Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008)

– Digest Version –

JCS Joint Working Group

Table of Contents

Introduction of the Revised Guidelines 1990

I Current Epidemiology of Kawasaki Disease, and Advancement in and Topics Related to Acute Phase Treatment 1991

1. Current Epidemiology of Kawasaki Disease 1991

2. Mortality and Prognosis of Patients With Kawasaki Disease 1991

3. Advancement in Intravenous Immunoglobulin (IVIG) Therapy 1992

4. Changes Over Time in the Incidence of Coronary Artery Lesion 1992

5. Advancement in Treatment for Patients Not Responding to IVIG Therapy 1992

6. Problems With Incomplete (Atypical) Kawasaki Disease 1992

II Pathology, Pathophysiology, and Natural History of Cardiac Sequelae in Kawasaki Disease 1992

1. Coronary Artery Lesions 1992

2. Myocardial Injury 1993

3. Valvular Disease 1994

4. Arteriosclerosis (Especially Progression to Atherosclerosis) 1994

5. Non-Coronary Vessel Disorders 1994

6. Summary of Pathology, Pathophysiology, and Natural History of Cardiac Sequelae 1994

7. Genetic Background 1996

III Examinations 1996


2. Physiological Examinations (ECG) 1996

3. Diagnostic Imaging 1998

4. Summary of Examinations 2002

IV Treatment Methods 2004

1. Pharmacotherapy 2004

2. Non-Pharmacological Treatment 2004

3. Initial (Medical) Treatment for AMI 2008

4. Guidance on Activities of Daily Life and Exercise (Including the School Activity Management Table) 2009

V Follow-up Evaluation 2012

1. Classification of Severity of Coronary Artery Lesions Based on Echocardiographic Findings 2012

2. Relationship Between Echocardiography-Based Severity Classification and the Severity Classification of Cardiovascular Lesions in Kawasaki Disease 2012

3. Follow-up Evaluation According to the Echocardiography-Based Severity Classification 2012

4. Acute Phase Kawasaki Disease in Summary (Supervised by the Japan Kawasaki Disease Research Society) 2013

VI Management of Adults With a History of Kawasaki Disease and Cooperation With Cardiovascular Internists 2013

1. Diagnosis 2013

2. Treatment 2014


4. Understanding of Kawasaki Disease by Internists 2014

5. Coronary Aneurysms and Myocardial Infarction in Young Patients and Kawasaki Disease 2014

6. Comparison With Adult-Type Myocardial Infarction 2014

VII Summarized Guidelines 2015

References 2016

Introduction of the Revised Guidelines

More than forty years have passed since 1967, when the first case series of Kawasaki disease was reported. Currently, more than half of the patients diagnosed with Kawasaki disease are 16 years of age or older. In Japan, Kawasaki disease is now managed not only by pediatricians but also by internists. As this timeline suggests, it is expected that more than half of the patients with cardiovascular sequelae of Kawasaki disease have reached adulthood. However, since Kawasaki disease develops most frequently by around 1 year of age, many internists are still not familiar with it (Table 1). The main cardiovascular disease caused by Kawasaki disease is vasculitis, and in this respect patients with this disease differ significantly from other adult patients with arteriosclerosis and/or hypertension. Since the number of adult patients with a history of Kawasaki disease will increase over time, pediatric cardiologists need to accurately provide their findings on Kawasaki disease to cardiovascular internists. Reliable means are needed to ensure appropriate diagnosis, treatment, and determination of the prognosis of patients with cardiovascular sequelae in Kawasaki disease. We hope the present guidelines will help healthcare professionals diagnose and treat their patients with Kawasaki disease.

No major additions or corrections of the revised guidelines presented here have been made. The present guidelines basically follow the previous version of the guidelines. However, since the number of adult patients with coronary artery lesions and a history of Kawasaki disease is growing increasingly larger over time, in the present guidelines additional descriptions are included of the risk of development of arteriosclerosis, mechanism of development of arteriosclerosis, and prevention and treatment of arteriosclerosis in patients with a history of Kawasaki disease, particularly those with coronary artery lesions. The recent advancement of diagnostic imaging techniques has been impressive, and there are many techniques useful in the diagnosis and treatment of coronary artery lesions due to Kawasaki disease. The present

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Guidelines of Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.</td>
</tr>
<tr>
<td><strong>A. Principal symptoms</strong></td>
</tr>
<tr>
<td>1. Fever persisting 5 days or more (inclusive of those cases in whom the fever has subsided before the 5th day in response to therapy)</td>
</tr>
<tr>
<td>2. Bilateral conjunctival congestion</td>
</tr>
<tr>
<td>3. Changes of lips and oral cavity: Reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa</td>
</tr>
<tr>
<td>4. Polymorphous exanthema</td>
</tr>
<tr>
<td>5. Changes of peripheral extremities:</td>
</tr>
<tr>
<td>(Acute phase): Reddening of palms and soles, Indurative edema</td>
</tr>
<tr>
<td>(Convalescent phase): Membranous desquamation from fingertips</td>
</tr>
<tr>
<td>6. Acute nonpurulent cervical lymphadenopathy</td>
</tr>
<tr>
<td>At least five items of 1 to 6 should be satisfied for diagnosis of Kawasaki disease. However, patients with four items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm or dilatation is recognized by two-dimensional (2D) echocardiography or coronary angiography.</td>
</tr>
<tr>
<td><strong>B. Other significant symptoms of findings</strong></td>
</tr>
<tr>
<td>The following symptoms and findings should be considered in the clinical evaluation of suspected patients.</td>
</tr>
<tr>
<td>1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage QRS complexes, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly), 2D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (axillary, etc.), angina pectoris or myocardial infarction</td>
</tr>
<tr>
<td>2. Gastrointestinal (GI) tract: Diarrhea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase</td>
</tr>
<tr>
<td>3. Blood: Leukocytosis with shift to the left, thrombocytosis, increased erythrocyte sedimentation rate (ESR), positive C-reactive protein (CRP), hypoalbuminemia, increased α2-globulin, slight decrease in erythrocyte and hemoglobin levels</td>
</tr>
<tr>
<td>4. Urine: Proteinuria, increase of leukocytes in urine sediment</td>
</tr>
<tr>
<td>5. Skin: Redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the finger nails</td>
</tr>
<tr>
<td>6. Respiratory: Cough, rhinorrhea, abnormal shadow on chest X-ray</td>
</tr>
<tr>
<td>7. Joint: Pain, swelling</td>
</tr>
<tr>
<td>8. Neurological: Cerebrospinal fluid (CSF) pleocytosis, convulsion, unconsciousness, facial palsy, paralysis of the extremities</td>
</tr>
</tbody>
</table>

**Remarks**

1. For item 5 under principal symptoms, the convalescent phase is considered important.
2. Nonpurulent cervical lymphadenopathy is less frequently encountered (approximately 65%) than other principal symptoms during the acute phase.
3. Male: Female ratio: 1.3 to 1.5:1, patients under 5 years of age: 80 to 85%, fatality rate: 0.1%
4. Recurrence rate: 2 to 3%, proportion of siblings cases: 1 to 2%
5. Approximately 10% of the total cases do not fulfill five of the six principal symptoms, in which other diseases can be excluded and Kawasaki disease is suspected. In some of these patients coronary aneurysms (including so-called coronary artery ectasia) have been confirmed.

guidelines thus describe in detail current knowledge on diagnostic imaging techniques used to evaluate coronary artery lesions. We also discuss the genetic background of Kawasaki disease, although findings regarding this still limited. We previously discussed the classification of coronary artery lesions during the acute phase of Kawasaki disease. Although the criteria for small aneurysms and giant aneurysms were slightly questioned, we decided that no modifications of the criteria needed to be made, based on the opinions of members and collaborators such that no new evidence have been provided on this matter, and that the classification may not be revised in the present guidelines because it will not affect the contents of the present guidelines for the diagnosis and treatment of cardiovascular sequelae in Kawasaki disease. We used the conventional classification to prepare the present guidelines (Table 2).

Although the present guidelines are based in principle on available evidence, the diagnosis and treatment of sequelae in Kawasaki disease are often based on case reports.

Table 2. Classification of Severity of Cardiovascular Lesions in Kawasaki Disease

(a) Classification of coronary aneurysms during the acute phase

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small aneurysms (ANs) or dilatation (Dil)</td>
<td>localized dilatation with ≤4 mm internal diameter</td>
</tr>
<tr>
<td>Medium aneurysms (ANm)</td>
<td>aneurysm with an internal diameter from &gt;4 mm to ≤8 mm</td>
</tr>
<tr>
<td>Giant aneurysms (ANI)</td>
<td>aneurysm with an internal diameter of &gt;8 mm</td>
</tr>
</tbody>
</table>

(b) Severity classification

- I. No coronary dilatation: patients with no coronary dilatation including those in the acute phase
- II. Transient coronary dilatation during the acute phase: patients with slight and transient coronary dilatation which typically subsides within 30 days after onset
- III. Regression: patients who still exhibit coronary aneurysms meeting the criteria for dilatation or more severe change on day 30 after onset, despite complete disappearance of changes in the bilateral coronary artery systems during the first year after onset, and who do not meet the criteria for Group V
- IV. Remaining coronary aneurysm: patients in whom unilateral or bilateral coronary aneurysms are detected by coronary angiography in the second year or later and who do not meet the criteria for Group V
- V. Coronary stenotic lesions: patients with coronary stenotic lesions detected by coronary angiography

Other clinical symptoms of findings: When patients have moderate or severe valvular disease, heart failure, severe arrhythmia, or other cardiac disease, such conditions should be described in addition to the severity of Kawasaki disease.

Table 3. Levels of Recommendations

<table>
<thead>
<tr>
<th>Class</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.</td>
</tr>
<tr>
<td>II</td>
<td>Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of a procedure or treatment.</td>
</tr>
<tr>
<td>III</td>
<td>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.</td>
</tr>
</tbody>
</table>

Emphasis was therefore placed on case reports in the present guidelines as well. Table 3 lists the criteria for levels of recommendations on the procedure and treatment of cardiovascular sequelae in Kawasaki disease.

I Current Epidemiology of Kawasaki Disease, and Advancement in and Topics Related to Acute Phase Treatment

1. Current Epidemiology of Kawasaki Disease

According to the 19th national survey on Kawasaki disease (2005 to 2006), the number of patients diagnosed was 10,041 in 2005 and 10,434 in 2006, yielding a total of 20,475 patients. The mean prevalence during the 2-year survey period was 184.6 patients/100,000 children 0 to 4 years of age (male 209.3, female 158.6). The total number of patients with Kawasaki disease including those patients reported in the 19th national survey is 225,682 (male 130,827, female 94,855) as of December 31, 2006. About 90,000 patients were ≥20 years of age as of January 2006.

2. Mortality and Prognosis of Patients With Kawasaki Disease

The mortality of patients with Kawasaki disease has gradually decreased, from 0.13% in 1989 to 0.01% in the latest survey. In a cohort study of 6,576 patients followed for about 20
years, the standardized mortality ratio (SMR) was 1.14 overall and 0.71 in patients after the acute phase. The mortality rate in male patients with cardiac sequelae in Kawasaki disease was 2.55, and significantly higher than the overall rate.

3. Advancement in Intravenous Immunoglobulin (IVIG) Therapy

During the acute phase, about 86% of patients received IVIG therapy in the 19th national survey. Among patients undergoing initial IVIG therapy, 16.2% received an additional IVIG therapy after the initial therapy, and 4.5% of patients received steroids (including patients receiving additional IVIG therapy and those receiving a combination of IVIG and steroids). Pulse steroid therapy was performed in 3.0% of patients and non-pulse steroid therapy in 2.5% (including patients undergoing both pulse therapy and non-pulse therapy).

4. Changes Over Time in the Incidence of Coronary Artery Lesion

The prevalence of coronary artery lesion during the acute phase has decreased over time: 18.1% in 1997 to 2000 (coronary dilatation 14.7%, aneurysm 2.9%, giant aneurysm 0.50%), 14.8% in 2001 to 2004 (coronary dilatation 11.6%, aneurysm 1.9%, giant aneurysm 0.36%), and 11.9% in the 19th survey (coronary dilatation 10.1%, aneurysm 1.5%, giant aneurysm 0.35%).

The prevalence of coronary artery lesion observed as sequelae in Kawasaki disease has also decreased, from 6.2% in 1997 to 2000 (coronary dilatation 3.9%, aneurysm 1.9%, giant aneurysm 0.46%), to 4.5% in 2001 to 2004 (coronary dilatation 2.8%, aneurysm 1.3%, giant aneurysm 0.33%), and 3.7% in the 19th survey (coronary dilatation 2.3%, aneurysm 1.0%, giant aneurysm 0.35%). The improvement of clinical results may be explained by the increase in frequency of use of single-dose treatment with immunoglobulin 2 g/kg from 8% to 68%.

5. Advancement in Treatment for Patients Not Responding to IVIG Therapy

It is important to treat patients not responding to initial IVIG therapy, who account for about 15% of children with Kawasaki disease, and additional treatments with IVIG, steroid, ulinastatin, and plasmapheresis have been performed for them. Although immunosuppressive agents, such as cyclosporine and infliximab are also used currently, the efficacy and safety of these drugs in the treatment of Kawasaki disease have yet to be established.

6. Problems With Incomplete (Atypical) Kawasaki Disease

The incidence of coronary artery lesions in patients exhibiting 4 principal symptoms of Kawasaki disease is slightly higher than that in patients with 5 to 6 principal symptoms. Presentation of a small number of principal symptoms does not necessarily indicate mild disease. Patients with at least 4 principal symptoms require treatment identical to that for patients with complete (typical) Kawasaki disease, and patients with ≤3 principal symptoms should be treated similarly to those with complete Kawasaki disease.

II Pathology, Pathophysiology, and Natural History of Cardiac Sequelae in Kawasaki Disease

1. Coronary Artery Lesions

The incidence of coronary aneurysm as a sequelae of Kawasaki disease was 16.7% in 1983, when aspirin was the main component of acute phase treatment, but decreased to 3.8% in 2007 as the use of high-dose gamma globulin therapy increased. The mortality rate of children with Kawasaki disease was above 1% by 1974, but decreased to around 0.1% in 1990s and is currently 0.01%.

1 Development of Coronary Aneurysms

Coronary artery lesions are observed during the initial acute phase of Kawasaki disease by echocardiography in all patients as increased echo intensity of the coronary artery wall an average of 5.4 days after onset. Coronary dilatation subsides during the initial acute phase, ie, within 30 days after onset, and is referred to as transient coronary dilatation, while coronary aneurysms persisting during the convalescence phase or later are considered sequelae of Kawasaki disease. The incidences of coronary sequelae have decreased to 10.09%, 1.49%, and 0.35% in the case of coronary dilatation, aneurysms, and giant aneurysms, respectively. It is important to examine for persistent aneurysms using echocardiography during the early stage and about 30 days after the onset of Kawasaki disease.

2 Prognosis (Table 2 and Table 4)

(1) Reduction and Regression of Aneurysms

Coronary aneurysms remaining ≥30 days after the onset of Kawasaki disease typically decrease in size during the convalescence phase or later. “Regression” of coronary aneurysms, ie, disappearance of abnormal findings on coronary angiography (CAG), often occurs within 1 to 2 years after onset and typically occurs in the case of small or medium aneurysms. This regression has been reported to occur in 32% to 50% of patients. It has been reported that patients may develop stenosis of vessels that have exhibited regression, decrease in coronary diastolic function, abnormal vascular endothelial function, and substantial intimal hyperplasia, which have been suggested to lead to juvenile arteriosclerosis. Patients should thus be followed up even after regression of coronary aneurysms.

(2) Occlusion of Aneurysms

Medium and giant aneurysms are often associated with thrombotic occlusion in the relatively early stage of Kawasaki disease.
disease. While coronary occlusions are associated with myocardial infarction and sudden death, approximately two-thirds of such patients are asymptomatic.\textsuperscript{16} It is typical of Kawasaki disease that coronary occlusion is followed by the development of recanalized vessels and collateral flows which significantly improve findings of myocardial ischemia.\textsuperscript{17} However, patients may often suffer symptoms of myocardial ischemia during adolescence, and may require bypass surgery or develop heart failure and arrhythmias.

(3) Recanalization (Segmental Stenosis)
Neovascularization considered to represent recanalization after occlusion is referred to as segmental stenosis. Segmental stenosis is observed in 15\% of patients with coronary artery lesions due to Kawasaki disease, and occurs in the right coronary artery in 90\% of such patients.\textsuperscript{16} Occlusion and recanalization in the right coronary artery are considered more common. Angiographic findings of segmental stenosis are classified into three types according to their pathophysiology, time of onset, and prognosis\textsuperscript{17} (Figure 1).

(4) Localized Stenosis
During the period up to 10 to 21 years after onset, localized stenoses of \( \geq 75\% \) vessel diameter develop in 4.7 to 12\% of patients with coronary artery lesions, and often occur in the proximal segment or the main trunk of the left anterior descending artery.\textsuperscript{18} Although progression to stenosis is more common in the case of giant aneurysms, it has been suggested that even small aneurysms with a diameter of 5 to 6 mm on angiography may progress to stenosis during long-term follow-up.\textsuperscript{9} Evaluation with intravascular ultrasound (IVUS) has revealed intimal hyperplasia in aneurysms with an internal diameter of \( \geq 4 \) mm, which may progress to stenosis.\textsuperscript{19}

(5) Coronary Arteries Without Aneurysm Formation
Slight or moderate intimal hyperplasia in coronary arteries without aneurysm formation has been reported in patients with Kawasaki disease.\textsuperscript{12,14} and whether a history of Kawasaki disease is a risk factor for development of atherosclerotic lesions has been discussed.

### Table 4. Classification of Coronary Artery Lesions by Angiographic Findings

- Dilatation lesions: DL (ANI, ANm, ANs, or Dil, as defined in echocardiography-based classification [Table 2])
- Stenotic lesions: SL
- Occlusion: OC, 100\% SL
- Segmental stenosis: SS [recanalized vessel] (See Figure 1)
  - A. Braid-like lesion: multiple regions of neovascularizations within the thrombotic occlusion
  - B. Bridging lesion: development of nutrient arteries distal to an occluded aneurysm
  - C. Pericoronary artery communication: anterograde blood flow with a communication of two points in one coronary artery via an existing vessel
- Local stenosis: LS

Subcommittee on Standardization of Coronary Artery Lesions due to Kawasaki Disease, "the Kawasaki Disease Research Group", Ministry of Health and Welfare, 1983.

### Table 5. Characteristics of Myocarditis During the Acute Phase of Kawasaki Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis during the acute phase of Kawasaki disease</td>
<td>is often transient</td>
</tr>
<tr>
<td></td>
<td>is often associated with a slight decrease in left ventricular ejection fraction</td>
</tr>
<tr>
<td></td>
<td>is often associated with transient pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>is associated with transient abnormalities of all valves, among which slight mitral insufficiency and aortic insufficiency may persist</td>
</tr>
<tr>
<td></td>
<td>is rarely associated with severe myocarditis.</td>
</tr>
</tbody>
</table>

### 2. Myocardial Injury
Myocardial injury is classified mainly into two types: inflammatory myocardial injury associated with myocarditis or valvulitis during the acute phase, and ischemic myocardial injury secondary to coronary aneurysms or microcirculation disorder due to coronary arteritis.

1 Inflammatory Lesions
Interstitial myocarditis and pericarditis are major inflammatory heart diseases associated with Kawasaki disease. The presence of myocarditis during the acute phase has been detected with gallium (Ga)-67 myocardial scintigraphy.\textsuperscript{20} Cell infiltration mainly by monocytes is a main pathological finding, while degeneration and necrosis of myocytes are rare. Table 5 lists the characteristics of myocarditis in Kawasaki disease.

2 Ischemic Lesions
Acute myocardial infarction (AMI) due to stenotic lesions adjacent to coronary aneurysms caused by severe coronary arteritis tends to develop during the second week after onset or later. Progression of coronary aneurysms to stenotic lesions is more prevalent in aneurysms with an internal diameter of \( \geq 6 \) mm, and is especially prevalent in giant aneurysms with a diameter of \( \geq 8 \) mm. Chronic myocardial infarction is observed more often after the first 7 weeks of disease, following the acute phase.

3 Lesions in the Conducting System
During the acute phase, inflammation of the conducting system is observed, and transient atrioventricular block, premature ventricular contraction, supraventricular tachycardia, or ventricular tachycardia may develop as clinical manifestations of injury to the conducting system.
3. Valvular Disease

Slight and transient mitral, tricuspid, or pulmonary valve insufficiency is often observed by Doppler echocardiography during the acute phase of Kawasaki disease, and aortic valve insufficiency is also observed in rare cases. In addition to regurgitation due to myocarditis and valvulitis during the acute phase, regurgitation may also develop during the remote phase due to thickness or deformation of valves with fibrosis after valvulitis, or to papillary muscle dysfunction caused by ischemia (Figure 2). The incidence of valvular disease is reported to be 1.88% during the acute phase and 0.41% or later.2

4. Arteriosclerosis (Especially Progression to Atherosclerosis)

The progression of vessel disorders due to Kawasaki disease, and especially that of coronary artery lesions to sclerotic lesions, has been described in detail.14,25-32 Recent clinical studies have revealed that abnormal diastolic function of peripheral vessels and changes in endothelial cell biomarkers of vascular endothelial dysfunction are present during the remote phase regardless of the presence or absence of coronary artery lesions.33-35 However, there is no clinical evidence clearly indicating whether the incidence of atherosclerosis, a finding of lifestyle-related diseases commonly observed in adults, is higher in individuals with a history of Kawasaki disease. Long-term, large-scale, continuous clinical studies will be needed to answer this question. Careful and detailed investigations of the development and progression of arteriosclerotic lesions after Kawasaki disease are needed to clarify the mechanisms underlying them and determine how to prevent the development/progression of such lesions, in ensuring appropriate long-term management of patients.

5. Non-Coronary Vessel Disorders

Aneurysms of the axillary arteries, femoral arteries, iliac arteries, renal arteries, abdominal aorta, and internal mammary arteries have been observed in rare cases (0.633 to 2.34), and all patients with peripheral aneurysms in these arteries have large coronary aneurysms. Cases of necrotic lesions of the fingers, cerebral infarction due to cerebrovascular disorders, renovascular hypertension, shock due to rupture of femoral arteries, replacement of large abdominal aneurysms with vascular prostheses, and coating of aneurysms have been reported in patients with a history of Kawasaki disease. Although in many cases aneurysms in the axillary arteries and other vessels regress within 1 to 2 years, a case of abrupt occlusion after 35 years has been reported.35 Patients with aneurysms of the peripheral arteries should thus be followed for a long period of time.

6. Summary of Pathology, Pathophysiology, and Natural History of Cardiac Sequelae

1 Coronary Artery Lesions

Although significant infiltration of inflammatory cells in the coronary arteries during the acute phase of Kawasaki disease regresses over time, a large number of inflammatory cells may remain in the intima, and endarteritis may persist for a long period of time even after remission of clinical symptoms.16,37 During the remote phase, vascular smooth muscle cells continue to multiply actively at the inlet and outlet of the aneurysm, and concentric intimal hyperplasia may induce stenosis or occlusion. When an aneurysm becomes clogged by a clot, a new artery with multiple lumens is often formed through the clot. The prognosis in such cases of myocardial ischemia is thus often fair.37 However, such spontaneous recanalization develops only when sudden death or severe myocardial infarction does not occur at the time of occlusion. Patients with medium or giant aneurysms and those with progressive localized stenosis are continuously at risk of sudden death and/or myocardial infarction. It is therefore believed

<table>
<thead>
<tr>
<th>Acute phase</th>
<th>Myocarditis</th>
<th>Endocarditis</th>
<th>Coronary aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring dilatation</td>
<td>Valvulitis</td>
<td>Atrioventricular valve</td>
<td>Coronary occlusion</td>
</tr>
<tr>
<td>Papillary muscle dysfunction</td>
<td>Improvement/ disappearance of regurgitation</td>
<td>Aortic valve</td>
<td>Ischemic papillary muscle dysfunction</td>
</tr>
<tr>
<td>Transient atroventricular valvular regurgitation</td>
<td>Cusp deformation, Fibrous degeneration</td>
<td>Atrioventricular chordal rupture</td>
<td></td>
</tr>
<tr>
<td>Disappearance of regurgitation</td>
<td>Development/aggravation of regurgitation</td>
<td>Heart failure</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Mechanism of development of valvular diseases.
that such patients be followed for life with frequent selective CAG, magnetic resonance imaging (MRI), and/or multi-row detector computed tomography (MDCT) to monitor changes in the morphology of coronary arteries.

2 Myocarditis, Endocarditis, Valvulitis, and Pericarditis

These inflammatory cardiac diseases, which are often asymptomatic, are quite prevalent during the acute phase. They are often mild in severity throughout the course of disease, though heart failure, cardiac tamponade, and death due to arrhythmia induced by inflammation of atrioventricular and/or mitral valve, occurs in a few patients. Arrhythmia is usually observed in patients with severe KD, and various other arrhythmias, such as atrial fibrillation, supraventricular tachycardia, atrioventricular and/or multi-row dysfunction, are often seen in such patients. In addition, patients with KD often have cardiac arrhythmia, which is often observed in patients with severe KD.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>SNP</th>
<th>No. of patients</th>
<th>Ethnic group</th>
<th>Results</th>
<th>Reported by</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Susceptibility to KD</td>
<td>ITPKC</td>
<td>78 KD sibling pairs</td>
<td>Japanese</td>
<td>Linkage analysis of siblings of KD patients. High linkage disequilibrium was noted in 12q24, 4q35, 5q34, 6q27, 7q15, 8q24, 18q23, 19q13, Xp22, and Xq27.</td>
<td>Onouchi Y, et al</td>
</tr>
<tr>
<td>Risk for CAL</td>
<td>CD40L</td>
<td>427 KD patients and 282 controls</td>
<td>Japanese</td>
<td>CD40L gene was screened to detect 22 SNP, IVS4+121 A &gt; G in intron 4. G allele was high in KD.</td>
<td>Onouchi Y, et al</td>
</tr>
<tr>
<td>Susceptibility to KD</td>
<td>CCR3-CCR2-CCR5 cluster</td>
<td>170 KD patients</td>
<td>German</td>
<td>Two haplotypes of the CCR3-CCR2-CCR5 gene cluster appear to be at risk for KD, and one to be a protective haplotype.</td>
<td>Breunis WB, et al</td>
</tr>
<tr>
<td>Susceptibility to KD</td>
<td>CCR5 CCL3L1</td>
<td>160 KD families</td>
<td>Americans</td>
<td>An inverse relationship between the worldwide distribution of CCR5 Δ32 allele and the incidence of KD was observed. HHG<em>2, the CCR5 Δ32-containing haplotype of CCR5, was associated with decreased susceptibility to KD. Analysis of CCR5 ligands and CCL3L1 gene dose stratum revealed that Individuals who possessed both HHG</em>2 and 2 copies of CCL3L1 had a nearly 80% lower risk of developing KD.</td>
<td>Burns JC, et al</td>
</tr>
<tr>
<td>Susceptibility to KD</td>
<td>VEGF</td>
<td>170 KD patients</td>
<td>German</td>
<td>The VEGF haplotype CGGC (-259A/C, Ex1+405G/C, Ex1-73C/T, 236bp3’/STP CC) was correlated with susceptibility to KD.</td>
<td>Breunis WB, et al</td>
</tr>
<tr>
<td>Susceptibility to KD</td>
<td>IL-4</td>
<td>220 KD families (triplet)</td>
<td>Americans</td>
<td>TD analysis was performed for 98 SNPs of 58 genes in a cohort of 209 KD families (triplet). PON1, GPRK2L, IL-4, TGF-beta, and GC were screened. Only IL-4 was significant in another cohort. Haplotype analysis of genes near IL-4 did not reveal any correlations stronger than for IL-4. No correlation with CAL was noted. The C allele of the IL-4 C-589G was correlated with susceptibility to KD.</td>
<td>Burns JC, et al</td>
</tr>
<tr>
<td>Risk for CAL</td>
<td>TIMP-2</td>
<td>208 KD patients</td>
<td>Japanese</td>
<td>Expression of TIMP-2 in PBMCs was high in the CAL group. Analysis of 5 SNP in the 5’ flanking region revealed significantly higher expression of -806T &gt; C, -417G &gt; C, -177C &gt; G in the CAL group for both genotype and allele type. In the CCCAT haplotype, a significant decrease in expression of TIMP-2 was confirmed. CCCAT haplotype was significantly lower in the CAL group.</td>
<td>Furuno K, et al</td>
</tr>
<tr>
<td>Risk for CAL</td>
<td>ACE</td>
<td>246 KD patients</td>
<td>Japanese</td>
<td>The presence of the ACE ID D allele and AT1R 1168A/C C allele increased the incidence of coronary stenosis 2.71-fold.</td>
<td>Fukazawa R, et al</td>
</tr>
<tr>
<td>Disease severity</td>
<td>MCP-1, CCR2</td>
<td>184 KD patients</td>
<td>Japanese</td>
<td>The G/G allele of the MCP-1-2518C/G was associated with long duration of fever, and tended to be intractable to immunoglobulin therapy.</td>
<td>Fukazawa R, et al</td>
</tr>
</tbody>
</table>

*Comprehensive gene expression analysis.

KD, Kawasaki disease; CAL, coronary artery lesion; SNP, single nucleotide polymorphism; ITPKC, inositol 1,4,5-triphosphate 3-kinase C; CD40L, cluster differentiation 40 ligand; CCR, chemokine CC motif receptor; CCL, chemokine CC motif ligand; VEGF, vascular endothelial growth factor; IL, interleukin; TIMP-2, tissue inhibitor of metalloproteinase-2; ACE, angiotensin converting enzyme; MCP-1, monocyte chemoattractant protein-1; PON1, paraoxonase; TGF, transforming growth factor; PBMCs, peripheral blood mononuclear cells.
sinoatrial conducting system may occur in rare cases.

3 Ischemic Myocardial Injury
Although ischemic heart disease is the major cause of death of patients with Kawasaki disease, many such deaths occur suddenly, and the number of patients exhibiting histopathological findings of AMI at autopsy is thus small. However, lesions of chronic myocardial infarction are often observed at autopsy in patients who did not experience cardiac episodes or exhibit findings of ischemia.

7. Genetic Background
Although Kawasaki disease is not a genetic disease, the possibility of a genetic predisposition toward it has been suggested by the findings that (1) the incidence of Kawasaki disease in Japan is 10 to 20-fold that in Western countries, (2) the incidence of Kawasaki disease among siblings of patients is about 10-fold that in the general population, and (3) the incidence in offspring of parents with a history of Kawasaki disease is about twice that in the general population.

There have been reports suggesting that genetic polymorphisms are associated with "susceptibility to Kawasaki disease", "risk for abnormal changes in the coronary arteries", and "severity of disease and responses to immunoglobulin therapy". Table 6 lists case-control studies conducted after comprehensive analysis of genes associated with Kawasaki disease, and case-control studies on previously specified genes in at least 150 patients.

III Examinations

1. Blood Tests

1 Myocardial Infarction
Since no reference values for diagnosis have been established for blood biochemical markers of AMI in children, reference values in adult patients should be used instead.

Blood biochemical markers of injury to cardiomyocytes include creatine kinase (CK) located in the cytoplasmic soluble fraction, CK-myocardial band (MB), myoglobin, heart-type fatty acid-binding protein (H-FABP), myosin light chain (MLC) in myofilibril, and troponin T and troponin I (TnT, TnI). It is important to use appropriate markers based on the duration of time after onset of myocardial infarction.

Myoglobin and H-FABP (with H-FABP ≥ 6.2 ng/mL classified as positive) are useful in the diagnosis of myocardial infarction immediately after onset, while CK-MB and TnT (with TnT ≥ 0.10 ng/mL classified as positive) are useful for the diagnosis of myocardial infarction ≥ 6 hours after onset. The principal biochemical markers of myocardial infarction are CK-MB and TnT (Table 7).

2 Arteriosclerosis
The criteria for diagnosis of metabolic syndrome, which include hyperlipidemia and insulin resistance, are important in the diagnosis of arteriosclerosis. In the diagnosis of hyperlipidemia, levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride (TG) are commonly used. Homocysteine level has attracted attention as an independent risk factor for arteriosclerosis. Since metabolic syndrome, for which visceral fat deposition is one of the principal criteria, may often lead to the development of type 2 diabetes and cardiovascular diseases in later life, it has been proposed that abdominal obesity and metabolic syndrome should be cared early in life.

Table 8 lists the criteria for diagnosis of metabolic syndrome in children in Japan. Table 9 lists the reference values of serum lipid levels in children, and Table 10 lists the reference values of markers of hyperlipidemia in adults with a history of Kawasaki disease.

2. Physiological Examinations (ECG)

1 ECG at Rest
During the acute phase of Kawasaki disease, the ECG reveals findings suggestive of myocardial injury and abnormal repolarization such as prolonged PR interval, deep Q waves, prolonged QT interval, low voltage, ST-T changes, and arrhythmias. When myocardial infarction occurs in patients who still have coronary artery lesions, especially giant coronary aneurysms, during the remote phase, ST-T changes and abnormal Q waves that are consistent with the lesion of infarction are observed.

2 Holter ECG
Holter ECG recording is worthwhile in patients complaining of frequent chest pain, chest discomfort, and/or palpitations. Patients with stenosis or giant aneurysms should undergo Holter ECG recording at least once to determine whether ischemic findings are present or development of high-risk arrhythmias is possible.

3 Stress ECG
(1) Exercise ECG
a) Double or Triple Master’s Two-Step Test
Although it has been reported that the Master’s two-step test can be routinely performed from infancy, and may provide a load equivalent to that observed during treadmill testing in terms of oxygen consumption in preschool children 4 to 6 years of age, exercise ECG cannot detect abnormal findings in patients without severe ischemia.

b) Treadmill Test and Ergometer Stress Test
Treadmill tests and ergometer stress tests can be administered to school-age or older children, though their sensitivity in detecting ischemic findings is less than that of myocardial scintigraphy. It has therefore been recommended that pharmacological stress be added to increase the rate of detection, or that signal-averaged ECG be used.

(2) Pharmacological Stress Tests and Body Surface Potential Mapping
It has been reported that dipyridamole or dobutamine stress
tests using body surface potential mapping are useful in patients with myocardial ischemia due to Kawasaki disease with or without significant stenosis, including infants in whom exercise stress testing is not feasible.

(3) Electrophysiological Tests
Studies of patients with a history of Kawasaki disease who underwent electrophysiological evaluation with intracardiac catheters have revealed that the prevalence of abnormal sinus or atrioventricular nodal function is significantly higher in patients with than in those without cardiac sequelae, although the findings of abnormal nodal function were not consistent with the presence of coronary stenosis/occlusion, and are believed to result from myocarditis or abnormal microcircu-

Table 7. Blood Biochemical Markers of Acute Myocardial Infarction (AMI)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>1) Rapid and accurate test 2) Reinfarction can be detected promptly</td>
<td>1) Low myocardial specificity (specificity for AMI is low in patients with musculoskeletal disorder) 2) Low detection rate within 6 hours after onset</td>
<td>CK-MB is one of the principle biochemical markers, and can be used as a standard test in almost all institutions</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>1) Detectable 1 to 2 hours immediately after onset 2) Highly sensitive 3) Reperfusion can be detected</td>
<td>1) Poor myocardial specificity 2) Since the level returns to normal in 1 to 2 days after onset, it cannot be detected in patients who present late after AMI</td>
<td>Due to poor myocardial specificity, AMI cannot be diagnosed with myoglobin alone</td>
</tr>
<tr>
<td>H-FABP</td>
<td>1) Detectable 1 to 2 hours immediately after onset 2) Infarct size can be estimated 3) Reperfusion can be detected</td>
<td>Rapid test kits are available. It is highly sensitive during the early diagnosis, but its specificity is relatively low</td>
<td>Rapid test kits are available throughout Japan and useful in early diagnosis</td>
</tr>
<tr>
<td>TnT</td>
<td>1) Highly sensitive and highly specific 2) Diagnosis is possible 8 to 12 hours after onset 3) Diagnosis is possible when testing is performed in the first 2 weeks after onset 4) Prompt diagnosis is possible with rapid test kits 5) Reperfusion can be detected</td>
<td>1) Sensitivity is low within 6 hours after onset (Retest 8 to 12 hours after onset) 2) Sensitivity to late-onset small reinfarction is low</td>
<td>Rapid test kits are available throughout Japan, and TnT is a principle biochemical marker</td>
</tr>
<tr>
<td>MLC</td>
<td>1) Detectable 4 to 6 hours after onset 2) Diagnosis is possible when testing is performed in the first 2 weeks after onset</td>
<td>1) Sensitivity is relatively low 2) MLC is excreted renally and may be abnormal in patients with renal failure</td>
<td>Rapid diagnostic tests are not available</td>
</tr>
</tbody>
</table>

Table 8. Criteria for Diagnosis of Metabolic Syndrome in Japanese Children 6 to 15 Years of Age (Final Draft In 2006)

| Children meeting (1) and at least 2 of items (2) to (4) should be diagnosed with metabolic syndrome. |
|---|---|---|
| (1) Abdominal girth | ≥80 cm (note) |
| (2) Serum lipid | Triglyceride ≥120 mg/dL and/or HDL cholesterol <40 mg/dL |
| (3) Blood pressure | Systolic pressure ≥125 mmHg and/or Diastolic pressure ≥70 mmHg |
| (4) Fasting blood glucose | ≥100 mg/dL |

Note: Children with an waist-to-height ratio of ≥0.5 fulfill item (1). In elementary school children (6 to 12 years of age), those with an abdominal girth of ≥75 cm should be considered to fulfill item (1). HDL, high-density lipoprotein.

Table 9. Criteria for Diagnosis of Pediatric Hyperlipidemia (Serum Lipid levels in Fasting Blood)

<table>
<thead>
<tr>
<th>Total cholesterol (mg/dL)</th>
<th>LDL cholesterol (mg/dL)</th>
<th>HDL cholesterol (mg/dL)</th>
<th>Triglyceride (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;190</td>
<td>Normal</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Borderline</td>
<td>190 to 219</td>
<td>Borderline</td>
<td>110 to 139</td>
</tr>
<tr>
<td>Abnormal</td>
<td>≥220</td>
<td>Abnormal</td>
<td>≥140</td>
</tr>
<tr>
<td>Cut-off value</td>
<td>40</td>
<td>Cut-off value</td>
<td>140</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 10. Criteria for Management of Hyperlipidemia in Adult Japanese for the Prevention and Treatment of Coronary Artery Disease

| Hypercholesterolemia | Total cholesterol ≥220 mg/dL |
| Hyper LDL cholestrolemia | LDL cholesterol ≥140 mg/dL |
| Hypo HDL cholestrolemia | HDL cholesterol <40 mg/dL |
| Hypertriglyceridemia | Triglyceride ≥150 mg/dL |

LDL, low-density lipoprotein; HDL, high-density lipoprotein.
4 Summary of Physiological Examinations
Table 11 summarizes the physiological examinations commonly used for patients with Kawasaki disease and their rates of detection of cardiac complications.

3. Diagnostic Imaging

1 Chest X Ray
(1) X-Ray Finding of Calcified Coronary Aneurysms
Since the presence of calcification of coronary aneurysms on chest X-ray suggests the presence or progression of giant aneurysms or stenotic lesions, CAG using MDCT or selective CAG is required.

(2) Enlarged Heart Shadow due to Myocardial Ischemia or Valvular Diseases
An enlarged heart shadow is observed in patients with poor cardiac function due to chronic myocardial infarction, and in patients with volume overload caused by mitral or aortic insufficiency.

2 Echocardiography
(1) Echocardiography at Rest
Echocardiography at rest is the most commonly performed test, because it is non-invasive and convenient, and can be used to evaluate coronary morphology over time to detect coronary dilatations specific to the coronary artery lesions associated with Kawasaki disease. Adults may be diagnosed with Kawasaki disease based on the visualizing of coronary aneurysms. The presence/absence of thrombi within aneurysms can also be determined with echocardiography. Although it is sometimes difficult to evaluate stenotic lesions with echocardiography, it has been reported that following the improvement of ultrasonic device, measurement of coronary blood flow with Doppler echocardiography enables accurate diagnosis of stenotic lesions. It has also been reported that 3-dimensional (3D) echocardiography is useful in visualizing the right coronary artery and the circumflex artery, and in visualizing mural thrombi in coronary aneurysms. This technique is expected to become useful for the detection of coronary artery lesions due to Kawasaki disease. Echocardiography is the most useful method for evaluation of deterioration of cardiac function due to myocardial injury and the severity of valvular disease. Detailed reports have been published on evaluation of myocardial injury during the acute phase using tissue Doppler imaging.

(2) Stress Echocardiography
Stress echocardiography is a method enabling real-time evaluation of left ventricular wall motion in patients during exercise (treadmill or ergometer) or with administration of dobutamine or dipyridamole. Dobutamine stress echocardiography is particularly useful for detecting coronary stenotic lesions and evaluating the viability of myocardium. In dobutamine stress echocardiography, dobutamine is administered in incremental doses, which are increased by 5 to 10 μg/kg/min every 5 minutes to a highest dose of 30 to 40 μg/kg/min to check visually for abnormal wall motion in each slice.

(3) Others
Transesophageal echocardiography (TEE) may be useful in visualizing coronary arteries in adults suspected to have coronary aneurysms which are difficult to evaluate using trans-thoracic echocardiography. It also may be used to evaluate coronary blood flow. Myocardial contrast echocardiography, the use of which has advanced through the widespread use of intravenous myocardial contrast echocardiography and the improvement of ultrasonic device, is now able to provide evaluation equivalent to that by myocardial scintigraphy and is expected to prove useful in the future because of its convenience.

3 Radionuclide Imaging
Myocardial perfusion imaging techniques available for patients with Kawasaki disease include Planar and single photon emission computed tomography (SPECT), the latter of which is more commonly used. Thallium (201Tl) is often used, and technetium (Tc)-labeled myocardial perfusion agents (Tc-99m sestamibi, Tc-99m tetrofosmin) which are low in photon emission computed tomography (SPECT), the latter of which is more commonly used. Thallium (201Tl) is often used, and technetium (Tc)-labeled myocardial perfusion agents (Tc-99m sestamibi, Tc-99m tetrofosmin) which are low in

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Table 11. Detection of Cardiac Complications by Common Physiological Examinations

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Examination</th>
<th>Target disease</th>
<th>Criteria</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osada M, et al°</td>
<td>OT dispersion</td>
<td>Coronary artery lesions</td>
<td>QT≥60 ms</td>
<td>56</td>
<td>100% (6/6)</td>
<td>92%</td>
</tr>
<tr>
<td>Nakanishi T, et al°</td>
<td>12-lead ECG</td>
<td>Inferior wall infarction</td>
<td>deep Q in II, III, aVF</td>
<td>3</td>
<td>86%</td>
<td>97%</td>
</tr>
<tr>
<td>Ogawa S, et al°</td>
<td>Signal-averaged ECG</td>
<td>Anterior wall infarction</td>
<td>deep wide Q in V1-6</td>
<td>8</td>
<td>75%</td>
<td>99%</td>
</tr>
<tr>
<td>Genma Y, et al°</td>
<td>Dobutamine stress signal-averaged ECG</td>
<td>Myocardial ischemia</td>
<td>LP positive</td>
<td>198</td>
<td>69.2%</td>
<td>93.5%</td>
</tr>
<tr>
<td>Takechi N, et al°</td>
<td>Dobutamine stress body surface potential</td>
<td>Myocardial ischemia</td>
<td>nST&gt;1</td>
<td>115</td>
<td>94.1%</td>
<td>98.9%</td>
</tr>
</tbody>
</table>

LP, late potential; nST, non-stress test; I map, isopotential map.

lation in the conducting system.

(4) Signal-Averaged ECG
Signal-averaged ECG is believed to feature a better rate of detection of myocarditis associated with Kawasaki disease than standard 12-lead ECG, Holter ECG, echocardiography, and blood tests for cardiac enzymes. Positive ventricular late potential adjusted for body surface area is highly specific for the detection of ischemia and chronic myocardial infarction, and dobutamine stress tests may improve specificity further in children who cannot tolerate exercise testing.

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Circulation Journal Vol.74, September 2010
evaluation of myocardial fatty acid metabolism with $^{123}\text{I}$ β-methyl-p-iodophenyl-pentadecanoic acid ($^{123}\text{I}$ BMIPP)\(^{94}\) and evaluation of cardiac sympathetic nerve activity with $^{123}\text{I}$ metaiodobenzylguanidine ($^{123}\text{I}$ MIBG)\(^{95}\) are also used in the clinical setting. Ga-67 myocardial scintigraphy is useful in the diagnosis of myocarditis due to Kawasaki disease.\(^{20}\)

(1) **$^{201}$Tl Myocardial Perfusion Scintigraphy**
Lesions of myocardial ischemia may be located by obtaining stress images under administration of $^{201}$Tl and then obtaining delayed images to investigate redistribution in areas with poor perfusion. Redistribution images are considered especially useful in predicting cardiac events due to coronary artery lesions associated with Kawasaki disease.\(^{96}\) Specifically, $^{201}$Tl is administered during stress at 37 MBq (1 mCi) in infants under one year of age, 37 to 56 MBq (1 to 1.5 mCi) in children 1 to 10 years of age, and 56 to 74 MBq (1.5 to 2 mCi) in children ≥10 years of age, and delayed images (redistribution images) are obtained 3 to 4 hours after administration of $^{201}$Tl.\(^{97}\) To obtain clear images, physicians should (1) exercise special caution in avoiding body movement by children during imaging, (2) obtain stress images promptly after administration of $^{201}$Tl, since redistribution of $^{201}$Tl occurs within a short period of time, and (3) ensure that patients do not eat from administration of $^{201}$Tl until the time of delayed imaging.

(2) **Tc-Labeled Myocardial Perfusion Scintigraphy**
Tc-labeled myocardial perfusion agents such as Tc-99m sestamibi and Tc-99m tetrofosmin have been developed as alternatives to $^{201}$Tl for use in myocardial perfusion imaging. These agents allow high-resolution, low-exposure imaging because of their short half-life. Once absorbed into the myocardium, Tc-labeled myocardial perfusion agents remain in the myocardium for a long period of time and are not redistributed, as occurs with $^{201}$Tl. Images can thus be obtained regardless of time after administration, though images at rest should be obtained separately. Tc-labeled myocardial perfusion scintigraphy is performed under stress at a dose of 10 MBq/kg (maximum 370 MBq, 10 mCi), and the second dose is administered 2 to 3 hours after the first administration at 2 to 3 times the first dose (maximum 740 MBq, 20 mCi).\(^{97}\) To obtain clear images, physicians should (1) exercise special caution in avoiding body movement by children during imaging, (2) continue stress for at least one minute after administration of perfusion agents under stress, (3) promote elimination of perfusion agents from the liver and gallbladder by ingestion of egg products, milk or cocoa, and (4) obtain images at least 30 minutes after administration of perfusion agents to ensure elimination of perfusion agents accumulated in the liver.

(3) **ECG-Gated Myocardial Perfusion SPECT**
The availability of 3D automatic quantitative analysis of ECG-gated myocardial perfusion SPECT (quantitative gated SPECT, QGS) has allowed physicians to calculate left ventricular volume and ejection fraction (EF) by evaluating wall motion and to visualize the endocardium based on multidimensional 3D images.\(^{98}\) In patients with severe coronary artery lesions due to Kawasaki disease, detailed evaluation of postischemic myocardial stunning\(^{99}\) and viability of infarcted myocardium may be performed with QGS,\(^{100,101}\) though this method cannot be used effectively in patients with a small heart (diastolic volume of about ≤50 mL) under 6 years of age.

(4) **Imaging of Myocardial Fatty Acid Metabolism**
Imaging of myocardial fatty acid metabolism using $^{123}\text{I}$ BMIPP is a better technique for specification of segments with abnormal wall motion than myocardial perfusion imaging because it can specify abnormal energy production in the myocardium. Since areas with low myocardial uptake of $^{123}\text{I}$ BMIPP are strongly consistent with segments perfused by the culprit coronary vessel in patients with myocardial infarction or angina, this technique can be used in the evaluation of myocardial injury in patients with severe coronary artery lesions due to Kawasaki disease.\(^{94}\)

(5) **Imaging of Cardiac Sympathetic Nerve Activity**
Imaging of cardiac sympathetic nerve activity can be obtained with $^{123}\text{I}$ MIBG imaging. Since abnormal cardiac sympathetic nerve activity follows the development of severe myocardial ischemia or myocardial infarction, $^{123}\text{I}$ MIBG imaging in patients suspected of having cardiac events including infarction may allow physicians to specify culprit vessel(s) promptly, and is thus quite useful in patients with coronary artery lesions due to Kawasaki disease who often experience asymptomatic myocardial ischemia.\(^{95,102}\)

(6) **Positron Emission Tomography (PET)**
Quantitative evaluation of myocardial flow reserve can be performed in the evaluation of blood flow by PET using [O-15]-water or [N-13]-ammonia. Low myocardial flow reserve and poor vascular endothelial function have been observed in patients with regression of coronary aneurysms. Evaluation of glucose metabolism in PET using [F-18]-fluorodeoxyglucose (FDG) permits precise evaluation of the viability of infarcted myocardium.\(^{103,104}\)
(7) Administration of Drugs During Myocardial Perfusion Scintigraphy

Figure 3 illustrates how drugs are administered during pharmacological myocardial perfusion scintigraphy.

4 Magnetic Resonance Coronary Angiography (MRCA) and MDCT

Selective CAG has been considered a gold standard for the diagnosis of coronary artery lesions due to Kawasaki disease, and IVUS has been used concomitantly to observe for thrombi in aneurysms and intimal hyperplasia. Recently, MDCT and coronary artery imaging using MRI (MRCA) have been developed, and are increasingly used to obtain additional findings supportive of those of CAG.

(1) MDCT

Although it has been believed that MDCT is not feasible in children because of the extensive X-ray exposure associated with it, use of contrast media, administration of β-blockers to slow heart rate, and the need for breath-holding, recent reports have indicated that 64-row MDCT provides clear images in young children who do not hold their breath during imaging and do not undergo induction of slow heart rate, and may overcome the problems regarding breath and heart rate control when used more widely in the future (Figure 4).

(2) MRCA

MRCA is a completely non-invasive imaging technique which requires neither X-ray exposure nor contrast media. Since MRCA can be performed during spontaneous breathing without slowing of the heart rate, infants and young children may undergo it during sleep.

There are two imaging techniques of MRCA, the bright blood technique (steady-state free precession (SSFP)) which indicates blood flow as white, and the black blood technique, which indicates blood flow as black and occlusions and intimal hyperplasia as gray (Figure 4). The black blood technique includes M2D black blood turbo spin echo imaging and 2D Black blood Spiral k-space order TFE technique (indicates coronary transection) which allows physicians to observe for thrombi and intimal hyperplasia.

Although the rate of visualization of stenotic lesions is lower with MRCA than MDCT, MRCA is more useful in visualization of localized stenosis with calcification because it does not hinder visualization of vascular lumens.

(3) Magnetic Resonance (MR) Myocardial Imaging

MR myocardial imaging, which may be performed in a short time following MRCA, is a less expensive imaging technique without the need for radioisotopes, and may provide clearer 3D images than MRCA.

Cine MRI is performed using SSFP without contrast media to acquire images from the left ventricular short axis view, long axis view, and four-chamber view to observe ventricular wall motion, and perfusion MRI is performed after infusion of gadolinium-based contrast media to evaluate the severity of myocardial ischemia by observing the first pass of contrast media in the myocardium during adenosine triphosphate (ATP) stress and at rest from the left ventricular short axis view.

Delayed-contrast enhanced MRI can visualize the extent and depth of subendocardial infarct lesions by obtaining images 15 minutes after the administration of contrast media with a sequence using T1-weighted gradient echo with myocardial T1 signal suppression. This technique can visualize subendocardial infarct lesions and small infarct lesions in the right ventricle, which cannot be visualized with radioisotope myocardial imaging. Since the prevalences of occlusions and recanalization of the right coronary artery are especially high in patients with Kawasaki disease, precise evaluation of the right ventricular myocardium is important.

5 Cardiac Catheterization and CAG

(1) CAG

a) Indications

(1) Evaluation of Severity of Coronary Artery Lesions and Patient Follow-up

Although in the case of adults CAG is indicated for those who exhibit findings of myocardial ischemia, it is recommended for patients with Kawasaki disease that CAG should be performed in those with medium or giant aneurysms during the convalescence phase or later to monitor for the development or progression of localized stenosis, since myocardial ischemia due to Kawasaki disease cannot be fully detected with other types of examinations and myocardial ischemia may manifest as sudden death.

(2) Percutaneous Coronary Intervention (PCI) Before and After Coronary Artery Bypass Grafting (CABG)

CAG is required before PCI to determine whether PCI is indicated, during angioplasty to ensure safe and effective intervention, and after angioplasty to evaluate the results of PCI and follow up patients.

(3) Intracoronary Thrombolysis (ICT)

Thrombi in coronary aneurysms may sometimes be observed during follow-up of medium to giant aneurysms with echocardiography. In such cases, cardiac catheterization and CAG are performed for ICT.
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. Since the development of stenosis after regression of not only large aneurysms but also smaller ones and the development of arteriosclerotic degeneration 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 develops 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 or other imaging techniques such as MRCA and MDCT 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 and PCI 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. 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.

(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...
In patients with occlusion, evaluation was performed in 210 vessels of patients with occlusion and 54 vessels of 18 patients with regional stenosis. **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.**

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

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Technique</th>
<th>Stress</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiraishi S, et al</td>
<td>Transthoracic echocardiography</td>
<td>At rest</td>
<td>18</td>
<td>85%, LAD: 80%</td>
<td>RCA: 98%, LAD: 97%</td>
</tr>
<tr>
<td>Noto N, et al</td>
<td>Stress echocardiography</td>
<td>Dobutamine</td>
<td>26</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Kondo C, et al</td>
<td>Tc-99m tetrofosmin</td>
<td>Exercise,</td>
<td>20</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>Karasawa K, et al</td>
<td>Diagnosis of stenotic lesions**</td>
<td>ATP</td>
<td>24</td>
<td>83%</td>
<td>92%</td>
</tr>
<tr>
<td>Kanamaru H, et al</td>
<td>MDCT</td>
<td>At rest</td>
<td>16</td>
<td>87.5% (25 vessels)</td>
<td>92.5% (52 vessels)</td>
</tr>
<tr>
<td>Miyagawa M, et al</td>
<td>Prediction of cardiac events</td>
<td>Dipyridamole</td>
<td>15</td>
<td>93%</td>
<td>83%</td>
</tr>
<tr>
<td>Suzuki A, et al</td>
<td>MRCA</td>
<td>At rest</td>
<td>70</td>
<td>occlusion 94.2%, stenosis 94.4%</td>
<td>occlusion 99.5%, stenosis 97.2%</td>
</tr>
</tbody>
</table>

*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.

一汽enal 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. Evaluation of lesions, and especially quantitative evaluation of calcified lesions with IVUS, is required when the means to be used for PCI are selected.

### b) Coronary Arterial Vasodilator Function

It has been reported that the absence of coronary vasodilation in coronary artery wall following administration of isosorbide dinitrate (ISDN) or acetylcholine suggests the presence of chronic intimal dysfunction in patients with Kawasaki disease. However, since evaluation of coronary arteriolar 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.

### 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

<table>
<thead>
<tr>
<th>Patients without angina or detectable ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Combination therapy using antiplatelet drugs</td>
</tr>
<tr>
<td>° Examination revealed obvious ischemia</td>
</tr>
<tr>
<td>° Antiplatelet drugs + Ca-blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ In addition to combination therapy using antiplatelet drugs</td>
</tr>
<tr>
<td>° Angina on exertion</td>
</tr>
<tr>
<td>° Nitrates, monotherapy or combination therapy of Ca-blockers, plus β-blockers if ineffective</td>
</tr>
<tr>
<td>° Angina at rest or during sleep</td>
</tr>
<tr>
<td>° Ca-blockers</td>
</tr>
<tr>
<td>° Angina at night</td>
</tr>
<tr>
<td>° Ca-blockers + nitrates or K-channel openers (nicorandil)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients complicated by cardiac dysfunction or valvular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ 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.</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme.

Table 15. Antiplatelet Drugs and Anticoagulant Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse drug reactions (ADRs) and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid (Bufferin or Bayaspirin)</td>
<td>30 to 50 mg/kg divided into 3 doses during the acute phase, 3 to 5 mg/kg once daily after defervescence</td>
<td>Hepatic function disorder, gastrointestinal ulcer, Reye syndrome (higher incidence at ≥40 mg/kg), bronchial asthma Use other drugs during varicella infection and influenza.</td>
</tr>
<tr>
<td>Flurbiprofen (Froben)</td>
<td>3 to 5 mg/kg, divided into 3 doses</td>
<td>Hepatic function disorder, gastrointestinal ulcer Use when severe hepatic disorder due to aspirin develops.</td>
</tr>
<tr>
<td>Dipyridamole (Persantin, Anginal)</td>
<td>2 to 5 mg/kg, divided into 3 doses</td>
<td>May induce angina in patients with severe coronary stenosis. Coronary steal phenomenon, headache, dizziness, thrombocytopenia, hypersensitivity, dyspepsia</td>
</tr>
<tr>
<td>Ticlopidine (Panaldine)</td>
<td>5 to 7 mg/kg, divided into 2 doses</td>
<td>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.</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>1 mg/kg, once daily</td>
<td>TTP, gastrointestinal symptoms, malaise, myalgia, headache, rash, purpura, pruritus Bleeding tendency may develop when used with aspirin.</td>
</tr>
<tr>
<td>Unfractionated heparin (IV)</td>
<td>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)</td>
<td>Major ADRs: Shock/anaphylactoid reaction, bleeding, thrombocytopenia, thrombocytopenia/thrombosis associated with heparin-induced thrombocytopenia (HIT)</td>
</tr>
<tr>
<td>Low-molecular-weight heparin (SC)</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Warfarin (Warfarin)</td>
<td>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</td>
<td>Dose should be adjusted to an INR of 1.6 to 2.5 (2.0 to 2.5 in the AHA guidelines) and a thrombostest (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.</td>
</tr>
</tbody>
</table>

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.
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. 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.

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 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.

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. 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 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 vasodilative effects of nitrates are not expected to be beneficial in the treatment of acute ischemia due to lesions with poor endothelial cell function, nitrates in sublingual or oral spray form should be attempted in treating AMI.

(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 morbidity, 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...
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

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

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

<table>
<thead>
<tr>
<th>Drugs for angina</th>
<th>Dose</th>
<th>Adverse drug reactions and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine (Adalat)</td>
<td>0.2 to 0.5 mg/kg/dose, TID (available as 5 and 10 mg capsules)</td>
<td>Hypotension, dizziness, headache. Care is needed in patients with poor cardiac function.</td>
</tr>
<tr>
<td>Slow-release nifedipine (Adalat-CR, Adalat-L)</td>
<td>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)</td>
<td>Same as above</td>
</tr>
<tr>
<td>Amlodipine (Norvasc)</td>
<td>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)</td>
<td>Same as above</td>
</tr>
<tr>
<td>Diltiazem (Herbesser)</td>
<td>1.5 to 2 mg/kg/day, TID (maximum dose 6 mg/day) (30 mg tablets)</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs for heart failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol (Seloken)</td>
<td>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)</td>
</tr>
<tr>
<td>Carvedilol (Artist)</td>
<td>Start at 0.08 mg/kg/day, maintain at 0.46 mg/kg/day (average)</td>
</tr>
<tr>
<td>Enalapril (Renivace)</td>
<td>0.08 mg/kg/dose, OD (Tablets of 2.5 mg and 5 mg are available)</td>
</tr>
<tr>
<td>Cilazapril (Inhibace)</td>
<td>0.02 to 0.06 mg/kg/day, divided into 1 to 2 doses (1 mg tablets)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs for ischemic attacks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide dinitrate (Nitorol)</td>
<td>Sublingual: one-third to one-half tablet/dose (5 mg tablets)</td>
</tr>
<tr>
<td>Nitroglycerin (NTG)</td>
<td>One-third to one-half tablet/dose sublingual</td>
</tr>
<tr>
<td>Nitroglycerin (Nitopen)</td>
<td>(0.3 mg tablet)</td>
</tr>
</tbody>
</table>

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.
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). 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 intra-coronary 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. The recommended balloon pressure is ≤8 to 10 atm. 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.

(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. 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.

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.
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 should also be considered 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 predominating. 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.

(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. 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.

(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%. 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%. 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. Lesions exhibiting anastomotic stenosis can be sufficiently treated with dilatation with POBA without stenting, and restenosis is rare.

b) Outcome of Surgery

Following CABG, patients exhibit improvement in left ventricular function during exercise. 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%, 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.
(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.\textsuperscript{158,159}

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{158,159,162-165} 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,\textsuperscript{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®, Grpia®): 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.
– Pamipetase (Solinase®): 6.5×10^4 units/kg. Administer intravenously over 1 minute.

• ICT
a) UK: Administer at a dose of 0.4×10^5 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 antithrombotic drugs (aspirin, Plavix®,...
and Pletal® 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

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.

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

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. 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 severe coronary aneurysms
### Table 19

<table>
<thead>
<tr>
<th>Name</th>
<th>M / F</th>
<th>Birth date (___ years)</th>
<th>School</th>
<th>Grade</th>
<th>Class</th>
<th>Date</th>
</tr>
</thead>
</table>

#### 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

<table>
<thead>
<tr>
<th>Sport activity</th>
<th>Intensity of exercise</th>
<th>Mild exercise (C, D, E - allowed)</th>
<th>Moderate exercise (D, E - allowed)</th>
<th>Intense exercise (E - allowed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warming-up exercise</td>
<td>Light exercise, rhythmic movement, basic movement (exercise-play)</td>
<td>Exercise to improve flexibility, techniques, high-force movement, and endurance</td>
<td>Performance, competition, combination of actions</td>
<td></td>
</tr>
<tr>
<td>Strenth-training exercise</td>
<td>Calisthenics, light mat exercise, light exercise, light jumping, rotation</td>
<td>Practice of low-grade technique, running to perform actions such as holding, jumping, and rotation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basketball</td>
<td>Passing, shooting, dribbling, passing</td>
<td>Dribble shoot, combination play (offense, defense)</td>
<td>Goalkeeping</td>
<td></td>
</tr>
<tr>
<td>Soccer</td>
<td>Passing, serving, receiving, feinting</td>
<td>Dribbling and head shooting, volley shot, combination play (ofense, defense)</td>
<td>Goalkeeping, tackling</td>
<td></td>
</tr>
<tr>
<td>Tennis</td>
<td>Ground strokes, serving, lobbing, volleys, serve and receive</td>
<td>Smash, strong serve, receive, rally</td>
<td>Rock, marl, scrum, line-out, tackle</td>
<td></td>
</tr>
<tr>
<td>Rugby</td>
<td>Passing, kicking, handling</td>
<td>Passing, kicking, combination play (offense, defense)</td>
<td>Time under pressure, point-based pressure, gate pressure</td>
<td></td>
</tr>
<tr>
<td>Table tennis</td>
<td>Forehand, backhand, serving, receiving</td>
<td>Forehand, backhand, serve, receive</td>
<td>Time under pressure, point-based pressure, gate pressure</td>
<td></td>
</tr>
<tr>
<td>Softball</td>
<td>Throwing, catching, batting</td>
<td>Base-running, combination play, running-catch</td>
<td>Time under pressure, point-based pressure, gate pressure</td>
<td></td>
</tr>
<tr>
<td>Golf</td>
<td>Grip, swing, stance</td>
<td>Short course golf (e.g. ground golf)</td>
<td>Stroke under pressure, point-based pressure, gate pressure</td>
<td></td>
</tr>
<tr>
<td>Martial arts</td>
<td>Expertise, basic movement, ukei, swinging</td>
<td>Practicing sample techniques and forms</td>
<td>Applied practice, competition</td>
<td></td>
</tr>
<tr>
<td>Dance</td>
<td>Improved performance, hand gesture, steps</td>
<td>Dance with rhythmic movement (excluding rock and samba), Japanese folk dance</td>
<td>Rhythmic dance, original dance, dance recital</td>
<td></td>
</tr>
<tr>
<td>Outdoor activity</td>
<td>Playing on snow or on ice, skiing, skating, camping, climbing, swimming marathon, water-front activities</td>
<td>Hiking on flatlands, playing while floating in the water, surfing, wind surfing</td>
<td>Climbing, swimming marathon, dive, canoe, boat, scuba diving</td>
<td></td>
</tr>
<tr>
<td>Cultural activities</td>
<td>Cultural activities not requiring long-term physical activity</td>
<td>Most cultural activities not described in the right column</td>
<td>Playing instruments requiring physical exertion (such as trumpet, trombone, oboe, bassoon, horn), playing or conducting quick rhythmic music, playing in a marching band</td>
<td></td>
</tr>
</tbody>
</table>

#### School events, other activities

- Follow the above criteria of exercise during athletic festival, during athletic meetings, ball sport 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 school activities such as class trips, camps, feedback, or camps, and training camps.
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 not be 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. 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”.

### 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. 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.

### 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. 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. 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, echocardiography, chest X-ray (when necessary), and exercise ECG (when feasible) until dilatation is no longer observed on echocardiography. 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 convalescent 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. 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 convalescent 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.

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”. 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
- MRCA
- Multislice 3D-computed tomography (CT) CAG

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, the possibility that a history of Kawasaki disease...
is associated with progression of arteriosclerosis in midlife or later cannot be ruled out. 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.

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. 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. 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. 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, antiplatelet 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.

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. 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.
### VII Summarized Guidelines

#### Table 20

<table>
<thead>
<tr>
<th>Severity</th>
<th>Pathophysiology</th>
<th>Diagnosis / clinical course</th>
<th>Treatment</th>
<th>Daily life/exercise management*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I No dilatation</td>
<td>There is no evidence whether or not a history of Kawasaki disease is a factor associated with arteriosclerotic lesion.</td>
<td>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.</td>
<td>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.</td>
<td>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 management. 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).</td>
</tr>
<tr>
<td>II Transient dilatation during the acute phase</td>
<td>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.</td>
<td>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**.</td>
<td>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 significant stenotic lesions when myocardial ischemia has occurred.</td>
<td>No restriction is placed on daily life or exercise. Follow the recommendations for Categories I and II.</td>
</tr>
<tr>
<td>III Regression</td>
<td>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.</td>
<td>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.</td>
<td>Continue treatment with antiplateletlet agents such as aspirin. Use Ca-blockers, nitrates, β-blockers, ACE inhibitors, and angiotensin receptor II blockers to prevent ischemic attacks and heart failure.</td>
<td>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.</td>
</tr>
<tr>
<td>IV Remaining coronary aneurysms</td>
<td>Aneurysms remaining during the convalescence phase or later are considered sequela. 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.</td>
<td>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.</td>
<td>Continue treatment with antiplateletlet drugs such as aspirin. Use Ca-blockers, nitrates, β-blockers, ACE inhibitors, and angiotensin receptor II blockers to prevent ischemic attacks and heart failure.</td>
<td>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.</td>
</tr>
<tr>
<td>V-a Coronary stenotic lesions (no findings of ischemia)</td>
<td>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.</td>
<td>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.</td>
<td>Continue treatment with antiplateletlet drugs such as aspirin. Use Ca-blockers, nitrates, β-blockers, ACE inhibitors, and angiotensin receptor II blockers to prevent ischemic attacks and heart failure.</td>
<td>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.</td>
</tr>
<tr>
<td>V-b Coronary stenotic lesions (with findings of ischemia)</td>
<td>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.</td>
<td>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.</td>
<td>Exercise should 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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

*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.
References


Appendix

Chair:
- Shunichi Ogawa, Department of Pediatrics, Nippon Medical School

Members:
- Teiji Akagi, Cardiac Intensive Care Unit, Okayama University Hospital
- Kiyoshi Baba, Department of Pediatrics, Osaka Developmental Rehabilitation Center
- Hisayoshi Fujiwara, Hyogo Prefectural Amagasaki Hospital
- Kenji Hamaoka, Department of Pediatric Cardiology and Nephrology, Kyoto Prefectural University of Medicine Graduate School of Medical Science
- Masahiro Ishii, Department of Pediatrics, Kitasato University
- Kensuke Karasawa, Department of Pediatrics, Nihon University School of Medicine
- Tsutomu Saji, First Department of Pediatrics, Toho University
- Tomoyoshi Sonobe, Department of Pediatrics, Japanese Red Cross Medical Center
- Atsuko Suzuki, Department of Pediatrics, Tokyo Teishin Hospital

Collaborators:
- Mamoru Ayusawa, Department of Pediatrics, Nihon University School of Medicine
- Ryuji Fukazawa, Department of Pediatrics, Nippon Medical School
- Kazuhiko Nishigaki, Second Department of Internal Medicine, Gifu University
- Hirotaro Ogino, Department of Pediatrics, Kansai Medical University
- Tomoo Okada, Department of Pediatrics, Nihon University School of Medicine

Independent Assessment Committee:
- Shigeyuki Echigo, Echigo Clinic
- Makoto Nakazawa, Pediatric and Lifelong Congenital Cardiology Institute, Southern Tohoku General Hospital
- Masami Ochi, Division of Cardiovascular Surgery, Nippon Medical School
- Tetsu Yamaguchi, Toranomon Hospital

(The affiliations of the members are as of March 2010)