b) Coronary Artery Lesions Indicated for CAG

(1) Dilatation Lesions

In patients with aneurysms classified as medium or giant according to the severity classification of cardiovascular lesions in the present guidelines, it is desirable to perform CAG during the early part of the convalescence phase for detailed evaluation of the morphology and extent of coronary artery lesions and to specify the methods and duration of follow-up and treatment strategies. Since precise evaluation of coronary stenotic lesions is feasible with MRCA and MDCT, it is expected that in the future it will be possible to omit catheterization for the diagnosis of coronary stenotic lesions in some patients.[105] Since the development of stenosis after regression of not only large aneurysms but also smaller ones[12] and the development of arteriosclerotic degeneration[14] have been observed in patients over 10 years after the onset of Kawasaki disease, patients should be followed for a long period of time using coronary imaging techniques such as MRCA and MDCT if follow-up CAG is not feasible.

(2) Localized Stenosis

During the remote phase, progressive localized stenosis develop mainly in the inlet and outlet of aneurysms. Multidirectional imaging is required to evaluate stenotic lesions. A significant stenosis is defined as a ≥75% stenosis in lumen diameter in the major coronary arteries and a ≥50% stenosis in lumen diameter in the left main coronary trunk. Patients with significant stenosis should be followed with angiography[16] or other imaging techniques such as MRCA[105] and MDCT[114] at appropriate intervals based on the speed of progression of the stenosis (from 6 months to several years), even when no signs/symptoms of myocardial ischemia are present, and should be considered for aggressive treatment such as CABG[113] and PCI[90] based on the results of the above-described follow-up imaging as well as the results of other studies such as myocardial scintigraphy, exercise ECG, and evaluation of coronary flow reserve (CFR).

(3) Occlusion

Complete occlusion of a coronary artery is observed in about 16% of patients with coronary artery lesion due to Kawasaki disease, and 78% of occlusions are visualized with imaging within 2 years after the onset of Kawasaki disease.[16] The finding of occlusion of the coronary arteries in asymptomatic patients on routine follow-up imaging is not uncommon. Collateral flows are visualized during angiography in all patients with coronary occlusion. Since the extent of collateral flow and growth/development of recanalized vessels differ among individuals and depend on the time after occlusion and cause of occlusion (thrombi vs intimal hyperplasia), follow-up angiography is required.[17]

(2) Cardiac Function Test

Cardiac function is evaluated by determining ventricular pressure, cardiac output, ventricular volume, EF, and/or other parameters.

(3) IVUS

a) Morphological Evaluation of Coronary Artery Lesions

IVUS is used to evaluate the severity of intimal hyperplasia, presence/absence of thrombi or calcification, and the severity of luminal narrowing. Severe intimal hyperplasia is observed not only in lesions of localized stenosis but also in

Table 12. Indications of Imaging Techniques by Classification of Severity of Coronary lesions Due to Kawasaki Disease

• **Chest X ray**		
▷Class I	Severity classification	III, IV, V
▷Class II	Severity classification	I, II
▷Class III	None	
• **Echocardiography/12-lead ECG at rest**		
▷Class I	Severity classification	I, II, III, IV, V
▷Class II	None	
▷Class III	None	
• **Exercise ECG**		
▷Class I	Severity classification	III, IV, V
▷Class II	Severity classification	I, II
▷Class III	None	
• **Holter ECG, signal-averaged ECG**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Body surface mapping, drug stress ECG, magnetocardiography**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Stress echocardiography, myocardial contrast echocardiography**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Myocardial perfusion scintigraphy**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Evaluation of myocardial fatty acid metabolism, evaluation of cardiac sympathetic nerve activity**		
▷Class I	Severity classification	V
▷Class II	Severity classification	I, II, III, IV
▷Class III	None	
• **MRI, MDCT**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **PET**		
▷Class I	Severity classification	V (b)
▷Class II	Severity classification	I, II, III, IV, V(a)
▷Class III	None	
• **Cardiac catheterization**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	III
▷Class III	Severity classification	I, II

MRI, magnetic resonance imaging; MDCT, multi-row detector computed tomography; PET, positron emission tomography.

Class I	Conditions for which there is general agreement that the procedure is useful and effective.
Class II	Conditions for which there is a divergence of opinion regarding the usefulness/efficacy of a procedure.
Class III	Conditions for which there is general agreement that the procedure is not useful/effective and may in some cases be harmful.

Table 13. Performance of Common Imaging Techniques (Not Including Cardiac Catheterization)

Investigator	Technique	Stress	N	Sensitivity	Specificity
Hiraishi S, et al[73]	Transthoracic echocardiography Diagnosis of stenotic lesions	At rest	18	RCA: 85%, LAD: 80%	RCA: 98%, LAD: 97%
Noto N, et al[78]	Stress echocardiography Diagnosis of stenotic lesions	Dobutamine	26	90%	100%
Kondo C, et al[88]	^{201}Tl Diagnosis of stenotic lesions	Dipyridamole	34	88%	93%
Karasawa K, et al[124]	^{201}Tl Diagnosis of stenotic lesions	Dobutamine	24	71%	95%
Karasawa K, et al[124]	^{201}Tl Diagnosis of stenotic lesions	ATP	24	83%	92%
Karasawa K, et al[124]	Tc-99m tetrofosmin Diagnosis of stenotic lesions	Exercise, ATP, Dobutamine	20	90%	85%
Fukuda T, et al[125]	Tc-99m tetrofosmin Diagnosis of stenotic lesions	Dipyridamole	86	90%	100%
Hoshina M, et al[94]	^{123}I BMIPP Diagnosis of stenotic lesions	At rest	10	90%	73.9%
Kanamaru H, et al[114]	MDCT Diagnosis of stenotic lesions*	At rest	16	87.5% (25 vessels)	92.5% (52 vessels)
Miyagawa M, et al[89]	^{201}Tl Prediction of cardiac events	Dipyridamole	15	93%	83%
Suzuki A, et al[36]	MRCA Diagnosis of stenotic lesions**	At rest	70	occlusion 94.2%, stenosis 94.4%	occlusion 99.5%, stenosis 97.2%

*Of 80 vessels in 16 patients with coronary lesions, 77 vessels could be evaluated with MDCT.
**Among 70 patients with coronary lesions, evaluation was performed in 210 vessels of patients with occlusion and 54 vessels of 18 patients with regional stenosis.
Tl, thallium; Tc, technetium; BMIPP, β-methyl-p-iodophenyl-pentadecanoic acid; MDCT, multi-row detector computed tomography; MRCA, magnetic resonance coronary angiography; ATP, adenosine triphosphate; RCA, right coronary artery; LAD, left anterior descending coronary artery.

aneurysms that have regressed. Intimal narrowing and calcification, not detected with angiography may be visualized with IVUS. It has been found that obvious intimal hyperplasia may develop during the remote phase in aneurysms with an internal diameter during the acute phase of >4 mm.[19] Evaluation of lesions, and especially quantitative evaluation of calcified lesions with IVUS, is required when the means to be used for PCI are selected.[28]

b) Coronary Arterial Vasodilator Function

It has been reported that the absence of coronary vasodilatation in coronary artery wall following administration of isosorbide dinitrate (ISDN) or acetylcholine suggests the presence of chronic intimal dysfunction in patients with Kawasaki disease.[27,115] However, since evaluation of coronary arterial vasodilator function may induce coronary spasm or other adverse reactions, its potential benefits and risks should be carefully weighed before it is performed.

c) PCI

Preoperative examination should be performed to determine the severity of stenosis and its calcification and the condition of the intima in detail in order to select appropriate means for the performance of PCI. IVUS should be performed in every step of PCI to ensure the safety and efficacy of treatment. IVUS is also useful in the evaluation of postoperative restenosis.[28,116]

(4) Functional Severity Evaluation Using Flow Wires or Pressure Wires

Determination of average peak flow velocity (APV), CFR, and myocardial fractional flow reserve (FFRmyo) using a 0.014-inch guidewire equipped with an ultrasonic probe and a high-sensitivity pressure sensor (Doppler wires or pressure wires) is useful in evaluation of the functional severity of coronary artery lesion in patients with coronary artery lesions due to Kawasaki disease. CFR (CFR=[stress APV]/[APV at rest], where APV is the value at peak dilatation after infusion of papaverine hydrochloride injection) and FFRmyo (FFRmyo=[Mean pressure at a site distal to the coronary lesion of interest]−{[mean right atrial pressure]/[mean pressure at the coronary ostium]}−[mean right atrial pressure]), where these pressures are obtained simultaneously at peak dilatation after infusion of papaverine hydrochloride) are particularly suitable for the evaluation of the presence/absence and severity of myocardial ischemia and presence/absence of peripheral coronary circulatory disorder. These values are also useful in selecting appropriate treatment strategies (catheter intervention vs CABG) and postoperative evaluation. Measurements obtained with pressure wires are useful in the evaluation of stenotic lesions, and those with Doppler wires in the evaluation of dilatation lesions.[117]

The reference values in children are 2.0 for CFR and 0.75[117] for FFRmyo, and identical to those in adults.[118–121]

4. Summary of Examinations

As Table 12 shows, appropriate imaging techniques should be selected based on the severity of coronary artery lesions. Table 13 lists the diagnostic performance of the imaging techniques mainly used in the evaluation of cardiovascular sequelae in Kawasaki disease.

Selection of treatment strategies for cardiovascular sequelae in Kawasaki disease must be made on the basis of careful consideration of the pathological condition of each patient and the results of comprehensive multimodal analysis of findings obtained with different imaging techniques.

Table 14. Guidelines for Treatment of Patients With Persistent Coronary Aneurysms/Dilatation During the Chronic Phase

I **Patients without angina or detectable ischemia**
- Combination therapy using antiplatelet drugs
  - ° Examination revealed obvious ischemia — Antiplatelet drugs + Ca-blockers

II **Patients with angina**
- In addition to combination therapy using antiplatelet drugs
  - ° Angina on exertion — Nitrates, monotherapy or combination therapy of Ca-blockers, plus β-blockers if ineffective
  - ° Angina at rest or during sleep — Ca-blockers
  - ° Angina at night — Ca-blockers + nitrates or K-channel openers (nicorandil)

III **Patients complicated by cardiac dysfunction or valvular disease**
- Severity of cardiac dysfunction should be evaluated appropriately. Monotherapy or combination therapy using β-blockers, ACE inhibitors, angiotensin II receptor blockers, or statins should be added to antianginal drugs.

ACE, angiotensin converting enzyme.

Table 15. Antiplatelet Drugs and Anticoagulant Drugs

Drug	Dose	Adverse drug reactions (ADRs) and precautions
Acetylsalicylic acid (Bufferin or Bayaspirin)	30 to 50 mg/kg divided into 3 doses during the acute phase, 3 to 5 mg/kg once daily after defervescence	Hepatic function disorder, gastrointestinal ulcer, Reye syndrome (higher incidence at ≥40 mg/kg), bronchial asthma Use other drugs during varicellainfection and influenza.
Flurbiprofen (Froben)	3 to 5 mg/kg, divided into 3 doses	Hepatic function disorder, gastrointestinal ulcer Use when severe hepatic disorder due to aspirin develops.
Dipyridamole (Persantin, Anginal)	2 to 5 mg/kg, divided into 3 doses	May induce angina in patients with severe coronary stenosis. Coronary steal phenomenon, headache, dizziness, thrombocytopenia, hypersensitivity, dyspepsia
Ticlopidine (Panaldine)	5 to 7 mg/kg, divided into 2 doses	Thrombotic thrombocytopenic purpura (TTP), leukopenia (granulocytopenia), serious hepatic function disorder Blood tests must be performed every other week during the first 2 months of treatment.
Clopidogrel (Plavix)	1 mg/kg, once daily	TTP, gastrointestinal symptoms, malaise, myalgia, headache, rash, purpura, pruritus Bleeding tendency may develop when used with aspirin.
Unfractionated heparin (IV) Low-molecular-weight heparin (SC)	Loading dose 50 units/kg, maintenance dose 20 units/kg to maintain an APTT of 60 to 85 sec (1.5 to 2.5 times baseline) • Infants <12 months of age Treatment: 3 mg/kg/day, divided into 2 doses (every 12 hours) Prevention: 1.5 mg/kg/day, as above • Children/adolescents Treatment: 2 mg/kg/day, divided into 2 doses (every 12 hours) Prevention: 1 mg/kg/day, as above	Major ADRs: Shock/anaphylactoid reaction, bleeding, thrombocytopenia, thrombocytopenia/thrombosis associated with heparin-induced thrombocytopenia (HIT)
Warfarin (Warfarin)	0.05 to 0.12 mg/kg, once daily (0.05 to 0.34 mg/kg/day in the AHA guidelines) 3 to 7 days required to obtain efficacy	Dose should be adjusted to an INR of 1.6 to 2.5 (2.0 to 2.5 in the AHA guidelines) and a thrombotest (TT) value of 10 to 25%. Sensitivity to this drug, hepatic function disorder, and bleeding ADRs are possible. The effect of warfarin may be reduced by barbiturates, steroids, rifampicin, bosentan hydrate, and vitamin K-rich foods such as natto, spinach, green vegetables, chlorella, and green juices. The effect of warfarin may be increased by chloral hydrate, NSAIDs, amiodarone, statins, clopidogrel, ticlopidine, antitumor drugs, antibiotics, and antifungal drugs.

The safety and efficacy of the above drugs have not been established in children.
IV, intravenous; SC, subcutaneous; APTT, activated partial thromboplastin time; AHA, American Heart Association; INR, international normalized ratio; NSAIDs, nonsteroidal antiinflammatory drugs.

IV Treatment Methods

1. Pharmacotherapy

1 Treatment Policy

In assessment of cases of death during the remote phase in patients complicated by coronary artery lesion, the major cause of death has been found to be ischemic heart disease due to stenotic lesions resulting from coronary intimal hyperplasia or thrombotic occlusion.[122,123] In general, treatment of myocardial ischemia is performed to:

- Increase coronary blood flow
- Prevent or relieve coronary spasm
- Inhibit the formation of thrombi
- Decrease cardiac work

Accordingly, vessel wall remodeling and myocardial protection are the principal purposes of treatment.[126]

2 Treatment of Ischemic Attacks

(1) Treatment During Attacks

Sublingual administration of tablets of nitroglycerin, a fast-acting nitrate, is commonly performed to treat attacks of stable angina. Attacks will subside in 1 to 2 minutes in patients responding to sublingual nitroglycerin, while patients not responding to it should take additional sublingual tablets 5 to 10 minutes later. Since the standard dose for children has not been established, nitroglycerin should be administered at a dose calculated from the standard dose in adults.

(2) Prevention of Development of Angina Pectoris

Table 14 summarizes treatment policies for patients who still have coronary aneurysm or dilatation during the chronic phase.

(3) Prevention of Development (and Recurrence) of AMI

Among those with AMI complicated by coronary artery lesions due to Kawasaki disease, AMI occurred during sleep or at rest in 63% of patients and was not closely associated with physical activity and exertion.[127] In addition, asymptomatic AMI occurred in 37% of the patients. Pharmacotherapy for AMI should be designed to prevent the progression of intimal hypertrophy to stenotic lesions and inhibit the formation of thrombi, considering the poor myocardial oxygen consumption that may be present and possible involvement of coronary spasm in the development of myocardial infarction.

3 Pharmacotherapy

(1) Antiplatelet drugs (Table 15)

Platelet count decreases slightly immediately after the onset of Kawasaki disease (acute phase), and increases during the convalescence phase. Since platelet aggregation activity remains high during the first 3 months after onset and in some cases the first several months to 1 year after onset, it is preferable that patients with Kawasaki disease, including those without coronary sequelae, should be treated with antiplatelet drugs at low doses for about 3 months.[128–130]

On the other hand, patients with coronary aneurysm due to Kawasaki disease should receive antiplatelet drugs continuously to prevent ischemic heart disease and prevent the formation or growth of thrombi by platelet activation.

(2) Anticoagulant Drugs (Table 15)

Treatment with anticoagulant drugs is indicated for patients with medium or giant coronary aneurysms, patients with a history of AMI, and patients with abrupt dilatation of a coronary artery associated with a thrombus-like echo, among others. Patients with thrombi in coronary aneurysms should be treated with warfarin or heparin. Combined use of aspirin and warfarin is needed to prevent thromboembolism in patients with giant coronary aneurysms.[131,132] Patients should be carefully monitored for bleeding tendency due to excessive anticoagulant therapy. Children exhibit considerable individual differences in responses to anticoagulant therapy.

(3) Coronary Vasodilators and Antianginal Drugs (Table 16)

a) Ca-Blockers

In patients with Kawasaki disease, myocardial infarction may occur at rest or during sleep. Addition of Ca-blockers to the existing regimen should be considered for patients complicated by coronary spasm[133,134] and patients with post-infarct angina or myocardial ischemia.

b) β-Blockers

Among patients with Kawasaki disease, β-blockers may be administered to prevent reinfarction or sudden death in those with a history of myocardial infarction and to decrease long-term mortality. However, treatment with β-blockers may exacerbate already-existing coronary spasm.

β-blockers exerts antianginal effects by decreasing myocardial oxygen consumption.

c) Nitrates

Although the coronary vasodilatative effects of nitrates are not expected to be beneficial in the treatment of acute ischemia due to lesions with poor endothelial sell function, nitrates in sublingual or oral spray form should be attempted in treating AMI.[135,136]

(4) Drugs for Heart Failure (Table 16)

Angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs)

ACE inhibitors and ARBs may be administered to patients with left ventricular dysfunction (EF ≤40%) following myocardial infarction due to ischemic heart disease in order to decrease morbility, mortality, and the incidence of cardiac events. No study results have been published regarding the effects of ACE inhibitors and ARBs on the long-term prognosis of Kawasaki disease.

2. Non-Pharmacological Treatment

1 PCI

Unlike coronary lesions in adults, which are typically atherosclerotic lesions, the coronary lesions in patients with Kawasaki disease are often characterized by severe calcification and fibrous thickening. It is thus inappropriate and in some cases even dangerous to apply the indications for and procedures of PCI for adult patients to the treatment of patients

Table 16. Drugs for the Treatment of Angina, Heart Failure, and Ischemic Attacks

Drug	Dose	Adverse drug reactions and precautions
Drugs for angina		
Nifedipine (Adalat)	0.2 to 0.5 mg/kg/dose, TID (available as 5 and 10 mg capsules) Adult dose: 30 mg/day, divided into 3 doses	Hypotension, dizziness, headache Care is needed in patients with poor cardiac function.
Slow-release nifedipine (Adalat-CR, Adalat-L)	0.25 to 0.5 mg/kg/day, divided into 1 to 2 doses, maximum dose 3 mg/kg/day (Tablets of Adalat-CR 20 mg, L 10 mg, and L 20 mg are available) Adult dose: 40 mg/kg, OD (Adalat-L should be divided into 2 doses)	Same as above
Amlodipine (Norvasc)	0.1 to 0.3 mg/kg/dose, OD or BID (maximum dose 0.6 mg/kg/day) (Tablets of 2.5 mg and 5 mg are available) Adult dose: 5 mg/day, OD	Same as above
Diltiazem (Herbesser)	1.5 to 2 mg/kg/day, TID (maximum dose 6 mg/day) (30 mg tablets) Adult dose: 90 mg/day divided into 3 doses	Same as above
Drugs for heart failure		
Metoprolol (Seloken)	Start at 0.1 to 0.2 mg/kg/day, divided into 3 to 4 doses to titrate to 1.0 mg/kg/day (40 mg tablets) Adult dose: 60 to 120 mg/day, divided into 2 to 3 doses	Hypotension, poor cardiac function, bradycardia, hypoglycemia, bronchial asthma
Carvedilol (Artist)	Start at 0.08 mg/kg/day, maintain at 0.46 mg/kg/day (average) Adult dose: 10 to 20 mg/day, OD	Same as above
Enalapril (Renivace)	0.08 mg/kg/dose, OD (Tablets of 2.5 mg and 5 mg are available) Adult dose: 5 to 10 mg/day, OD	Hypotension, erythema, proteinuria, cough, hyperkalemia, hypersensitivity, edema
Cilazapril (Inhibace)	0.02 to 0.06 mg/kg/day, divided into 1 to 2 doses (1 mg tablets) Adult dose: Start at 0.5 mg/day, OD and titrate	Same as above
Drugs for ischemic attacks		
Isosorbide dinitrate (Nitorol)	Sublingual: one-third to one-half tablet/dose (5 mg tablets) Oral: 0.5 mg/kg/day, divided into 3 to 4 doses Adult dose: 1 to 2 tablets/dose (sublingual) Frandol tape S one-eighth to 1 sheet Adult dose: 1 sheet (40 mg)/dose Slow-release tablets (Nitrol-R, Frandol tablets) 0.5 to 1 mg/kg/dose Adult dose: 2 tablets/day (20 mg tablets)	Hypotension, headache, palpitations, dizziness, flushing
Nitroglycerin (NTG)	One-third to one-half tablet/dose sublingual	Same as above
Nitroglycerin (Nitropen)	(0.3 mg tablet) Adult dose: 1 to 2 tablets/dose	Same as above

The safety and efficacy of the above drugs have not been established in children. Doses should be determined according to the adult doses. NTG, nitroglycerin; TID, three times a day; OD, once daily; BID, two times a day.

with Kawasaki disease. The guidelines for catheterization in patients with Kawasaki disease published by the Taskforce on "Long-term Management of Kawasaki Disease" of the Ministry of Health and Welfare should be followed as basic guidelines.[137] Many aspects of the long-term prognosis following PCI in patients with Kawasaki disease have yet to be clarified; these aspects require further study. When patients with Kawasaki disease undergo PCI, pediatricians and cardiologists must be fully aware of the pathophysiology and natural history of Kawasaki disease as well as the risks and benefits of PCI in this patient population.

(1) Indications for PCI

a) Indications for PCI in Terms of Clinical Findings

- –Patients with signs/symptoms of ischemia
- –Asymptomatic patients who exhibit ischemic findings on stress tests, stress myocardial scintigraphy, dobutamine stress echocardiography, or other suitable tests
- –PCI may be considered for patients in whom testing did not reveal significant findings of ischemia but who have severe stenotic lesions which may progress to serious coronary artery ischemia in the future.

  Selection of an appropriate treatment from among three options, ie, surgical treatment, PCI, or follow-up, should be made according to the circumstances of individual patients.
- –PCI is not indicated for patients with left heart dysfunction.

b) Indications for PCI in Terms of Pathological Findings of Lesions

- –Patients with severe stenosis (≥75%)
- –Patients with localized lesions: PCI is contraindicated for patients with multivessel disease and those with significant stenosis or occlusion of the contralateral coronary arteries.
- –Patients without coronary ostial lesions

–Patients without long segmental lesions

(2) Types of PCI Techniques, Indications, and Precautions

a) ICT

ICT should be performed using urokinase (UK) at 1.0×10^4 units/kg (maximum daily dose for adults 96×10^4 units), or during the acute phase of myocardial infarction (within 6 hours after onset), tisokinase, a tissue plasminogen activator (t-PA) with high affinity for fibrin, at 2.5×10^4 units/kg (maximum daily dose for adults 640×10^4 units).[138,139] Since these agents may in rare cases induce cerebral hemorrhage or gastrointestinal hemorrhage, care is needed in their administration. Following ICT, heparin should be infused continuously for at least 12 to 24 hours to prevent reformation of thrombi. Following heparin therapy, oral antithrombotic therapy should be continued. However, in adults thrombolysis is frequently associated with bleeding complications. Since intravenous t-PA provides efficacy nearly equivalent to intracoronary t-PA, t-PA is administered intravenously rather than in intracoronary fashion. The recanalization rate is low in patients in which thrombotic occlusion developed long before medical attention, such as patients with asymptomatic myocardial infarction.

b) Plain Old Balloon Angioplasty (POBA)

Since catheters for POBA are smaller in diameter than those for other techniques and thus more accessible and flexible, this technique is feasible in young children in whom stenting and rotational ablation (Rotablator™) are difficult because of small body size. In addition, calcification is often mild in severity in coronary stenotic lesions that developed ≤6 years previously, and the efficacy of POBA is excellent in such lesions. However, it has been reported that the incidence of new aneurysms after POBA is higher in children with Kawasaki disease than in adult patients.[140] The recommended balloon pressure is ≤8 to 10 atm.[28,140,141] Children believed to require higher balloon pressures should be considered for other techniques such as rotablator treatment and CABG. Heparin should be infused continuously for 24 hours after POBA to avoid the development of thrombotic occlusion.

c) Stenting

Stenting is effective in older children in whom calcification of coronary lesions is relatively mild, when it is feasible. Stenting can achieve a larger lumen than POBA can. Stenting is also effective in the treatment of coronary arteries in which aneurysms and stenosis are present in succession. Since highly calcified lesions cannot be dilated sufficiently with balloon technique, stenting is not suitable for them. Heparin should be administered continuously immediately after stenting to avoid the development of thrombotic occlusion. It is very important to continue antithrombotic therapy and antiplatelet therapy after stenting. Only limited data are available on whether drug-eluting stents are more efficacious than conventional bare metal stents in the treatment of coronary artery lesions due to Kawasaki disease.

d) Coronary Angioplasty With Rotational Ablation

Rotational ablation is a technique that involves shaving off lesions with a high-speed conical burr covered with diamond microcrystals to obtain a larger lumen at the site of stenosis. Rotational ablation is considered the most optimal PCI technique for coronary stenotic lesions during the remote phase of Kawasaki disease, since it can obtain a larger lumen at locations with highly calcified lesions. Since this technique uses guiding catheters, and is thus difficult to perform in small children.

e) Applications of IVUS

It is quite important to accurately evaluate the severity and extent of calcification of coronary artery lesions due to Kawasaki disease before treatment and select an appropriate treatment strategy, in order to ensure the efficacy of PCI and decrease the incidence and severity of complications of PCI.

f) Therapeutic Angiogenesis Using Heparin Exercise Therapy

It has been reported that 10-day cycle ergometer exercise under intravenous heparin therapy may facilitate the development of collateral flow in patients with total occlusion of coronary artery lesion(s) due to Kawasaki disease.[142]

(3) Institutions and Backup System Requirements

PCI for patients with coronary artery lesions due to Kawasaki disease should be performed in institutions with PCI specialists, pediatric cardiologists, and CABG specialists.

(4) Postoperative Management, Evaluation, and Follow-up

During the 3 to 6 months after PCI, selective CAG should be performed to evaluate the outcome of treatment. Sufficient data do not yet exist regarding the incidence of restenosis and the long-term outcome of patients undergoing PCI for the treatment of coronary artery lesions due to Kawasaki disease. Even when progress after PCI is favorable, patients should continue antithrombotic and antiplatelet therapy and should be educated on their condition and treatment.

(5) Future Prospects: Especially Concerning the Use of CABG

The incidence of ischemic heart disease associated with Kawasaki disease is expected to decrease further with the use of advanced catheter techniques available for the treatment of coronary artery lesion in this patient population. However, patients undergoing new techniques of this type should be followed for a long period of time to clarify the long-term outcomes of such procedures in patients with Kawasaki disease.[143] PCI is not indicated for infants and young children, patients with multivessel disease, and patients with poor cardiac function. Appropriate combinations of less invasive bypass grafting and PCI are expected to enable less invasive, highly effective treatment.

2 CABG

Although the incidence of coronary artery lesion in patients with Kawasaki disease has tended to decrease as use of gamma globulin therapy during the acute phase has become more common, coronary artery lesion persists or progresses during the remote phase, and eventually leads to pediatric ischemic heart disease in a small number of patients. For patients with ischemia not responding to medical treatment, CABG using pedicle internal mammary artery grafts is a reliable technique.[144–146]

Since death after the acute phase of Kawasaki disease is mainly due to sudden death or myocardial infarction, it is essential to specify those children indicated for CABG in a timely fashion. Following CABG, no further cardiac events occurred in 70 to 80% of children, who also exhibited significant improvement of quality of life and exercise capacity as well as quality of school life.[147,148]

Table 17. Indications for Surgical Treatment of Kawasaki Disease

Coronary artery bypass grafting (CABG) may be effective in patients who have severe occlusive lesions in main coronary arteries (especially in the central portions of these arteries) or rapidly progressive lesions with evidence of myocardial ischemia. It is preferable to perform CABG using autologous pedicle internal mammary artery grafts regardless of age. Treatment such as mitral valve surgery should be considered when mitral insufficiency not responding to medical therapy is present, although such cases are rare.

1. **CABG**

CABG is indicated for patients with angiographically evident severe occlusive lesions of the coronary arteries and viability of myocardium in the affected area. Viability should be evaluated comprehensively, based on the presence/absence of angina and findings of ECG, thallium myocardial scintigraphy, two-dimensional echocardiography, left ventriculography (regional wall movement), and other techniques.

Findings of coronary angiography

The following findings are most important. When one of the following findings is present, consider surgical treatment.

- Severe occlusive lesions in the main trunk of the left coronary artery
- Severe occlusive lesions in multiple vessels (2 or 3 vessels)
- Severe occlusive lesions in the distal portion of the left anterior descending artery
- Jeopardized collaterals

In addition, the following conditions should also be considered in determining treatment strategy.

(1) When the event is considered a second or third infarction due to the presence of chronic infarct lesions, surgery may be indicated. For example, surgery may be considered to treat lesions limited to the right coronary artery.

(2) Lesions associated with recanalization of the occluded coronary artery or formation of collateral vessels should be evaluated especially carefully. Surgery may be considered for patients with findings of severe myocardial ischemia.

(3) Whether CABG is indicated should be considered carefully in younger children based on long-term patency of grafts. In general, young children controllable with medical therapy are followed carefully with periodic coronary angiography to allow them to grow, while patients with severe findings have undergone surgery at 1 to 2 years of age. It is recommended that pedicle internal mammary artery grafts be used in such cases as well.

Findings of left ventricular function testing

It is desirable that patients with favorable left ventricular function be treated with surgery, though patients with regional hypokinesis may also be indicated for surgery. Patients with serious diffuse hypokinesis must be evaluated with particular care and comprehensively based on findings for the coronary arteries and other available data. Heart transplantation may be indicated in rare cases.

2. **Mitral valve surgery**

Valvuloplasty and valve replacement may be indicated for patients with severe mitral insufficiency of long duration not responding to medical treatment.

3. **Other surgery**

In rare cases, Kawasaki disease has been complicated by cardiac tamponade, left artery aneurysm, aneurysms of the peripheral arteries, or occlusive lesion, patients with these conditions may be indicated for surgery.

Source: "Study on Kawasaki Disease", a psychosomatic disorder study supported by the Ministry of Health and Welfare in 1985, with modification.

(1) Indications for CABG

Table 17 lists the criteria for indications for surgical treatment of cardiovascular sequelae in Kawasaki disease. Candidates for CABG should be comprehensively evaluated on the basis of clinical signs and symptoms as well as findings of CAG, exercise ECG, echocardiography, stress myocardial scintigraphy, left ventriculography, and other techniques to determine whether CABG is appropriate for them.

(2) Age at Surgical Treatment

Patients undergoing CABG for the treatment of coronary artery lesion due to Kawasaki disease are 11 years of age on average and range between 1 month and 44 years of age at the time of surgery, with children aged 5 to 12 years predominant.[149] It has been reported that, with recent advances in technology, CABG can be performed safely even in children younger than those for whom it was previously considered indicated.[150,151]

(3) Surgical Techniques

The most common surgical technique is CABG using pedicle internal mammary artery grafts or pedicle right gastroepiploic artery grafts. It has been reported that the diameter and length of such grafts increase with the somatic growth of children.[147,152] CABG without cardiopulmonary bypass (off-pump CABG, OPCABG) is also performed in this patient population. The surgical techniques used for CABG in this population are becoming less invasive.[153]

(4) Outcome of Surgery

a) Graft Patency

The patency of internal mammary artery grafts and right gastroepiploic artery grafts is quite favorable, as high as 91 to 98%,[147,154,155] at 1 to 3 years after CABG. The patency of internal mammary artery grafts 20 years after CABG was 87.1%. When the patency of grafts is calculated for patients, not including those ≤12 years of age at the time of CABG, who were considered at risk of graft stenosis due to the previous technical difficulty of treatment in younger children, the patency of internal mammary artery grafts 20 years after CABG was 92.8%.[147] Recent findings (1994 to 2006) indicated that the patency of internal mammary artery grafts 10 years after CABG was 94.4% in patients who were ≤12 years of age at the time of CABG.[147] Lesions exhibiting anastomotic stenosis can be sufficiently treated with dilatation with POBA without stenting, and restenosis is rare.[148]

b) Outcome of Surgery

Following CABG, patients exhibit improvement in left ventricular function during exercise.[156,157] Favorable outcomes have been reported in patients 20 years after CABG, with a survival rate and cardiac event-free survival of 98.4% and 78.1%,[148] respectively. According to national survey data in patients evaluated 15 years after CABG, the rate of avoidance of sudden death was 94.3% in patients receiving internal mammary artery grafts.[149]

(5) Other Surgery

a) Downsizing Operation of Giant Coronary Aneurysms

Attempts have been made to use the combination of CABG and downsizing operation to treat giant coronary aneurysms to improve flow rate and flow pattern in lesions by decreasing the diameter of the aneurysms, and to prevent the formation of thrombi by increasing shear stress on vessel walls. It has been reported that warfarin therapy could be terminated in some patients treated in this fashion.[150,158]

b) Surgical Treatment of Mitral Valve Insufficiency

Unlike valvular disease due to rheumatic fever, mitral valve insufficiency due to Kawasaki disease is characterized by 1) the frequent development of complex coronary artery lesions requiring concurrent surgery and 2) the presence of severe myocardial injury and poor left ventricular function in many patients. Since valvar calcification may develop early after surgery in children undergoing valve replacement, mechanical valves are commonly used.[159]

c) Surgical Treatment of Aortic Aneurysms and Peripheral Aneurysms

In addition to coronary aneurysms, patients with Kawasaki disease may develop aneurysms in the ascending aorta, abdominal aorta, iliac artery, or axillary artery.[160] Surgical treatment of aneurysms is indicated only for large or progressive lesions.

d) Heart Transplantation

More than ten cases of heart transplantation for the treatment of Kawasaki disease have been reported in the world. In 1996, Checchia et al[161] reported 13 patients with Kawasaki disease who underwent heart transplantation. Heart transplantation is beneficial in (1) patients with significant left ventricular dysfunction, and (2) patients who have life-threatening arrhythmia and significant lesions in peripheral segments of the coronary arteries.

3. Initial (Medical) Treatment for AMI

• General Guidelines for Treatment

The main purpose of treatment of AMI in children is, as in adult patients, to decrease mortality during the acute phase and improve long-term prognosis.[138,139,162–165] Since AMI in children with a history of Kawasaki disease is caused by thrombotic occlusion of the coronary arteries, it is essential to initiate thrombolytic therapy or PCI as soon as possible to achieve reperfusion,[166,167] as in the case of AMI in adult patients. During the initial treatment immediately after arrival at the emergency department or admission to hospital, prompt diagnosis and initial treatment should be performed to determine the treatment strategy for AMI and prepare for emergency CAG and reperfusion therapy.

• Initial Treatment

1 General Treatment

(1) Oxygen therapy
Oxygen is administered to control myocardial injury.

(2) Establishment of vascular access
More than one means of vascular access should be established to ensure prompt treatment of complications possibly associated with AMI.

(3) Nitrates
Nitroglycerin should be administered intravenously or sublingually.

(4) Pain control
Continuous chest pain increases myocardial oxygen consumption. Morphine hydrochloride (0.1 to 0.2 mg/kg) is the most effective agent for this, and should be slowly administered intravenously. Treatment with morphine may be avoided when symptoms are tolerable and blood pressure and pulse are stable.

(5) Intravenous heparin therapy
Use of heparin therapy prior to reperfusion therapy may increase the rate of recanalization rate. Heparin should be infused continuously at 10 to 20 units/kg/hr.

(6) Treatment of complications
Complications of AMI such as heart failure, cardiogenic shock, and arrhythmia should be treated accordingly.

2 Reperfusion Therapy

(1) Thrombolytic Therapy

Since AMI associated with Kawasaki disease is mainly caused by thrombotic occlusion of coronary aneurysms, thrombolytic therapy is of great importance. The sooner initiate thrombolytic therapy, the better effect of therapy will be expected. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for diagnosis, treatment, and long-term management of Kawasaki disease recommend that thrombolytic therapy be performed within 12 hours after the onset of AMI.

There are no standard pediatric doses of the drugs used for thrombolytic therapy listed below. Thrombolytic agents should thus be administered carefully on the basis of the condition of individual patients. It has been reported that the rate of recanalization is 70 to 80% after intravenous thrombolytic therapy, and may be increased by about 10% when intracoronary administration of thrombolytic agents is added to intravenous therapy. Since thrombolytic therapy may be complicated by subcutaneous hemorrhage at the site of catheter insertion, cerebral hemorrhage, and reperfusion arrhythmia, patients should be carefully observed during and following thrombolytic therapy. t-PAs and pro-urokinase (pro-UK) are proteins and may induce anaphylactic shock.

• Intravenous thrombolysis
  a) UK: 1.0 to 1.6×10^4 units/kg (maximum dose 96×10^4 units). Infuse over 30 to 60 minutes.
  b) t-PAs
     – Alteplase (Activacin®, Grtpa®): 29 to 43.5×10^4 units/kg. Administer 10% of the total dose over 1 to 2 minutes intravenously and infuse the remainder over 60 minutes.
     – Monteplase (Cleactor®): 2.75×10^4 units/kg. Administer intravenously over 2 to 3 minutes.
     – Pamiteplase (Solinase®): 6.5×10^4 units/kg. Administer intravenously over 1 minute.

• ICT
  a) UK: Administer at a dose of 0.4×10^4 units/kg over 10 minutes. Administration may be repeated at most four times.

(2) PCI

In general, PCI is indicated for patients within ≤12 hours after onset. Stenting is the most prevalent PCI technique, and the combination of thrombolysis and stenting is also common. Early treatment with oral antitplatelet drugs (aspirin, Plavix®,

and Pletaal®) or intravenous heparin is promptly begun after PCI to prevent the development of in-stent thrombosis.

3 Anticoagulant Therapy and Antiplatelet Therapy to Prevent Recurrence of AMI

(1) Heparin
Heparin should be infused intravenously at a dose of 200 to 400 units/kg/day, and the dose should be adjusted to maintain an activated partial thromboplastin time (APTT) 1.5 to 2.5 times the baseline value.

(2) Warfarin
Warfarin should be administered at a dose of 0.1 mg/kg/day once daily, and the dose should be adjusted to maintain an international normalized ratio (INR) of about 1.6 to 2.5.

(3) Aspirin[168]
3 to 5 mg/kg/day (maximum dose of 100 mg)

Table 18 lists the indications of treatment by classification of severity of coronary artery lesions.

Table 18. Indications of Treatment by Classification of Severity of Coronary Artery Lesions

• Antithrombotic drugs (aspirin, dipyridamole, ticlopidine)		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	III
▷Class III	Severity classification	I, II
• Anticoagulant drugs (warfarin)		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	III
▷Class III	Severity classification	I, II
• Coronary vasodilators (Ca-blockers, β-blockers, nitrates, etc.)		
▷Class I	Severity classification	V
▷Class II	Severity classification	IV
▷Class III	Severity classification	I, II, III
• Drug for heart failure (ACE inhibitors, angiotensin II receptor blockers, β-blockers)		
▷Class I	Severity classification	V
▷Class II	Severity classification	IV
▷Class III	Severity classification	I, II, III
• PCI		
▷Class I	Severity classification	V (b)
▷Class II	Severity classification	V (a)
▷Class III	Severity classification	I, II, III, IV
• CABG		
▷Class I	Severity classification	V (b)
▷Class II	Severity classification	V (a)
▷Class III	Severity classification	I, II, III, IV

ACE, angiotensin converting enzyme; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Class I	Conditions for which there is general agreement that the treatment is useful and effective.
Class II	Conditions for which there is a divergence of opinion regarding the usefulness/efficacy of a treatment.
Class III	Conditions for which there is general agreement that the treatment is not useful/effective and may in some cases be harmful.

4. Guidance on Activities of Daily Life and Exercise (Including the School Activity Management Table)

As in the previous guidelines, the guidance on activities of daily life and exercise mainly includes management of daily activities in school.[168] Since no definitive evidence have been obtained on the effects of daily activities on long-term prognosis and lifestyle-related risk factors for the development of arteriosclerotic lesions or cardiomyopathy during the remote phase, the present guidelines indicate preferable management of school activities in students with a history of Kawasaki disease. The 2002 edition of the School Activity Management Table is available for elementary school students and junior and senior high school students. **Table 19** shows the table for junior and senior high school students.

1 Children Without Evidence of Coronary Artery Lesions During the Acute Phase

No restriction of activities of daily life or exercise is needed.

In the School Activity Management Table, physicians may indicate "no management needed" for children ≥5 years after onset. During the 5-year period after onset, "E-Allowed" (ie, Category E [intense exercise is allowed] in terms of management, with school sport club activities "allowed") should be selected in the Table. Follow-up evaluation should be performed at 1 month, 2 months, 6 months, 1 year, and 5 years after the onset of Kawasaki disease. School activity management after this follow-up period should be performed based on discussion with parents (or patients). It is preferable that physicians provide patients with the "Acute phase Kawasaki disease in summary" (**Figure 6**) when they are assigned the no management needed rating.

2 Patients Not Evaluated for Coronary Artery Lesions During the Acute Phase

(1) Patients in whom examination after the acute phase revealed no coronary lesions
No restriction of activities of daily life or exercise is needed. Follow the instructions in Section 1 (**1 Children Without Evidence of Coronary Artery Lesions During the Acute Phase**) above.

(2) Patients in whom examination after the acute phase revealed persistent coronary artery lesions according to the criteria for severity of coronary artery lesions in this guideline

a) Patients in whom CAG revealed the absence (or regression) of coronary artery lesions
No restriction of activities of daily life or exercise is needed. Follow the instructions in Section 1 (**1 Children Without Evidence of Coronary Artery Lesions During the Acute Phase**) above.

b) Patients who did not undergo CAG
Follow the instructions on activities of daily life and exercise in Section 3 (**3 Patients Who Have Been Evaluated for Coronary Artery Lesions During and After the Acute Phase**) below.
Patients should be categorized into the following groups, and provided with instructions accordingly. It is desirable that patients in groups (2) and (3) undergo CAG.
(1) Patients in whom echocardiography detected small coronary aneurysms or dilatation
(2) Patients in whom echocardiography detected medium aneurysms
(3) Patients in whom echocardiography detected

Table 19

[Edited in 2002]

School Activity Management Table (for junior and senior high school students)

Date

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

Name of institution _____

Name of physician: _____ (seal)

① Diagnosis (findings)	② Level of management Management required: A, B, C, D, E No management required	③ School sport club activity Name of club ( ) Allowed (Note:) · Prohibited	④ Next visit __ years __ months later 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 exercises, rhythmic movement, basic movement (exercise-play) (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, horizontal bar, balance beam, and vaulting box)	Calisthenics, light mat exercise, balance exercise, light jumping, rotation	Practice of low-grade technique, running to perform actions such as holding, jumping, and rotation	Performance, competition, combination of actions
	Athletics	(racing, jumping, throwing)	Standing broad jump, light throwing, basic motion, light jumping	Jogging, short run and jump	Long-distance running, sprint race, competition, time race
	Swimming	(freestyle, breaststroke, backstroke, butterfly, sidestroke)	Easy movement in water, float, prone float, kick and float, etc.	Slow swimming	Competition, performance, time race, diving
	Ball sports	Basketball	Slow exercise without running: Passing, shooting, dribbling, feinting	Training with footwork (with no close body contact): Dribble shoot, combination play (offense, defense)	Time race, applied practice, simplified game, game, competition:
		Handball	Passing, shooting, dribbling	Dribble shoot, combination play (offense, defense)	Goalkeeping
		Volleyball	Passing, servicing, receiving, feinting	Spiking, blocking, combination play (offense, defense)	
		Soccer	Dribbling, shooting, lifting, passing, feinting, trapping, throwing	Dribbling and head shooting, volley shot, combination play (offense, defense)	Goalkeeping, tackling
		Tennis	Ground stroking, servicing, lobbing, volleys, serve and receive	Smash, strong serve, receive, rally	
		Rugby	Passing, kicking, handling	Passing, kicking, handling	Ruck, maul, scrum, line-out, tackle
		Table tennis	Forehand, backhand, servcing, receiving	Forehand, backhand, serve, receive	
		Badminton	Servcing, receiving, flight	High clear, drop, drive, smash	
		Softball	Throwing, catching, batting	Base-running, combination play, running-catch	
		Baseball	Pitching, catching, batting	Base-running, combination play, running-catch	
		Golf	Grip, swing, stance	Short course golf (e.g. ground golf)	
	Martial art	Judo, kendo, (sumo, kyudo, naginata, wrestling)	Etiquette, basic movement, ukemi, swinging	Practicing simple techniques and forms	Applied practice, competition
	Dance	Original dance, folk dance, modern dance	Improvised performance, hand gesture, steps	Dance with rhythmical movement (excluding rock and samba), Japanese folk dance	Rhythmical dance, original dance, dance recital
	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 on ice/snow or slow skiing/skating Hiking on flatlands, playing while floating in the water, surfing, wind surfing	Common outdoor activities Climbing, swimming marathon, dive, canoe, boat, scuba diving
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
School events, 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.		

giant aneurysms

c) Patients in whom CAG revealed persistent coronary lesions

Follow the instructions on activities of daily life and exercise in Section 3 (**3 Patients Who Have Been Evaluated for Coronary Artery Lesions During and After the Acute Phase**) below.

Patients should be categorized into the following groups, and provided with instructions accordingly.

(1) Patients in whom CAG revealed small aneurysms or dilatation remaining

(2) Patients in whom CAG revealed medium aneurysms remaining

(3) Patients in whom CAG revealed giant aneurysms remaining

Since the accuracies of MDCT and MRI in evaluating the coronary arteries have recently improved, physicians may consider classifying patients on the basis of findings of these techniques in order to instruct them on daily life and exercise, provided that the limitations of MDCT and MRI are fully understood.

3 Patients Who Have Been Evaluated for Coronary Artery Lesions During and After the Acute Phase

(1) Patients in whom transient coronary dilatation disappeared after the acute phase

No restriction of activities of daily life or exercise is needed. Follow the instructions in Section 1 (**1 Children Without Evidence of Coronary Artery Lesions During the Acute Phase**) above.

(2) Patients with remaining small aneurysms or dilatation

No restriction of activities of daily life or exercise is needed. "E-allowed" should be selected in the School Activity Management Table.

a) Follow the instructions in Section 1 (**1 Children Without Evidence of Coronary Artery Lesions During the Acute Phase**) above when coronary lesions regress.

b) Patients with remaining coronary artery lesions should be followed up at 2 months, 6 months, and 1 year after onset and annually or later. Since findings of echocardiography may be not consistent with those of CAG, it is desirable that patients be evaluated with CAG at least once. Cardiologists should determine the need and type of drug treatment.

(3) Patients with remaining medium or giant coronary aneurysms

It is desirable that patients of this type be followed by cardiologists.

a) Patients with no findings of stenosis or myocardial ischemia

No restriction of activities of daily life or exercise is needed. "E-allowed" should be selected in the School Activity Management Table not including giant aneurysms. Patients should receive a full explanation of the importance of drug treatment and instructed to take drugs as prescribed. Patients should also be educated regarding the signs and symptoms of myocardial ischemia and actions to take if they are observed. Patients with remaining coronary artery lesions should undergo follow-up evaluation at least annually until regression of them is confirmed. The severity of exercise allowed must be determined on the basis of examinations. Patients with giant aneurysms should not be allowed to participate in school sport club activities. In the School Activity Management Table, "D-prohibited" (Category D [moderate exercise is allowed] in terms of management, with school sport club activities "prohibited") should be selected. Patients with no change after the first year after onset may be instructed with "E-prohibited".

b) Patients with findings of stenosis or myocardial ischemia

Severe exercise should be restricted. The level of allowable exercise should be rated at "D" or more severe category. School sport club activities should be "prohibited". The level of management should be selected from "A" to "D" on the basis of the results of exercise testing and evaluation of myocardial ischemia. Patients should receive a full explanation of the importance of drug treatment. When patients undergo catheter-based therapy, the level of management may be changed.

c) Patients with a history of myocardial infarction

Activities of daily life and exercise should be restricted: Patients should be rated as Category "A" to "E" on the basis of their condition. School sport club activities should be "prohibited" in principle. Level of management ("A" to "E") should be determined on the basis of results of cardiac function tests or other examinations. Patients should be educated regarding possible adverse drug reactions such as bleeding tendency.

4 Lesions Other Than Coronary Lesions

(1) Valvular Disease

Cardiologists should evaluate patients with valvular disease due to Kawasaki disease to determine whether their activities of daily life and exercise should be restricted. Cardiac functions and indications for surgical treatment should be evaluated. Patients exhibiting improvement of echocardiographic findings may assigned the rating "no management needed".

(2) Arrhythmia

Cardiologists should evaluate patients with arrhythmia due to Kawasaki disease to determine whether their activities of daily life and exercise should be restricted. The criteria for management of patients with arrhythmia should be followed when cardiac function is normal and myocardial ischemia can be ruled out. Arrhythmia patients with findings of abnormal cardiac function or myocardial ischemia should be collectively evaluated based on all available data.

(3) Aneurysms Other Than Coronary Aneurysms

Cardiologists should manage these lesions individually based on their location and severity.

5 Management After Heart Surgery

Cardiologists should follow patients undergoing heart surgery such as CABG, valvular surgery, and heart transplantation to ensure appropriate follow-up evaluation and patient education.

6 Vaccinations

Maternal antibodies play important roles in preventing measles, rubella, mumps and varicella infections.[169] Vaccinations against these diseases should be performed in order at least 6 months after high-dose gamma globulin therapy.

7 Lifestyle Changes to Prevent Arteriosclerosis

Since there is concern that a history of Kawasaki disease may

be a risk factor for the development of arteriosclerosis in later life, it is preferable that patients be educated on the prevention of lifestyle-related diseases when they receive their "Acute phase Kawasaki disease in summary".

8 Cooperation With Cardiovascular Internists

Patients with sequelae of Kawasaki disease should be followed by cardiovascular internists when they grow up. Attending physicians should discuss with patients (or family) the schedule of follow-up by different departments in order to ensure lack of interruption of follow-up evaluation.

V Follow-up Evaluation

There are no clearly defined policies on the timing and duration of non-invasive follow-up evaluation of patients with a history of Kawasaki disease in Japan. The following guidelines are designed for patients who underwent periodic echocardiography during the acute phase of Kawasaki disease. Patients are classified by severity of coronary artery lesions on the basis of echocardiographic findings for the coronary arteries during roughly the first 30 days after onset, and guidance on how to follow up coronary artery lesions by cardiologists is provided based on the severity of echocardiographic coronary findings.

1. Classification of Severity of Coronary Artery Lesions Based on Echocardiographic Findings

A-1. Patients with no dilatation of coronary arteries: The coronary arteries tend to be larger in patients during the acute phase of Kawasaki disease than in control children.[170,171] The absence of dilatation is defined for purposes of reporting as the absence of localized dilatation detectable with echocardiography.
A-2. Patients with slight and transient dilatation of coronary arteries which subsides within 30 days after the onset of Kawasaki disease.
A-3. Patients who have small coronary aneurysms at 30 days after the onset of Kawasaki disease.
A-4. Patients who have medium coronary aneurysms at 30 days after the onset of Kawasaki disease.
A-5. Patients who have giant coronary aneurysms at 30 days after the onset of Kawasaki disease.

2. Relationship Between Echocardiography-Based Severity Classification and the Severity Classification of Cardiovascular Lesions in Kawasaki Disease (Figure 5)

The severity of cardiovascular lesions evaluated according to the severity classification of cardiovascular lesions in Kawasaki disease (**Table 2-b**) changes over time depending on the duration after onset. **Figure 5** shows typical relationships between the two classification systems.

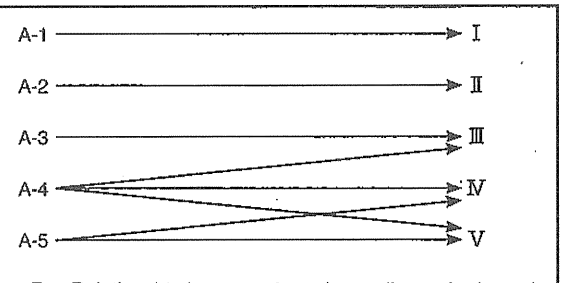


Figure 5. Relationship between the echocardiography-based severity classification (**Left**) and the severity classification of cardiovascular lesions in Kawasaki disease (**Right**).

3. Follow-up Evaluation According to the Echocardiography-Based Severity Classification

A-1: This category corresponds to Category I of the severity classification of cardiovascular lesions for Kawasaki disease.

Since patients in this category have not been followed in detail for a long period of time, findings regarding them are quite limited and their long-term prognosis remains unclear. However, it is believed that these patients have no significant problems in terms of coronary artery lesions.[13,19,27,115,135] Patients in this category should be followed for 5 years, ie, at 1, 2, and 6 months and 1 and 5 years after the onset of Kawasaki disease. Further follow-up should be scheduled individually through consultation between patients/family and attending physicians.

Follow-up evaluation should include ECG, echocardiography, and, if required, chest X-ray. It is desirable that patients be evaluated with exercise ECG at the time of final evaluation.

A-2: This category corresponds to Category II of the severity classification of cardiovascular lesions of Kawasaki disease.

As in the case of Category A-1, findings regarding the patients in this category are limited. However, it is believed that these patients have no significant problems in terms of coronary artery lesions.[13,19,27,115,135] Follow-up examination should be performed as specified in the section on Category A-1.

A-3: This category corresponds to relatively mild cases among those classified in Category III of the severity classification of cardiovascular lesions in Kawasaki disease.

In principle, patients should be followed every 3 months until findings of dilatation disappear and then annually until entry into elementary school (age of 6, 7), then in 4th grade (age 9, 10), at entry into junior high school (age of 12, 13), and at entry into senior high school (age of 15, 16). Follow-up examination should be performed as specified in the section on Category A-1, and exercise ECG should be added in children at ages when it is feasible.

A-4: This category corresponds to some cases among those classified in Categories III, IV, and V.

Since long-term prognosis in this category differs significantly among patients, the duration of follow-up should be determined individually according to patient

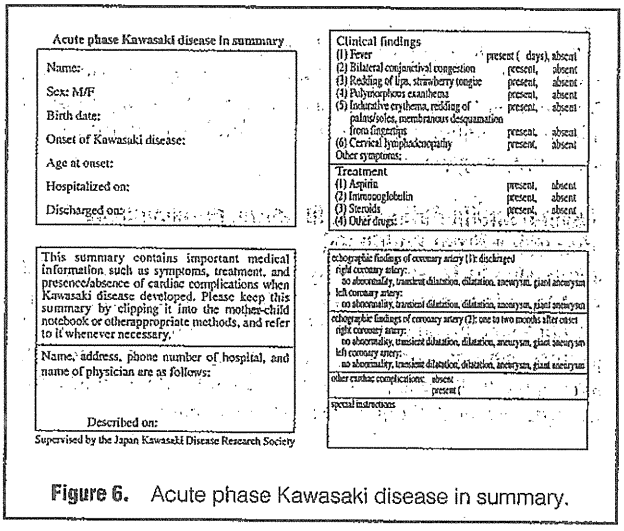
condition.

Patients should be evaluated once every 1 to 3 months with ECG, echocardiology, chest X-ray (when necessary), and exercise ECG (when feasible) until dilatation is no longer observed on echocardiology. Following the disappearance of dilatation, patients should be evaluated annually. Patients with aneurysms remaining 1 year after onset should be evaluated once every 3 to 6 months. Although selective CAG may be considered on an individual basis, patients who had aneurysms with a diameter of ≥6 mm during the acute phase must undergo follow-up with CAG at least once during the early convalescence phase and at the time of disappearance of echocardiographically evident coronary dilatations. Patients with persistent aneurysms should be followed appropriately or later. When signs/symptoms or laboratory findings suggestive of ischemia are obtained on clinical examination, echocardiography, ECG, or exercise ECG, patients should undergo stress myocardial scintigraphy and then CAG. Patients in this category, including those with regression of aneurysms, should be evaluated once every 2 to 5 years with stress myocardial scintigraphy, MRI, MRCA, MDCT or other appropriate techniques to identify the progression of the stenotic lesion.

A-5: This category corresponds to Categories IV and V of the severity classification of cardiovascular lesions in Kawasaki disease.

It is believed that aneurysms in patients in this category do not regress completely and may frequently progress to coronary occlusive lesions[172–174] Patients with persistent giant aneurysms must be followed for life and receive treatment continuously, and should be individually evaluated to design tailor-made treatment.

All patients in this category should undergo initial selective CAG during the early convalescence phase of Kawasaki disease to specify the extent of lesions. Patients should be carefully observed for clinical signs/symptoms and followed with appropriate combinations of ECG, exercise ECG, echocardiography, stress myocardial scintigraphy, selective CAG, MRI, MRCA, MDCT or other appropriate techniques. The duration of follow-up differs among individual patients. In general, patients should be evaluated once every 1 to 3 months during the first year, and once every 3 to 6 months or later.


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 otherappropriate 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) Reddling of lips, strawberry tongue present, absent
(4) Polymorphous exanthema present, absent
(5) Indurative erythema, reddling 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): discharge)
right coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
left coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
echographic findings of coronary artery (2): one to two months after onset
right coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
left coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
other cardiac complications: absent
present ( )
special instructions

Figure 6. Acute phase Kawasaki disease in summary.

4. Acute Phase Kawasaki Disease in Summary (Supervised by the Japan Kawasaki Disease Research Society) (Figure 6)

Although correct information on the clinical course of Kawasaki disease is required for the diagnosis and treatment of children with a history of Kawasaki disease, parents may be unable to recall the history or course of Kawasaki disease in their children in detail. It is therefore considered important that pediatricians describe medical information (eg, clinical symptoms, treatment, and cardiac complications) and provide it to parents so that patients may refer to it whenever necessary and thus ensure appropriate subsequent management of patients. In 2003, the Japan Kawasaki Disease Research Society developed "Acute phase Kawasaki disease in summary".[175] Pediatricians are encouraged to include findings during the acute phase on the summary and provide it to their parents.

VI Management of Adults With a History of Kawasaki Disease and Cooperation With Cardiovascular Internists

Currently, No data with a high level of evidence on the treatment or prognosis of adults with a history of Kawasaki disease have been obtained in scientifically sound studies, and no standards are available for the diagnosis and treatment of such patients.

1. Diagnosis

In adult patients, correct evaluation of coronary artery lesions is often difficult with transthoracic echocardiography, the principal technique used in the diagnosis of Kawasaki disease when they were children. The following noninvasive techniques or catheter-based methods of CAG are required for the evaluation of coronary artery lesions.

- Exercise ECG
- Exercise or pharmacological stress myocardial scintigraphy
- Holter ECG
- TEE[176]
- MRCA[177,178]
- Multislice 3D-computed tomography (CT) CAG[179]

Patients should be evaluated as follows, depending on the presence/absence of coronary aneurysm during childhood.

1 Patients Without Coronary Aneurysms During Childhood

Although it is believed that patients with normal echocardiographic findings after the acute phase may not require treatment,[180] the possibility that a history of Kawasaki disease

is associated with progression of arteriosclerosis in midlife or later cannot be ruled out.[181] Family and patients should discuss with attending physicians the need for follow-up evaluation on an individual basis, and patients may undergo noninvasive evaluation once every several years during adulthood if they request it.[182]

2 Asymptomatic Patients With Coronary Aneurysms Persisting From Childhood

Patients should be stratified by cardiac risk factors and followed for a long period of time.[183] It is desirable that patients with coronary aneurysms persisting into adulthood, including those who are asymptomatic, should be evaluated with noninvasive techniques 2 to 3 times each year and that CAG should be performed once every several years.

3 Patients With Angina Pectoris, Myocardial Infarction, Heart Failure, or Severe Arrhythmia in Adulthood

Patients with angina pectoris, myocardial infarction, heart failure, or severe arrhythmia in adulthood should be followed in a fashion similar to patients with such conditions associated with etiologies other than Kawasaki disease. It is desirable that patients should be evaluated with noninvasive techniques 3 to 4 times each year and CAG as appropriate.

4 Adult Patients With Coronary Aneurysms With Unknown History of Kawasaki Disease

The presence/absence of history of Kawasaki disease is unknown in many young adults with coronary aneurysms.[184,185] It is considered appropriate for such patients to be diagnosed as having sequelae in Kawasaki disease if other diseases causing secondary coronary aneurysms can be ruled out.[186] Basically, young adults with coronary aneurysms should be followed similarly to patients who had coronary aneurysms in childhood as described in Section 2 (**2 Asymptomatic Patients With Coronary Aneurysms Persisting From Childhood**) above.

2. Treatment

1 Patients Without Coronary Aneurysms During Childhood

Patients without coronary aneurysms during childhood may discontinue antiplatelet treatments such as aspirin.

2 Asymptomatic Patients With Coronary Aneurysms Persisting From Childhood

Asymptomatic patients with coronary aneurysms persisting from childhood must in principle continue to take aspirin and other appropriate drugs. In addition to improvements of lifestyle such as weight control and smoking cessation, prevention and appropriate treatment of coronary risk factors such as diabetes mellitus, hyperlipidemia, and hyperuricemia are necessary.

3 Patients With Angina Pectoris, Myocardial Infarction, Heart Failure, or Severe Arrhythmia in Adulthood

These patients should be treated in a fashion similar to patients with such conditions associated with etiologies other than Kawasaki disease. In addition to aspirin, antitplatelet drugs, antianginal drugs, diuretics, and other drugs for the treatment of heart failure, or antiarrhythmic drugs may be required. When ischemia is demonstrated on exercise ECG or radionuclide imaging, PCI should be performed as appropriate.

4 Adult Patients With Coronary Aneurysms With Unknown History of Kawasaki Disease

Basically, young adults with coronary aneurysms should be treated as described in Sections 2 (**2 Asymptomatic Patients With Coronary Aneurysms Persisting From Childhood**) and 3 (**3 Patients With Angina Pectoris, Myocardial Infarction, Heart Failure, or Severe Arrhythmia in Adulthood**) above.

3. Management of Daily Life and Exercise

History of Kawasaki disease may be an unavoidable risk factor for arteriosclerosis in adulthood. Coronary risk factors, at least those known to promote arteriosclerosis during adulthood, should be controlled through substantial improvement of daily life and exercise management.

1 Improvement of Lifestyle and Treatment of Coronary Risk Factors

- Antihypertensive therapy according to the relevant guidelines
- Smoking cessation
- Diabetes management
- Antihyperlipidemic therapy
- Weight control in obese patients
- Reduction of psychological/social stress

2 Management of Exercise

Exercise training may decrease body weight, yield a sense of well-being, and decrease the need for pharmacological treatment of coronary artery lesions. Patients should be evaluated to determine the risks associated with exercise testing or other appropriate techniques, and prescribed exercise accordingly.

4. Understanding of Kawasaki Disease by Internists

General internists are not sufficiently aware of the pathophysiology of Kawasaki disease during the acute phase. It is important for internists, especially cardiovascular internists, to understand the pathophysiology of Kawasaki disease in adults.

5. Coronary Aneurysms and Myocardial Infarction in Young Patients and Kawasaki Disease

Young adults with myocardial infarction or cardiovascular findings should be investigated to determine the presence/absence of Kawasaki disease during early childhood.[187]

6. Comparison With Adult-Type Myocardial Infarction

In the pathologic evaluation of patients with Kawasaki disease, no severe atherosclerotic lesions are observed although substantial arteriosclerosis is present.[185] It is thus currently unclear whether sequelae of vasculitis due to Kawasaki disease promote atherosclerosis. Remodeling of coronary artery lesions in patients with sequelae in Kawasaki disease may persist for years after onset, and is associated with intimal hyperplasia and neovascularization. These findings differ from those in juvenile patients with arteriosclerosis not associated with Kawasaki disease.[29]

VII Summarized Guidelines

Table 20

Severity	Pathophysiology	Diagnosis / clinical course	Treatment	Daily life/exercise management*
I No dilatation	There is no evidence whether or not a history of Kawasaki disease is a factor associated with arteriosclerotic lesion.	Follow up patients for 5 years. Evaluate at 30 days, 60 days, 6 months, 1 year, and 5 year after onset with ECG, echocardiography, and, if necessary, chest X-ray. It is desirable that patients be evaluated with exercise ECG at the final examination.	Basically, no treatment is required during the remote phase. Patients with no coronary aneurysms after the acute phase may discontinue antiplatelet drugs such as aspirin.	No restriction is placed on daily life or exercise. Management Table: "No management needed" for children ≥5 years after onset. Consult with parents (or patients) to determine further man-agement. Lifetime prevention of lifestyle-related diseases is important. Junior and senior high school students should be educated on lifestyle-related diseases (blood lipid measurement, education on smoking cessation, and prevention of obesity).
II Transient dilatation during the acute phase	During the acute phase, histopathologically vasculitis develops in the outer layer of the tunica media and then expands to the intima in coronary arteries. Echocardiography reveals diffuse dilatation of coronary arteries, but these changes subside within 30 days after onset.			
III Regression	In many cases regression may occur 1 to 2 years after onset, particularly in small or medium aneurysms. In the segment with regression, decrease in coronary diastolic function, abnormal function of vascular endothelium, and substantial intimal hyperplasia have been reported.	Basically, follow patients annually with ECG, echocardiography, and chest X-ray up to entry into elementary school (age of 6, 7), and then with the same methods and exercise ECG in 4th grade (age 9, 10), at entry into junior high school (age 12, 13), and entry into senior high school (age 15, 16). Follow patients who had coronary aneurysms with a large internal diameter during the acute phase with an appropriate combination of imaging techniques**.		No restriction is placed on daily life or exercise. Follow the recommendations for Categories I and II.
IV Remaining coronary aneurysms	Aneurysms remaining during the convalescence phase or later are considered sequelae. Histopathologically, progression of inflammation leads to rupture of the internal elastic band, causing panangiitis. The internal and external elastic bands are broken into fragments and ruptured by arterial pressure to form aneurysms. Patients with giant aneurysms must be observed carefully for myocardial ischemia, since in such patients myocardial ischemia may develop even if no significant stenotic lesions are present.	Patients must be followed with exercise ECG and an appropriate combination of imaging techniques.** It is desirable that patients who had coronary aneurysms with a large internal diameter during the acute phase be evaluated with stress myocardial scintigraphy every 2 to 5 years to monitor for progression to stenotic lesions.	Continue treatment with antiplatelet agents such as aspirin. Anticoagulant therapy may be needed in patients with giant coronary aneurysms or thrombi in coronary aneurysms. CABG may be indicated for patients with giant coronary aneurysms not accompanied by signifcant stenotic lesions when myocardial ischemia has occurred.	No restriction is placed on daily life or exercise. Management Table: "E-allowed". Patients with giant aneurysms: Instruct as "D-prohibited" in the Management Table. In the second year after onset or later, "E-prohibited" is possible when no changes are noted.
V-a Coronary stenotic lesions (no findings of ischemia)	Thrombotic occlusion of medium or giant aneurysms may develop during the relatively early stage after onset. Sudden death may occur, though two-thirds patients with occlusion are asymptomatic. Patients often show improvement of myocardial ischemia due to the development of recanalized vessels and collateral flow after occlusion. Development/progression of regional stenosis during the remote phase is more prevalent in the left coronary artery than in the right coronary artery. The segments with greatest prevalence are the proximal segment or the main trunk of the left anterior descending artery. The risk of progression to stenosis/occlusion is higher in larger aneurysms. Stenosis may develop during long-term follow up.	Patients must be followed for life, and physicians must design the tailor-made management plan for individual patients. Follow-up examination must include exercise ECG and an appropriate combination of imaging techniques**. Although schedule may differ among individuals, patients are generally evaluated every 3 to 6 months.	Continue treatment with antiplatelet drugs such as aspirin. Use Ca-blockers, nitrates, β-blockers, ACE inhibitors, and angiotensin receptor II blockers to prevent ischemic attacks and heart failure.	No restriction is placed on daily life or exercise. Management Table: "E-allowed" for patients other than those with giant aneurysms. Explain the importance of drug treatment and ensure adherence, as well as symptoms which may occur and actions to be taken when ischemia develops. Patients must be followed at least annually until regression of aneurysms is documented.
V-b Coronary stenotic lesions (with findings of ischemia)			Follow the instructions for drug treatment in Category V-a. Consider CABG or appropriate PCI technique when exercise ECG or stress myocardial scintigraphy reveals ischemia.	Exercise shuld be restricted. Categorize in "D" or higher category based on patient condition. School sport club activities should be "prohibited". Select the most appropriate category from "A" to "D" on the basis of findings of exercise testing and evaluation of severity of myocardial ischemia. Educate patients well about the importance of drug treatment.

*See Table 19.
**Imaging techniques include echocardiography (including stress echocardiography), stress myocardial scintigraphy, selective CAG, IVUS, MRI, MRA, and MDCT.
CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; PCI, percutaneous coronary intervention; CAG, coronary angiography; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; MDCT, multi-row detector computed tomography.

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Appendix

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- Kiyoshi Baba, Department of Pediatrics, Osaka Developmental Rehabilitation Center
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- Kensuke Karasawa, Department of Pediatrics, Nihon University School of Medicine
- Tsutomu Saji, First Department of Pediatrics, Toho University
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Independent Assessment Committee:
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- Makoto Nakazawa, Pediatric and Lifelong Congenital Cardiology Institute, Southern Tohoku General Hospital
- Masami Ochi, Division of Cardiovascular Surgery, Nippon Medical School
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