, there have been no serious cardiac accidents reported in this population.[427–429] A case report describes a probable KD patient who had an AMI 10 days after delivery undergoing CABG.[430] Other patients delivered and were not diagnosed as having CAL caused by KD.

3.3.2 Delivery

Female KD patients with normal cardiac function without myocardial ischemia should be assessed using standard obstetric criteria to determine the method of delivery (Class I, Level C). Those with left ventricular ejection fraction of 40–50% should be monitored carefully for hemodynamic changes during childbirth.[431] When patients with cardiac dysfunction undergo vaginal delivery, the use of forceps or vacuum extractor and epidural anesthesia are beneficial as measures to avoid the risk of cardiac overload because of pain during the second stage of labor[431] (Class IIa, Level C). Cesarean section should be considered for women with signs and symptoms of myocardial ischemia (Class IIa, Level C). If a patient has had an AMI, the mode of delivery should be selected based on left ventricular function and general condition after stabilization of hemodynamics.[427,432]

3.3.3 Drugs During Pregnancy and the Perinatal Period

It is unknown if the risk of thrombus in aneurysms during pregnancy is higher than that in non-pregnancy. Physicians should carefully consider the benefits and potential risks of drugs used during pregnancy and the perinatal period. Drugs used during this period may induce anomaly in the fetus or excessive bleeding during delivery, and may be excreted in the mother's milk.[431]

a. Anticoagulant Drugs and Antiplatelet Drugs

i. Aspirin

A small dose of aspirin suppresses coagulation of platelets in the mother, and will not affect the neonate.[433,434] When women with CAL become pregnant and need antithrombotic therapy during pregnancy, they should be treated at a small dose (81–100 mg) and carefully observed. Aspirin must be stopped at 37–38 weeks of pregnancy.[429,431]

ii. Warfarin

It has been reported that the incidence of warfarin fetal complications is dose-dependent, and that the risk of fetal complications is high in patients receiving warfarin ≥5 mg/day.[434,435] Warfarin should be discontinued during the first 12 weeks of pregnancy, when the major organ systems are developing, and at weeks 34–36 of pregnancy and thereafter. The risk of thrombogenesis increases during discontinuation of warfarin, physicians should consider subcutaneous administration of heparin.[429,431,436,437]

b. Other Drugs

ACEI should be discontinued during pregnancy, as they are teratogenic.[438,439] Other drugs should be used only when the benefits overweigh the risk. The beta-stimulants should be carefully used in patients with systolic ventricular dysfunction. The use of ergonovine should be avoided in patients with vasospastic angina.

3.3.4 Cardiac Events

Cardiologist who understand the management for CAL caused by KD should collaborate closely with obstetricians to prepare measures according to the individual patient's condition (Class I, Level C).

a. AMI

The presence of a gAN is one of the biggest factors that influence the development of AMI.[7] However, whether pregnancy or delivery increases the risk of MI in this population is unknown.[430] At older ages of childbearing age, most MI reported in the literature occurred in patients with multiple risk factors for atherosclerosis.[432,440] In the rare occurrence of AMI, prompt diagnosis is essential. The outcome of MI during pregnancy depends on whether the cardiac event is managed successfully.[441,442] Women at 20 weeks of pregnancy or thereafter may undergo catheter intervention via the RA approach,[430] but physicians should be careful about body position as the supine position may cause inferior cava syndrome.[431]

b. Arrhythmia

Patients with myocardial involvement may develop ventricular arrhythmias during the latter half of pregnancy and in the peripartum period. Physicians should conduct Holter ECG monitoring in such women in the second and third trimesters,[443,444] and consider treatment such as β-blockers when ventricular tachycardia occurs.[444]

Evidence Required in the Future

- Prevalence of cardiac events related to pregnancy and delivery in patients with CAL caused by KD.
- Usefulness of anticoagulant therapy based on the severity of CAL in preventing cardiac and obstetric complications.

3.4 Medical Practice System for Adult Kawasaki Disease Patients

- It is important that a physician, particularly a circulatory organ physician, deeply understands the clinical condition of adult KD.
- After follow-up by pediatric physicians, it is necessary to share information on the clinical course and laboratory findings with the pediatricians.
- The adult patient's clinical condition can become complicated by accompanying atherosclerosis in addition to the cardiovascular sequelae in KD.

In view of the present conditions that the medical practice for patients with KD becomes the general physician center for adulthood, we include the problem at the following points.

(1) Insufficient understanding and experience of the cardiovascular sequelae in adult KD by physicians, (2) lack of information about the cardiovascular sequelae in adult KD by medical personnel including paramedics, (3) the special pathology and clinical condition of cardiovascular sequelae in adult KD, and the shortage of specialists in this area, and (3) need for cooperation and improvement in cardiac rehabilitation institutions to practice effective therapy including cardiac rehabilitation.

3.4.1 Understanding KD for Physicians

Because general physicians are rarely involved in the diagnosis of KD of the acute phase, and thus the opportunity to treat it in infancy, they have insufficient understanding of the pathology of acute-phase KD. However, 35 years or more have passed since a general pediatrician diagnosed KD, and infant KD patients are reaching the adulthood. Furthermore, there is case report of adult KD developing in a 17-year-old boy,[445] and so it is becoming more and more important that physicians, particularly cardiologists, fully understand the clinical condition of adult KD. Therefore, the training of specialist physicians in particular is required. Also, medical personnel, including paramedics, require education on the cardiovascular sequelae of adult KD through periodic seminars to deepen their understanding.

3.4.2 Cooperation of Pediatricians and Cardiologists

In the follow-up by pediatricians, it is necessary to share the clinical course and laboratory findings with physicians dealing with adult cases of KD. It is essential for physician, especially cardiologist, to cooperate with pediatricians and to perform a diagnosis, treatment, and the prognostic follow-up in cases of the cardiovascular sequelae in adult KD.

3.4.3 Coronary Aneurysm of Young Patients, MI and KD

The onset of IHD is mostly on average 20 years after the time symptoms suspected to be KD developed, which is the point in time to pay attention to patients with a CAA.[446] In other words, the case of KD with CAA in childhood, but has no clinical manifestations after puberty (i.e., as an adult), becomes a case of IHD.[447] Also, there are more cases of MI than angina in adult KD patients, and it is thought this characteristic stems from the coronary aneurysms. Thus, a history of KD in childhood should be confirmed when we encounter young adult patients with MI and cardiovascular symptoms.[448] To this end, childhood medical information must be accurately recorded and disclosed as required.

3.4.4 Comparison With Adult-Type MI

The main cause of adult-type MI is thought to be collapse and thrombogenesis of atheroma. However, interestingly, a severe atherosclerotic lesion is not to be seen, despite significant arteriosclerosis as a pathologic finding, in KD.[449] Therefore, it is currently unknown whether cardiovascular sequelae in adult KD are accelerators of atherosclerosis. Also, the remodeling of the coronary lesion of patients with cardiovascular sequelae in KD continues several years after onset, and intimal hyperplasia and neovascularity are found. This is different from the findings in young patients with atherosclerosis.[128] There is a case report of severe triple-vessel disease including giant coronary aneurysm, indicating KD sequelae.[450] The remodeling of the coronary lesion of patients with cardiovascular sequelae in adult KD is thought to become a problem in future adulthood.

The clinical condition becoming complicated by accompanying atherosclerosis in addition to cardiovascular sequelae in adult KD is expected in the future, so the request for specialists who understand the pathology and clinical condition and can treat the cardiovascular sequelae of adult KD is expected. This education cannot be accomplished without the cooperation of the pediatricians.

VI. Relationship Between Sequelae of Coronary Arteritis and Atherosclerosis

1. Progression to Atherosclerosis (Pathological Point of View)

- Kawasaki disease (KD) cardiovascular sequelae are called post-inflammatory arteriosclerosis after vasculitis and differ greatly to atherosclerosis in adults in terms of etiology, pathophysiology, and histopathology (Class I).
- In KD cardiovascular sequelae, vascular endothelial dysfunction continues, which may promote atherosclerosis.
- In acute coronary syndromes (ACSs) in adults with KD, thrombus formation is often caused by erosion of the intima rather than by atheroma rupture (Class I).

Advance Publication

- There is still no consensus on the relationship between post-inflammatory arteriosclerosis and atherosclerosis.

Vascular remodeling continues within the coronary arterial lesions (CAL) even during the remote phase of KD.[128] However, there are few histopathological findings concerning the relationship between the sequelae of coronary arteritis and atherosclerosis.

Histological studies have been performed on autopsy cases of coronary aneurysms, and the findings compared with pathological reports on atherosclerosis of the coronary arteries in age-matched Japanese.[101] The findings confirmed more severe atherosclerotic lesions in the coronary aneurysms of subjects in their 30 s compared with control subjects having no aneurysms. It could be thought that the coronary artery with residual aneurysms caused by KD becomes a risk factor for atherosclerosis.[451]

On the other hand, many coronary arteries with no residual aneurysms in KD show scarring from arteritis, but comparison with age-matched control subjects reveals no clear differences.[451] There are still many unknown aspects regarding the long-term prognosis of patients who have comparatively mild scarring from vasculitis. Further study of these subjects is warranted.

2. Progression to Atherosclerosis (Clinical Point of View)

- Patients with CAL have coronary endothelial dysfunction (Class II).
- In patients with CAL, progress to atherosclerosis cannot be denied, and life guidance such as the elimination of arteriosclerosis-promoting factors is necessary.

2.1 Difference Between Arteriosclerosis in KD Patients With Long-Term Follow-up and General Atherosclerosis

General atherosclerosis is typically explained by the hypothesis of endothelial dysfunction.[452] It is thought that reactive inflammation is the start of the pathologic formation, and that atherosclerosis is a composite of various mechanisms, including acceleration of chronic inflammation and oxidative stress. When the glycocalyx of the blood vessel endothelial surface is affected by hypertension or hyperglycosemia, barrier failure occurs. Monocytes are derived to the involved site of the endothelium by chemotactic factors, and migrate into the subendothelium through adhesion molecules where they differentiate into macrophages. Monocytes that have eclipsed oxidative low-density lipoprotein (oxLDL) ingested from the blood differentiate into foam cells. These cells accumulate in the intima of the vessel wall, and atheroma develops. That is the usual etiology of atherosclerosis observed in adult patients. Arteriosclerosis observed in KD patients is a post-inflammatory related arteriosclerosis, mainly consisting of hyalinized fibrous tissues with diffuse calcification.[101] These findings substantially and histologically differ from those of general atherosclerosis, and it is often controversial when discussing the long-term prognosis of arteritis in KD patients. Recent clinical and pathological research reveals, in part, the presence of atherosclerotic lesions in the remote phase of KD,[453] and further study is needed.

2.2 Assessment of Vascular Injury in the Remote Phase of KD

2.2.1 Assessment Using Markers of Vascular Injury

The level of high sensitive C-reactive protein (hs-CRP) is significantly high in KD patients with CAL compared with both KD patients without CAL and healthy controls; therefore, it is suggested that subclinical inflammation exists in the coronary arteries of patients with CAL.[454] It is reported that the level of hs-CRP is elevated and inflammation continues in KD patients accompanied by regression of CAL. This suggests that a low level of inflammation exists in the remote phase of KD, particularly in KD patients with CAL, followed by early progression to arteriosclerosis. In the remote phase of KD with CAL, oxidative stress may affect both the occurrence and development of injury to vascular endothelial cells. Furthermore, other markers, such as oxLDL, urinary Nitrogen oxide/creatinine (Nox/Cre), Asymmetnical Dimethyl Arginine (ADMA), von Willebrand Factor (vVW), adhesion molecules, matrix metaroproteinase (MMP), and homocysteine, are used to assess endothelial cell dysfunction.

2.2.2 Morphological Evaluation Using Clinical Imaging

Morphological assessment of the coronary arteries has been performed with transthoracic echocardiography and X-ray coronary angiography (CAG). However, intravascular ultrasound (IVUS) has shown cardiologists the importance of a detailed assessment of the coronary arteries because it can reveal the presence of intimal hyperplasia in coronary arteries that appeared normal with conventional procedures. It was reported that CAL in adolescents and young adults were evaluated using virtual histology IVUS, which made a detailed pathological examination possible.[375] In both regressed and persistent aneurysms, fibrous tissue was mainly found, and intimal thickening and small amounts of calcification were also observed. It was also reported that a heterogeneous area with calcification, but not with fibrous thickening was found, and these findings were similar to atherosclerotic lesions in severe lesions of the coronary arteries.

The carotid artery intima-media thickness (cIMT) in the remote phase of KD has been evaluated using carotid ultrasound.[455] The cIMT, which is thought to be a marker of atherosclerosis, was significantly greater in the remote phase of KD with or without CAL compared with control subjects without a history of KD. A positive correlation between cIMT and both pulse wave velocity (PWV) and LDL-cholesterol was reported. Multi detector row computed tomography (MDCT) and magnetic resonance CAG using the black blood method have become available as less invasive methods of morphological assessment. These new modalities can detect the calcification of coronary arteries that frequently develops in the remote phase of KD.[176] Calcified lesions often accompany intimal thickening, and are thought to be related to the progression of stenotic lesions.

2.2.3 Evaluation Using Vascular Endothelial Function

It is widely known that endothelial cell dysfunction occurs as a precursor to morphological changes such as intimal hyperplasia. Because such morphological changes decrease the plasticity of arteries, assessment of vascular function is drawing attention as a procedure to facilitate early intervention.

Advance Publication

PWV is effective for evaluating arterial stiffness and is used for assessment of atherosclerosis in adult patients. It is reported that brachial-ankle PWV (baPWV) is significantly higher in patients with a history of KD compared with healthy controls, and there was no significant difference in the PWV between the KD patients with or without CAL.[456] It was also reported that baPWV is significantly high only in KD patients with CAL. Flow-mediated dilation (FMD), a new measure of vascular function using reactive hyperemia that stimulates the release of nitric oxide (NO) from the endothelium, may accurately detect vascular dysfunction. It is thought that FMD is more sensitive than PWV for detecting vascular dysfunction, so FMD is used for the evaluation of drug intervention study.

In the case of diabetes, dyslipidemia, high blood pressure, smoking, and aging involved with the factors of vascular endothelial cell injury, the %FMD is significantly decreased in the adult population. Recent studies have reported a decrease in FMD during the remote phase of KD.[457] On the other hand, it has been reported that FMD is decreased in patients with CAL compared with healthy control subjects and that there was no significant difference in FMD between the KD patients without CAL and healthy control subjects.

2.3 Atherosclerosis in Remote Phase of KD

In KD patients with CAL, endothelial dysfunction or morphological disorders are more likely to progress, and the degree and site of these disorders are thought to be affected by the degree of vascular remodeling after acute inflammation. The presence of atherosclerosis during the remote phase of KD has not been clarified, and there is little evidence of atherosclerotic lesions in KD patients. Therefore, there is a possibility that arteriosclerosis without atheroma may be mainly observed, and that stenotic lesions occasionally with calcification will increase the risk of IHD event.

On the other hand, it has been reported that a high cholesterol diet induced the development of atherosclerosis in an animal model of vasculitis similar to KD.[458] These findings suggest that if KD with CAL is accompanied by other atherosclerosis risk factors such as dyslipidemia in the remote phase of KD, arteriosclerosis will easily develop and progress in young adult KD patients, and these lesions will then progress to atherosclerosis. Attention should be paid to the overlap of atherosclerosis-promoting factors, and lifestyle guidance such as smoking cessation, prevention of obesity, and healthy diet, is indispensable at least for patients in the remote phase of KD.

VII. Summary

As a summary of this guideline, **Table 21** shows the frequency of each examination, treatment, and lifestyle guidance according to the severity classification of KD. Authors would be pleased if it could be used as a reference for medical staff who handle the remote stage of KD. On the other hand, the higher the severity, the more likely it is that various disorders will be complicated, and specialists are required to manage each case individually. Keeping in mind that the policy shown in this guideline is general, authors would like readers to deal with each case with the best policy. Most of the long-term treatment and management of KD still have a low level of evidence, and the treatments that could show strong recommendation level in this guideline are very limited. Authors would like to emphasize that the accumulation of evidence is urgent in the future.

Table 21. Summary of Remote-Phase Management of Kawasaki Disease

Severity classification of CAL			ECG * echocardiogram	Assessment for inducible ischemia (stress test)	Coronary imaging modalities (CT, MRI, CAG)	Pharmacological therapy	PCI, CABG	School activity management	Life guidance
I	No dilation		Assess at 1, 2, 6, 12 months, and 5 years (or yearly) until 5 years	Not necessary	Not necessary	Not necessary after acute phase	Not necessary	No limitations for life or exercise E allowed No management required after 5 years from onset	Provide guidance on lifestyle improvement (exercise, prevention of obesity, smoking cessation, recommendation of Japanese food, etc.) to control coronary risk factors that promote atherosclerosis
II	Transient dilation								
III	Regression	(Acute phase) small aneurysm	Yearly	Not necessary	Consider at convalescent phase, 1 year from onset, or at the time when aneurysm regresses Recommend on finishing high school	Cancellation can be considered Consider aspirin or statin when necessary		No limitations for life or exercise E allowed	
		(Acute phase) medium/ giant aneurysm	Every 6–12 months	Consider every 3–5 years	Consider at convalescent phase, 1year, then every 3–5 years				In addition to the above guidance, patients should understand the importance of medication and the importance of follow-up, and preventing withdrawal from medical care Instruct the AYA generation to become independent and prepare for the transition of care
IV	Remaining coronary aneurysm	Small aneurysm	Yearly	Consider every 3–5 years	Consider at convalescent phase, 1 year, then every 3–5 years	In addition to aspirin, other antiplatelet drugs and warfarin are considered Consider ACEI, ARB, and statins		No limitations for life or exercise E allowed	
		Medium aneurysm	Every 6–12 months	Consider every 2–5 years	Consider at convalescent phase, 1 year, then every 2–5 years				
		Giant aneurysm	Every 6–12 months	Consider every 1–5 years	Consider at convalescent phase, 1 year, then every 1–5 years			D "E prohibited" is possible when there is no change for >1 year	
V	Coronary artery stenosis	Without ischemia	Every 6–12 months	Consider yearly	Consider at convalescent phase, 1 year, then every 1–5 years	In addition to above drugs, consider coronary dilator/ antianginal drugs	Consider according to stenosis	E prohibited ("D" for giant aneurysm. "E prohibited" is possible when there is no change for >1 year)	
		With ischemia	Consider timely	Consider timely	Consider timely		Indication	A–D	

*Stress ECG when necessary. ACEI, angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor antagonist; AYA, adolescent/young adult; CABG, coronary artery bypass grafting; CAG, coronary angiography; CT, computed tomography; MRI, magnetic resonance imaging PCI, percutaneous coronary intervention.
Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise. Exercise intensity: Mild exercise: Physical activities that do not increase respiratory rate in average children at the same age, Intermediate exercise: Physical activities that increase respiratory rate without causing shortness of breath. Players may talk with others during exercise, and Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath. Express the allowed exercise intensity from "A" to "E". Only "E" will be noted as "Allowed" or "Prohibited" for school sport club activities, and will be referred to as "E-allowed" or "E-prohibited".

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Appendix 1 Details of Members

Chair:
- Ryuji Fukazawa, Department of Pediatrics, Nippon Medical School
- Junjiro Kobayashi, Department of Cardiovascular Surgery, National Cerebral and Cardiovascular Center

Members:
- Mamoru Ayusawa, Department of Pediatrics and Child Health, Nihon University School of Medicine
- Hiroyuki Matsuura, Department of Pediatrics, Toho University Omori Medical Center
- Yoshihide Mitani, Department of Pediatrics, Mie University Graduate School of Medicine
- Masaru Miura, Department of Cardiology, Tokyo Metropolitan Children's Medical Center
- Hiroyuki Nakajima, Department of Cardiovascular Surgery, Saitama Medical University International Medical Center
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- Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine
- Soichiro Kitamura, President Emeritus, National Cerebral and Cardiovascular Center & Board of Director, Japan Cardiovascular Research Foundation
- Masami Ochi, Professor Emeritus, Nippon Medical School
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Appendix 2 Disclosure of Potential Conflicts of Interest (COI): JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease

Author	Potential COI of the participant									Potential COI of the marital partner, first-degree family members, or those who share income and property	Potential COI of the head of the organization/ department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department)	
	Employer/ leadership position (private company)	Stakeholder	Patent royalty	Honorarium	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards		Research grant	Scholarship (educational) grant
Members: Mamoru Ayusawa				Japan Blood Products Organization Teijin Pharma Limited								
Members: Hiroyuki Suzuki							Astellas Pharma Inc.					
Members: Kenji Suda						Actelion Pharmaceuticals Japan Ltd.						
Members: Kazuhiko Nishigaki				Sanofi K.K. Mochida Pharmaceutical Co.,Ltd.								
Members: Hiroyuki Matsuura						Tokyo Health Service Association						
Members: Hiroyoshi Yokoi				Cardinal Health Japan MSD K.K. Amgen Astellas BioPharma K.K. AstraZeneca K.K. Abbott Vascular Japan Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Cook Medical Japan G.K. Sanofi K.K. Sumitomo Bakelite Co., Ltd. Daiichi Sankyo Company, Limited Takeda Pharmaceutical Company Limited Mitsubishi Tanabe Pharma Corporation TERUMO CORPORATION W. L. Gore & Associates, Inc. Medtronic Japan Co., Ltd. HeartFlow Japan G.K. Bayer Yakuhin, Ltd. Philips Japan, Ltd. Boston Scientific Corporation Medicon Inc Otsuka Pharmaceutical Co., Ltd. Nihon Medi-Physics Co.,Ltd.			Daiichi Sankyo Company, Limited					
Collaborators: Hiromichi Hamada				TEIJIN HOME HEALTHCARE LIMITED								
Independent Assessment Committee: Hideaki Senzaki				Otsuka Pharmaceutical Co., Ltd. Nippon Shinyaku Co., Ltd. AbbVie GK Actelion Pharmaceuticals Japan Ltd. Japan Blood Products Organization Teijin Pharma Limited Takeda Pharmaceutical Company Limited	AbbVie GK			Iwaki City Medical Center				
Independent Assessment Committee: Takeshi Kimura				Amgen Astellas BioPharma K.K. Abbott Vascular Japan Co., Ltd. Kowa Pharmaceutical Co., Ltd. Sanofi K.K. Daiichi Sankyo Company, Limited Boehringer Ingelheim Japan, Inc. Bristol-Myers Squibb Boston Scientific Corporation		Nipro Corporation EP-CRSU Co., Ltd. Edwards Lifesciences Corporation Daiichi Sankyo Company, Limited Pfizer Japan Inc.	Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Takeda Pharmaceutical Company Limited Boehringer Ingelheim Japan, Inc. Otsuka Pharmaceutical Co., Ltd. Astellas Pharma Inc.					

Notation of corporation is omitted.
No potential COI for the following members.

Chair: Ryuji Fukazawa, Absent
Chair: Junjiro Kobayashi, Absent
Members: Kisaburo Sakamoto, Absent
Members: Kei Takahashi, Absent
Members: Etsuko Tsuda, Absent
Members: Hiroyuki Nakajima, Absent
Members: Yoshihide Mitani, Absent
Members: Masaru Miura, Absent
Collaborators: Kazuyuki Ikeda, Absent
Collaborators: Yoshihiro Onouchi, Absent
Collaborators: Hiroshi Kamiyama, Absent
Collaborators: Tohru Kobayashi, Absent
Independent Assessment Committee: Masami Ochi, Absent
Independent Assessment Committee: Soichiro Kitamura, Absent
Independent Assessment Committee: Kenji Hamaoka, Absent