Background—Some patients with Kawasaki disease develop giant coronary aneurysms and coronary stenosis, leading to ischemic heart disease. The aim of this study was to determine the long-term prognosis of patients with Kawasaki disease with giant aneurysms.

Methods and Results—From our institutional database, 76 patients (57 men and 19 women) who developed giant aneurysms after January 1, 1972, were identified. Information on patient demographics, catheter and surgical interventions, and most recent status was collected from medical charts and patients’ contacts. From these data, we calculated the survival rate and cumulative coronary intervention rate. The average age at onset was 2.9±2.9 years, and the median observational period was 19 years. During this period, 7 patients died and 1 patient underwent a heart transplantation, resulting in 95%, 88%, and 88% survival rates at 10, 20, and 30 years after the onset of KD, respectively. On the other hand, catheter and surgical coronary interventions (median, 1 intervention; range, 1 to 7 interventions) were performed to alleviate coronary ischemia in 46 patients (61%) at 1 month to 21 years (mode at 1 month) after onset, resulting in 28%, 43%, and 59% cumulative coronary intervention rates at 5, 15, and 25 years after onset, respectively.

Conclusions—The long-term survival of patients with Kawasaki disease complicated by giant coronary aneurysms is moderately good with multiple catheter and surgical interventions. Further research should focus on the prevention of coronary vascular remodeling and on the indications for and effectiveness of percutaneous and surgical coronary interventions. (Circulation. 2011;123:1836-1842.)

Key Words: aneurysm ■ coronary artery disease ■ mucocutaneous lymph node syndrome ■ outcome assessment

Kawasaki disease (KD), a systemic vasculitis with an unknown origin, is the most common acquired cardiovascular disease in developed countries.1,2 Although intravenous immunoglobulin infusion is an effective treatment for this disease, some patients still develop coronary aneurysms.3–5 These coronary aneurysms undergo remodeling over time,6 leading to intimal thickening and calcification.7,8 The result of this pathological change in coronary arteries is stenosis adjacent to the aneurysms or occlusion of the coronary arteries, resulting in ischemic heart disease.9,10

Clinical Perspective on p 1842

Coronary aneurysms with a diameter ≥8.0 mm are categorized as giant coronary aneurysms (GAs) that do not regress, but persist or develop stenosis, leading to acute myocardial infarction.9,11 Indeed, in our last report on the 10-to 21-year follow-up of patients with KD, 146 patients had different-sized coronary aneurysms in the early phase of KD. All patients with small to medium coronary aneurysms showed regression of the coronary aneurysm, but none of the patients with GA showed complete regression.9 Furthermore, the remaining patients with moderate to giant aneurysms showed either persistent coronary aneurysms or the development of stenosis over time.

To treat this ischemic heart disease caused by KD, we have applied different types of catheter and surgical coronary interventions, including intracoronary thrombolysis, coronary artery bypass graft surgery (CABG), and percutaneous coronary intervention (PCI), such as standard balloon coronary angioplasty, percutaneous transluminal coronary rotational
ablation (PTCRA), and stent implantation. However, little is known about the long-term prognosis of patients with KD complicated by GA. Therefore, the aim of this study was to determine the long-term prognosis of patients with KD complicated by GA on the basis of a single-institution experience.

Methods
This is a retrospective descriptive study of 76 patients (57 men and 19 women) with KD complicated by GA treated at the Kurume University Hospital from January 1, 1972, until January 31, 2011. GAs were diagnosed by coronary angiography in all patients within 3 months after onset. In general, follow-up examinations included a physical examination, ECG, and echocardiography every 1 to 3 months. A second coronary angiography was performed 6 months after the initial coronary angiography. Follow-up coronary angiography was then performed every 2 to 3 years. In every coronary angiography, the minimal lumen diameter of the target coronary artery was measured with a quantitative cardiac analyzer (CAW-2000, version 1.0; Elk Corp., Osaka, Japan). Pharmacological stress 99mTc-tetrofosmin scintigraphy with dipyridamole infusion (0.56 mg/kg) was performed every 2 to 3 years, and a treadmill exercise stress ECG test was performed between the scintigraphic examinations. These follow-up examinations were also performed whenever patients complained of chest discomfort or other symptoms that could indicate ischemic heart disease.

Three indications for coronary intervention were identified to include patients presenting with clinical ischemic symptoms, patients presenting without clinical ischemic symptoms but having ischemic findings detected by several stress tests, and patients having no ischemic findings detected by any stress tests but having ≥75% stenosis in the left anterior descending artery with a risk of sudden cardiac death by its obstruction. In addition, CABG was considered in patients with findings of ischemia for which PCI is not indicated, including patients with a severe occlusive lesion of the left main coronary artery or the left anterior descending artery, with multivessel (2 or 3 vessels) severe occlusive lesions, and with jeopardized collaterals. The indications for reintervention were the same as for the first coronary intervention, and the specific coronary intervention was considered to be unsuccessful if the patient required another intervention.

The selection and indications for each catheter and surgical intervention technique have changed and evolved since the first patients in our cohort were treated, thus reflecting our experience with each intervention and our increasing understanding of the mechanisms of coronary stenosis in KD. We administered only aspirin, not warfarin, until 1990, and offered only intracoronary thrombolysis and CABG after 1990. After a successful case report in a patient with KD, we started to perform standard balloon coronary angioplasty and subsequently PTCRA in 1994. However, on the basis of our early experience, we confirmed that standard balloon coronary angioplasty with a higher pressure has a significant risk of neoauneymus formation and restenosis and is insufficient to dilate heavily calcified coronary arteries. In contrast, we demonstrated that PTCRA can dilate most coronary stenoses even with heavy calcification and after the failure of standard balloon coronary angioplasty. We therefore concluded that it was the most appropriate catheter intervention in this setting. In the late 1990s, we decided to restrict standard balloon coronary angioplasty to patients within 6 years after onset and without circumferential coronary artery wall calcification. Additionally, we started bare metal stent implantation for coronary arteries after either standard balloon coronary angioplasty or PTCRA in 1995. However, because of the requirement of a larger arterial access and the risk of intractable restenosis, we stopped coronary stent placement after 2000.

Before 1994, or when PCI was contraindicated, we offered CABG. We tried to offer CABG primarily to older patients because the rate of patency is generally not satisfactory in small children and insufficient graft vessels remain if the anastomosed graft vessels are obstructed.

From the medical charts, we collected data on sex, age at onset, site and size of the GA, treatment in the acute phase such as intravenous immune globulin, clinical course, and treatment history, including medications and catheter and surgical interventions. If patients were not followed up in our institution at their latest visit, their cardiologists were contacted, and up-to-date clinical data were obtained when available.

End Points
The primary end points of the study were death; the occurrence of the first cardiac event, clinical myocardial infarction, when ischemic changes were noted on ECG and confirmed by coronary angiography; and the occurrence of the first catheter and surgical intervention to the coronary arteries to relieve myocardial ischemia.

Statistical Analysis
Data are presented as medians and ranges or mean±SD, as appropriate. From these data, we calculated the survival rate using a Kaplan-Meier analysis. We performed a Cox proportional hazards regression analysis to determine the influence of the site of GA, sex of the patients, and administration of intravenous immunoglobulin on the survival rate and to compare the reintervention-free rate between PCI and CABG. We also determined the cumulative cardiac event rate and cumulative coronary intervention rate with competing risk adjustment. A statistical difference was considered to exist at P<0.05. All data analyses were performed with free or commercially available statistical analysis software packages (R 2.12.1, The R Foundation for Statistical Computing; Statview 5.0, SAS Institute Inc., Cary, NC; and PASW 17.0, SPSS Inc., Chicago, IL).

Results
The age at the onset of KD was 2.9±2.9 years. During the acute phase, we treated patients with aspirin alone until the mid-1980s and with aspirin and intravenous immunoglobulin after 1984. A total of 36 patients were treated with aspirin alone, 1 with steroids alone, 24 with aspirin plus intravenous immunoglobulin, 7 with aspirin plus intravenous immunoglobulin plus steroids, and the remaining 8 patients with unknown medications. After 1990, 23 patients were placed on warfarin as an antithrombotic treatment soon after the acute phase. The GA was located in the right coronary artery only in 17 patients, left coronary artery only in 13 patients, and both the right and left coronary arteries in 46 patients. The size of the GA in the right or left coronary artery was available for 80 of the 122 coronary arteries; the mean size of the right coronary artery aneurysm was 10.3 mm (range, 8 to 18 mm), and that of the left coronary artery aneurysm was 10.0 mm (range, 8 to 15 mm) in diameter.

We were able to obtain recent clinical information (within the last 3 years) in 70 patients (92%); 63 patients were followed up by us, and 7 patients had moved and were followed up at other institutions. Of the remaining 6 patients (8%), 4 patients had moved at 3, 8, 14, and 17 years after the onset of KD and had been followed up at other institutions, but no recent clinical information was available, and 2 patients were entirely lost to follow-up at 9 and 19 years after onset, respectively. As a result, the observational period was a median of 19 years, ranging from 2 months to 36 years.

During this observational period, 12 patients (16%) experienced a myocardial infarction, and ultimately 8 patients either died or underwent a heart transplantation (Figure 1). Among the 8 patients who died or underwent a heart transplantation (Figure 1).
transplantation, 2 patients died within a year (at 2 and 5 months), 1 died within 4 years, 4 died within 10 to 13 years, and the remaining 1 underwent a heart transplantation at 19 years after onset (Table 1). From the data obtained until the final follow-up, the calculated survival rates were 95%, 88%, and 88% at 10, 20, and 30 years, respectively (Figure 2). A Cox proportional hazards regression analysis showed no significant influence of the site of GA, sex of the patient, or administration of intravenous immunoglobulin on the survival rate.

Of the 8 patients who died or underwent a heart transplantation, we have detailed clinical information on 3 patients. Patient 3 had a bilateral GA with multivessel disease and underwent successful CABG with anastomosis of the right internal thoracic artery to segment 6 of the left anterior descending artery and of the left internal thoracic artery to segment 11 of the left circumflex artery because of anginal chest pain caused by 90% stenosis of the left coronary ostium at 4 years of age. At 6 years of age, coronary angiography showed occlusion of the right internal thoracic artery and stenosis of the left internal thoracic artery when he complained of anginal chest pain. He underwent successful PTCRA to treat stenosis of the left coronary ostium and experienced a transient relief of chest pain, but he fell into a state of shock during the second session of PTCRA for recurrent stenosis of the left coronary ostium 2 months later and died.28

Patient 7 died while awaiting a scheduled cardiac catheterization after he complained of chest discomfort. His last diagnostic cardiac catheterization showed a 6.5-mm left coronary aneurysm without stenosis, and his parents refused to have the patient undergo further cardiac catheterization for 9 years. Because the treadmill exercise stress test did not show any ischemic changes on his ECG, he was scheduled to undergo elective diagnostic cardiac catheterization. However, he collapsed in school and was brought to the emergency department where he underwent cardiac catheterization that showed 99% stenosis of the left anterior descending artery. Ultimately, he could not be saved because of extensive cardiac infarction.

Patient 8 previously underwent successful stent implantation into his left anterior descending artery. Five years after his last cardiac catheterization, which showed good patency of the implanted stent, he suffered an acute myocardial infarction. He underwent CABG, but his left ventricular function did not recover, and he was placed on a left ventricular assist device for 2 years. Fortunately, he eventually underwent a successful heart transplantation.

On the other hand, 46 of the total 76 patients (61%) underwent catheter and surgical coronary interventions, with a median of 1 intervention (mean, 1.7) and a range of 1 to 7 interventions for each patient. All of the coronary interventions performed are described in Table 2. In these patients, the

![Figure 1. Diagram showing the prognosis of each patient. AMI indicates acute myocardial infarction; w/, with; w/o, without.](http://circ.ahajournals.org/)

![Figure 2. Kaplan-Meier survival curve of the entire cohort of patients with giant coronary aneurysms.](http://circ.ahajournals.org/)
first coronary interventions were offered at 1 month to 21 years (median, 3.5 years; modal peak, 1 month) after the onset of KD, giving 28%, 43%, and 59% cumulative coronary intervention rates at 5, 15, and 25 years, respectively (Figure 3). Intracoronary thrombolysis was offered significantly sooner after the onset of KD than the remaining coronary interventions. In fact, 25 of 26 coronary interventions (96%) offered within 2 years after the onset were intracoronary thrombolysis.

In addition to the patients who received intracoronary thrombolysis, 22 patients underwent PCI (11 PTCRA, 6 stent implantation, and 5 standard balloon coronary angioplasty) at 11.5±5.3 years and 13 patients underwent CABG at 9.2±6.1 years after the onset as the first coronary intervention. During the mean follow-up of 6.1±4.9 years in patients with PCI and 9.8±5.6 years in patients with CABG, 10 of 22 patients (45%) with PCI required reintervention, but only 1 of 13 patients (8%) with CABG required reintervention. The calculated reintervention-free rate for PCI tended to be lower than that for CABG (P=0.056). In survivors after cardiac interventions, the median time of follow-up after the final intervention was 10.5 years, ranging from 8 months to 27 years. The final coronary intervention offered was CABG in 13, PTCRA in 10, intracoronary thrombolysis in 8, stent implantation in 7, and balloon angioplasty in 2 patients.

In the remaining 27 surviving patients who did not require coronary intervention, 10 patients (38%) had an obstructive coronary lesion potentially requiring cardiac interventions in the future. Five of these patients had an occluded right coronary artery with recanalization, 3 patients had 50% stenosis of the right coronary artery, and 2 patients had ≥50% stenosis of the left anterior descending artery. The remaining 17 patients showed persistent coronary aneurysms without a complete normalization of diameter.

At the latest visit, we had no information on medications for 2 survivors. Of the remaining 66 survivors, 9 had not received any medication, and 57 had received aspirin in addition to different combinations of medications such as vitamin C (n=8), dipyridamole (n=5), warfarin (n=4), β-blockers (n=6), ticlopidine (n=3), angiotensin-converting enzyme inhibitors (n=4), calcium antagonists (n=2), clopidogrel (n=1), nitrate (n=1), and cholesterol-reducing drug (n=1).

**Discussion**

This study indicates that the long-term prognosis of patients with KD complicated by GA is moderately good with multiple catheter and surgical interventions, and that the number of patients who require such catheter and surgical intervention increases over time after disease onset, probably reflecting the ongoing remodeling of the coronary vascular walls.

It has been >35 years since Kato et al4 first reported the development of coronary aneurysms after acute KD, but little information is available concerning the long-term prognosis of KD with GA. In our last report, we had 26 patients (20 men and 6 women) with GA, and 12 of them (46%) showed a progression to coronary stenosis or complete obstruction of the coronary artery, leading to myocardial infarction in 8 and eventually death in 4 (15.4%). The remaining 14 patients showed persistent coronary aneurysms without significant stenosis in the coronary artery over a follow-up period of 10 to 21 years. The present study is an extension of our past institutional experience, and represents the world’s largest cohort of patients with KD complicated by GA who have been followed up for the longest time. In this study, we have shown a high survival rate of 88% up to 30 years, with a 59% cumulative intervention rate at 25 years after the onset of KD.

Levy et al6 reported the outcome of 22 patients with GA with a much shorter follow-up period of 6.9 years in patients treated with warfarin and 13.3 years in patients who did not receive warfarin. In their study, 4 patients (18.2%) suffered an ischemic event, but no patients died. These numbers look somewhat better than our results, but their study included far fewer subjects, and substantial recent improvements in the

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Interventions, n</th>
<th>Time After the Onset of KD, y</th>
<th>Rate of Reintervention Failure, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracoronary thrombolysis</td>
<td>33 (10emergency)</td>
<td>1.1 (0–5.3)*</td>
<td>78</td>
</tr>
<tr>
<td>PTCRA</td>
<td>16</td>
<td>13.2 (2.9–23.8)</td>
<td>43</td>
</tr>
<tr>
<td>Standard angioplasty</td>
<td>6 (2 emergency)</td>
<td>11.1 (0.9–21.5)</td>
<td>75</td>
</tr>
<tr>
<td>Stent</td>
<td>9 (1 emergency)</td>
<td>12.0 (6.3–16.6)</td>
<td>33</td>
</tr>
<tr>
<td>CABG</td>
<td>17 (1 emergency)</td>
<td>7.4 (2.8–21.0)†</td>
<td>11†</td>
</tr>
</tbody>
</table>

**Table 2. Outcomes of Catheter and Surgical Interventions**

KD indicates Kawasaki disease; PTCRA, percutaneous transluminal coronary rotational ablation; and CABG, coronary artery bypass graft surgery. The time after the onset of KD is expressed as median (range).

*P<0.0001 versus the remaining coronary interventions.

†P<0.0002 versus percutaneous coronary catheter interventions.
management of acute coronary syndrome and the treatment regimen might have contributed to their better outcome.

On the other hand, our study indicates that ongoing remodeling of coronary arteries with GA might continue long after KD, leading to the development of coronary stenosis, even >21 years after the onset of disease. In our last study, we showed an increasing frequency of coronary stenosis in patients with coronary aneurysms up to 17 years after diagnosis, and in the present study, the frequency of coronary stenosis never leveled off. Furthermore, we have 10 more patients who had obstructive coronary lesions that may lead to myocardial ischemia in the future. The potential mechanisms underlying these findings include ongoing remodeling of the coronary arteries as a result of ongoing inflammation of the coronary arteries, demonstrated by higher levels of serum high-sensitivity C-reactive protein and amyloid A29 and increased oxidative stress.30 In addition, accelerated endothelial dysfunction and subclinical atherosclerosis have been reported in patients with a coronary aneurysm long after KD.31

Moreover, the fact that many patients required additional coronary intervention for the progression of myocardial ischemia as a result of recurrent stenosis of the treated vessels indicates the relative incompleteness of catheter coronary intervention. In fact, PCI tended to show a lower reintervention-free rate than CABG in this study. This finding is in agreement with several reports. For example, Tsuda et al32 reported that 4 of 6 patients with a history of KD treated by PTCRA developed restenosis. In addition, a recent Japanese multicenter study comparing CABG and PCI in patients with KD showed the rate of repeat revascularization therapy to be significantly higher for PCI than CABG.33 Conversely, even after CABG, one of our patients developed an obstruction of the graft vessels. Miyazaki et al34 reported successful balloon dilation of anastomotic stenosis after CABG in patients with KD. Therefore, it is necessary to accumulate more data concerning the indications and outcomes of these coronary interventions in KD patients and to determine the optimal measures to prevent restenosis of coronary arteries.

The clinical profiles of nonsurvivors highlight several important issues concerning the management of these patients. The first issue is the difficulty in treating small children with ischemic heart disease caused by KD. Both PCI and CABG in small children are very limited, and may be unsatisfactory.26 In fact, patient 7 underwent CABG at 4 years of age and PTCRA at 6 years of age, the youngest age for CABG and the second-youngest age for PTCRA in our series. To improve the outcomes of such interventions, it is necessary to accumulate more data in pediatric patients and perhaps to develop new devices suitable for small children. Meanwhile, neovascularization with heparin might be a new option to alleviate myocardial ischemia and to provide time to let small children grow before undergoing such procedures.35

The second issue is the timing and modalities used to detect myocardial ischemia in patients long after the onset of KD. Although a treadmill exercise stress test did not show ischemic changes on ECG, cardiac catheterization showed 99% stenosis of the left anterior descending artery in patient 7, who complained of chest discomfort. In agreement with this finding, Kamiya36 reported that the treadmill exercise test is the least sensitive method to detect myocardial ischemia in patients with KD. Although stress myocardial scintigraphy was reported to be useful for risk stratification,37 the diagnostic algorithm to detect myocardial ischemia in patients long after the onset of KD, including the most appropriate timing and modalities, must be reexamined.

The third issue is the follow-up system and education of young adult patients with GA long after the onset of KD to prevent unfavorable coronary vascular remodeling. Patient 8 suffered an acute myocardial infarction soon after he started living alone. Muta et al38 reported that the general health perception is erroneously excellent even in patients with GA/ischemia. These adolescent or young adult patients are easily lost to follow-up, and stop taking their medications. Therefore, a continuous follow-up system with close cooperation of a pediatric cardiologist and adult cardiologist must be established. In addition, it is necessary to educate not just the parents, but also the patients themselves, about the natural history of KD and the importance of medication and regular examinations to avoid a progression of premature atherosclerosis.

Study Limitations
This study suffers from several limitations owing to the retrospective nature of the study. Because different treatment regimens were used during the period of our study, the survival curves cannot be taken as representative of the outcome of any single regimen. Survival might have been better had the most current regimen been used in all patients. Furthermore, the rate of deterioration shown in this study might have been lower if optimal therapy had been applied to the earliest patients. Conversely, even the best current therapy is not always successful, and complications occurring over time are inevitable. As well, because other institutional series collected over a long time will be faced with the same heterogeneous collection of patients and treatments, this pooled experience should provide some guidance for other cardiologists.

In addition, because catheter or surgical intervention for coronary arteries in children is not a part of common practice in either cardiology or cardiothoracic surgery, the results may depend largely on institutional or personal experience, and may not be the same at other institutions. Historically, however, we have developed catheter intervention for coronary artery disease after KD, and the results presented here are from one of the institutions with the most experience with these procedures.

Conclusions
The long-term survival of patients with KD with GAs is moderately good for up to 30 years, with various types of catheter and surgical interventions used in more than half of the patients. Further careful follow-up of these patients is mandatory, with attention being paid not only to the patients who have already had some type of intervention, but also to those who have not yet required intervention. Further research should focus on the prevention of coronary vascular remodeling and on the indications for and effectiveness of percutaneous and surgical coronary interventions.
Acknowledgments
We thank Dr Julien LE. Hoffman, Professor of Pediatrics, University of California, San Francisco, for his kind assistance with the manuscript preparation. We also thank Dr Junichi Takagi at the Department of Pediatrics, Miyazaki University Hospital, and Dr Makoto Nishibatake at the Department of Pediatrics, Kagoshima Seiki Hospital, for their kind assistance with collecting current patient information.

Sources of Funding
This work was supported in part by the Academic Frontier Project, Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Disclosures
None.

References
CLINICAL PERSPECTIVE
Kawasaki disease, a systemic vasculitis with unknown origin, is the most frequent acquired cardiovascular disease in children in developed countries. Despite appropriate treatment, including high-dose intravenous immunoglobulin infusion and aspirin, a certain number of patients develop giant coronary aneurysms ($\geq 8$ mm) that could undergo remodeling, leading to ischemic heart disease. In the last 15 years, we have developed catheter and surgical interventions for this ischemic heart disease and proposed indications of these treatments. As a result, the long-term survival of patients with giant coronary aneurysms is moderately good, ie, 90% at 20 years and 87% at 30 years after onset. However, the result of catheter and surgical coronary intervention may not be satisfactory in this setting because many patients require repeat procedures. In addition, it is still difficult to treat small children with ischemic heart disease caused by Kawasaki disease. Further research should focus on medical treatment to prevent coronary vascular remodeling and the indications for and effectiveness of catheter and surgical coronary interventions.
Long-Term Prognosis of Patients With Kawasaki Disease Complicated by Giant Coronary Aneurysms: A Single-Institution Experience
Kenji Suda, Motofumi Iemura, Hiroshi Nishiono, Yozo Teramachi, Yusuke Koteda, Shintaro Kishimoto, Yoshiyuki Kudo, Shinichi Itoh, Haruka Ishii, Takafumi Ueno, Tadashi Tashiro, Masakiyo Nobuyoshi, Hirohisa Kato and Toyojiro Matsuishi

_Circulation_. 2011;123:1836-1842; originally published online April 18, 2011; doi: 10.1161/CIRCULATIONAHA.110.978213
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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