Cardiology in the Young

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Characteristics and outcomes of patients with stent implantation for coronary artery lesions caused by Kawasaki disease – insights from second-generation stent implantation

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Original Article

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Abstract

Background: Adult Kawasaki patients may require intervention for occlusive coronary artery disease. Some adverse effects of first-generation drug-eluting stent implantation with sirolimus have been reported in this population. *Methods:* A total of nine lesions in eight (seven males, one female) patients who underwent stent implantations in this population between 2000 and 2021 were reviewed. *Results:* The age at stent implantation ranged from 31 to 47 years, with a median of 37 years. There were six lesions treated by primary percutaneous transluminal coronary interventions, and three by elective procedures. A coronary aneurysm was found in two lesions, and coronary artery calcification was found in all culprit lesions. The numbers of everolimus-eluting stents, sirolimus-eluting stents and bare metal stents were six, two, and one, respectively. As anti- thrombotic therapy, aspirin, clopidogrel, and prasugrel were given to four, three, and one, respectively. Warfarin was given to five patients. The follow-up ranged from 2 to 12 years, with a median of 4 years. Follow-up angiograms were performed for eight lesions, at 2 to 38 months, with a median of 11 months. The patency of the target vessel was confirmed in all eight vessels. Slight malapposition, and peri-stent contrast staining were found in two lesions each. *Conclusion:* Acute coronary syndrome due to coronary artery lesions caused by Kawasaki disease occurred, even in lesions without any apparent coronary artery aneurysms. In our study, we show safe and efficacious placement of second-generation stent without adverse effects during the short-term follow-up, but long-term follow-up is needed to determine the efficacy and complication.

Introduction

More than 50 years have passed since the first report of Kawasaki disease in 1967. Coronary artery lesions caused by Kawasaki disease persist long into adulthood, and the number of patients exceeding 40 years of age has increased. Most are asymptomatic many years after childhood onset of Kawasaki disease until the onset of acute coronary syndrome.[1,2] Therefore, most adult patients drop out from follow-up after Kawasaki disease. Furthermore, there are undoubtedly some asymptomatic adult patients with coronary artery lesions caused by Kawasaki disease who remain undiagnosed in children.[2–4] Patients with acute coronary syndrome are taken to emergency hospitals, with most of them often as young adults having acute coronary syndrome due to atherosclerosis, without considering coronary artery lesions due to Kawasaki disease. Internists are not always familiar with the coronary artery lesions caused by Kawasaki disease, and the affected population is a very small subset of adult ischemic heart disease patients.[4] Primary percutaneous transluminal coronary intervention is an indispensable method for ischemic coronary artery disease, and coronary stent implantation is currently the standard method in adults.[5] However, the pathogenesis of the coronary artery disease differs between atherosclerosis and Kawasaki disease. There have been some reports of thrombotic occlusions, stent fractures, new aneurysm formation, and malapposition after first-generation sirolimus drug-eluting stenting in patients with coronary artery lesions caused by Kawasaki disease.[2,6,7] Generally, the results of coronary stent implantation in cases of severe calcification were poor in first-generation drug-eluting stenting. Therefore, the outcomes of stent implantation after-second generation stenting were investigated in this population.

Methods

A total of nine lesions in eight patients who underwent stent implantations for coronary artery lesions caused by Kawasaki disease and presumed Kawasaki disease between 2011 and 2021 were reviewed based on their medical records, selective coronary angiograms, intravascular ultrasound, and optical coherence tomography imaging. The characteristics and outcomes were retrospectively investigated in patients who underwent stent implantation. This study was approved by our institution (R19003-5).

Results

Characteristics of the patients who underwent stent implantation

There were seven male patients and one female patient (Table 1). The age at stent implantation ranged from 31 to 47 years, with a median of 37 years. The years of their birth ranged from 1968 to 1989, with a median of 1977. Five patients had a history of Kawasaki disease, and three of the five patients had dropped out from follow-up. One patient had a history of persistent fever with some principal symptoms of acute Kawasaki disease. One patient had a history of "scarlet fever". The history of fever was unknown in the female patient. The patients' body mass index ranged from 20.7 to 28.7 kg/m^2, with a median of 22 kg/m^2. The number of atherosclerotic risk factors was as follows: none, one patient; one, five patients, and $\geqq 2$, two patients. The risk factors were as follows: hypercholesterolemia (low-density-lipoprotein>140 mg/dl), five patients; obesity, two patients; smoking, three patients; and hypertension, one patient. Medication was not given before stent implantation to five patients. Six lesions were treated with primary percutaneous coronary intervention for acute coronary syndrome, and three lesions with elective percutaneous coronary intervention. The interval from the onset of Kawasaki disease to stent implantation ranged from 29 to 41 years, with a median of 38 years ($n = 5$).

A coronary aneurysm was found in two lesions, and coronary artery calcification was found in all culprit lesions. The numbers of everolimus-eluting stents, sirolimus-eluting stents, and bare metal stent were six, two, and one, respectively. As anti-thrombotic therapy, aspirin, clopidogrel, and prasugrel were given to four, three, and one, respectively. Warfarin was given to five patients. Follow-up ranged from 2 to 12 years, with a median of 4 years. Follow-up angiograms were performed for eight lesions, at 2 to 38 months with a median follow-up of 11 months.

Primary stenting in acute coronary syndrome

Primary stenting in patients with acute coronary syndrome after Kawasaki disease was performed in six patients (Table 2). The age at the time of stenting ranged from 31 to 48 years. The stented lesions were as follows: the left anterior ascending artery in five and the right coronary artery in one. The culprit lesions were complete occlusion in four and localized stenosis in two. The kinds of stents were everolimus-eluting stents in four, bare metal stent in one, and sirolimus-eluting stent in one. All initial results were successful without any complications. Follow-up coronary angiograms were performed for six lesions, and the interval from stenting ranged from 2 to 38 months, with a median of 11 months. The patency of the target vessel was confirmed in all six vessels. Slight malapposition and trivial peri-stent contrast staining were found in two lesions each (Figures 1 and 2). However, peri-stent contrast staining disappeared in the two patients in the follow-up coronary angiograms. Re-percutaneous coronary intervention for the target lesions was not performed in any patients. The left ventricular ejection fraction ranged from 46% to 52%.

Elective coronary stent implantation

Three male patients underwent stent implantation (everolimus-eluting stents two and sirolimus-eluting stents 1) in elective percutaneous coronary intervention (Table 3). Two patients had undergone a coronary artery bypass grafting, and one had stent implantation for the left anterior ascending artery. The target vessels were the left circumflex in two and the right coronary artery in one. The target lesions were chronic total occlusion, dissection, and segmental stenosis. All initial results were successful. Follow-up coronary angiograms were performed in two patients. The intervals from the procedure to the follow-up coronary angiograms was 2 years and 3 years, respectively. There was no re-stenosis in either patient. After stent implantation, one patient received a cardiac resynchronization therapy-defibrillator because of heart failure, and one had a left ventricular assist device implanted. The third patient underwent an implantable cardioverter defibrillator and ablation for ventricular tachycardia in the late period.

Discussion

The age of patients with acute coronary syndrome in this study was around 30 years, which was younger than the patients with acute coronary syndrome due to atherosclerosis. The number of atherosclerotic coronary risk factors was fewer in these patients than in those with ischemic heart disease due to atherosclerosis. The patients in the present study had several risk factors with aging. Therefore, decreasing the atherosclerotic risk factors with aging is also needed in this population. Most young adult patients with acute coronary syndrome due to coronary artery lesions caused by Kawasaki disease were not on medication, because of drop out from follow-up. That indicated the importance of follow-up.[8]

All culprit lesions in the present study were calcified coronary artery lesions. Calcified coronary artery lesions indicate abnormalities of the coronary artery wall after acute Kawasaki disease. Two of the six culprit lesions in acute coronary syndrome had giant coronary aneurysms. Generally, acute myocardial infarction immediately after acute Kawasaki disease in children is likely to occur due to thrombus in giant aneurysms of more than 8 mm. However, acute myocardial infarction due to coronary artery lesions caused by Kawasaki disease in the late period can occur, not only in coronary artery aneurysms, but also in coronary artery segments without coronary aneurysms. Acute myocardial infarction is not always induced by either thrombus in giant aneurysms or localized stenosis.[9] In such lesions, regression of coronary artery aneurysms with coronary artery calcification had usually been found. The segments of regressed coronary aneurysms induce thrombotic occlusion, because of endothelial abnormalities of coronary wall. Antithrombotic therapy such as with antiplatelets or warfarin and continuous follow-up are required in patients with coronary artery lesions caused by Kawasaki disease.

In most cases of acute myocardial infarction requiring percutaneous coronary intervention, the causes have been massive thrombi. Aspiration of thrombus has been recommended. In cases where the procedures are ineffective, percutaneous balloon

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Table 1. Characteristics of patients with coronary stent implantation

Patient characteristics	
Number of patients	7 males, 1 female
Median age at stent implantation [range]	37 [31–47]
Median body mass index (kg/m^2) [range]	22.0 [20.7–28.7]
Median year of birth [range]	1977 [1968–1989]
History of Kawasaki disease	Typical 5, Probable 2, Unknown 1
Median interval from acute KD to procedure[range](years)	38 [29–41] ($n = 5$)
Median follow-up period after procedure [range]	4 [2 – 12]
Number of coronary risk factors	none, 1 pt, 1, 5 pts, ≧2, 2 pts
Hypercholesterolemia (LDL>140 mg/dl)	5
Obesity (body mass index>25)	2
Smoking	3
Hypertension	1
Stent implantation	
Institution of stent implantation	Our hospital 5, Others 3
Number of stent implantation (Situations)	9 (Primary 6, Elective 3)
Symptom (acute coronary syndrome, ACS)	Chest pain 5, Palpitation 1
Before management of ACS	Regular follow-up 1, Drop-out 2
	Stop of follow-up 1, None 2
Antiplatelet therapy before ACS	Aspirin 1, None 5
Characteristics of coronary artery lesions	
Culprit lesion	LAD 5(Occlusion 4, 75%LS 1)
	RCA 2(75%LS 1, segmental stenosis 1);
	LCX 2 (CTO 1, Dissection* 1)
Calcification in the culprit lesion	9 (100%)
Coronary aneurysm in the culprit lesion	2

KD: Kawasaki disease; ACS: acute coronary syndrome; LAD: left anterior descending artery; LS: localized stenosis; RCA: right coronary artery; LCX: left circumflex; CTO: chronic total occlusion.
*Stent implantation was performed after dissection after balloon angioplasty for localized stenosis.

angioplasty is a useful add-on. If the cause of the occlusion is a massive thrombus without any significant coronary artery stenosis, stent implantation is not always needed.[7,9] However, re-occlusion with thrombus is often found, which may worsen the hemodynamic status of the patients. In such cases, confirmed coronary artery reperfusion is needed. Stent implantation in culprit lesions may also be useful in this population if long-term patency is preserved without complications. One must be careful not to underestimate the size of the selected stent because of massive thrombus. Progressive localized stenosis with aging in the late period after Kawasaki disease complicates severe coronary artery calcification. It is difficult to implant a stent in localized stenosis with severe calcification. Percutaneous transluminal coronary rotational atherectomy is suitable for such lesions.[10] To implant the optimal size stent for the periculprit portion, the culprit lesions with severe localized stenosis must be dilated by rotational atherectomy. Furthermore, an indication and effectiveness of stent implantation for chronic total occlusion and segmental stenosis will be investigated in the future. Anti-thrombotic therapy is indispensable in such patients after the procedure. In young adults, major hemorrhagic complications are rarer than in elderly patients. Therefore, warfarin in addition to antiplatelets agents may be effective in patients with coronary aneurysms. Direct oral anticoagulants may be also considered in such patients.[11]

Calcified giant aneurysms are usually suspected to be due to presumed Kawasaki disease. Patient 1 in this report had no history of Kawasaki disease. However, she had a severe intimal thickening and calcification in the proximal portion of the left anterior descending artery. She had no coronary risk factors, and other vasculitis was denied. Patient 3 was diagnosed with "scarlet fever" as a child; however, he had also had a severe calcification of the proximal portion of the left anterior descending artery. It might have been misdiagnosed. The presence of severely calcified coronary arteries in the proximal of epicoronary arteries in young adults should be cause for suspicion of presumed Kawasaki disease.[3] In the present study, the proximal segments of the left anterior ascending artery were the most commonly affected culprit vessels. Generally, most culprit lesions in acute coronary syndrome in patients with coronary artery lesions caused by Kawasaki disease are the proximal segments of the major coronary arteries, because coronary aneurysms during acute Kawasaki disease are likely to occur.[12]

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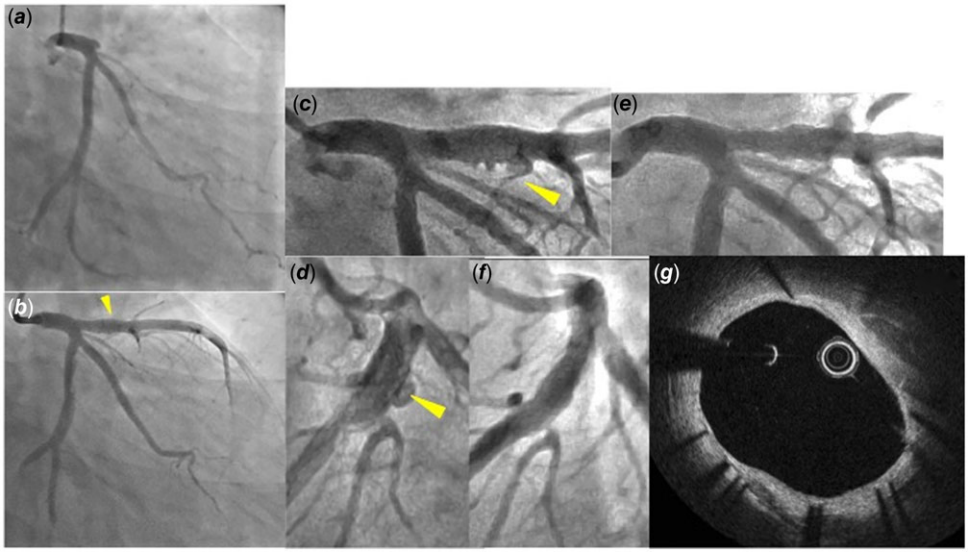

Figure 1. Coronary angiograms before and after stent implantation for acute coronary syndrome. (Left) Coronary angiograms before and after procedure. (Middle) Coronary angiograms 1 year after procedure. (Right) Coronary angiograms 2 years after procedure. A 32-year-old man developed acute myocardial infarction due to complete occlusion with severe calcification of the left anterior descending artery and underwent emergency stent implantation with an everolimus eluting stent (Xience) (A, B). On pathological examination of the aspiration sample, no atherosclerotic plaque was found. The patient had a history of "scarlet fever" as a child. One year after stent implantation, there was no restenosis. Peri-stent contrast staining was seen (C, D). Two years after the procedure, the peri-stent contrast staining had disappeared (E, F, G).

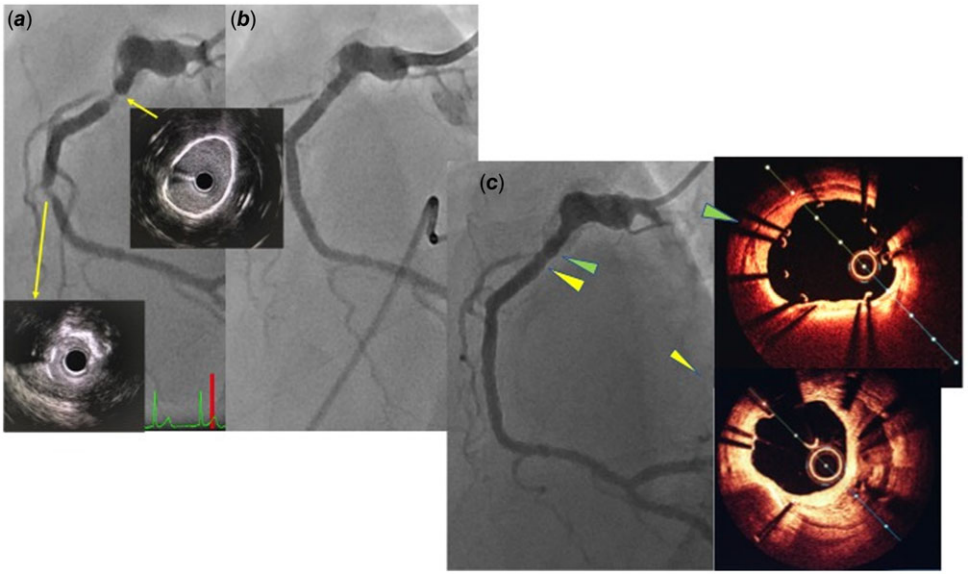

Figure 2. Coronary angiograms before and after percutaneous coronary intervention for acute coronary syndrome. (Left) Coronary angiograms before and after procedure. (Right) Coronary angiograms 1 year after procedure. A 31-year-old man had had localized stenosis with an aneurysm in the right coronary artery. However, he dropped out from follow-up at another hospital. He developed sudden chest pain with a cold sweat while walking. He was transferred to our emergency room. The electrocardiogram showed ST elevation in leads II, III, and aVF. His emergency coronary angiogram showed 90% stenosis with an aneurysm at segment 1(A). Severe coronary artery calcification was found in the culprit lesion on intravascular ultrasound (B, C). It was impossible to dilate it with a cutting balloon. After percutaneous transluminal rotational atherectomy, implantation of a Xience Sierra 2.5/15 mm stent in segment 2 and a Xience Sierra 3.0/15 mm stent in segment 1 was performed (D). warfarin, clopidogrel, statin, and enalapril were prescribed. There was no restenosis on CAG 1 year after emergency stent implantation (***E***). However, optical coherence tomography showed slight malapposition, however, there was no in-stent restenosis (F, G).

Calcified plaques at the culprit lesion are found in 10% of acute coronary syndrome cases due to atherosclerosis, and their outcomes after stent implantation are worse than those of other culprit lesions.[13] These findings in coronary artery lesions caused by Kawasaki disease differ from those in acute coronary syndrome due to atherosclerosis. On optical coherence tomography imaging in the short-term period after stenting, slight malapposition and peri-stent contrast staining were seen in some cases. The progression of intimal thickening after stent implantation in the culprit lesions must be observed carefully in the future.

In summarizing the previous literature review, 33 patients underwent stent implantation for 34 coronary arteries after Kawasaki disease. Follow-up coronary angiograms were performed or 28 vessels. Adverse effects in the late period affected 19 coronary arteries (68%).[7] New aneurysm formation was found in seven of the 19 vessels (37%), and most patients underwent sirolimus-eluting stents implantation. Those results indicated that stent implantations were not always acceptable as a safe method to maintain the patency of the culprit vessel for several years.[14–23] However, although the number of everolimus-eluting stent implantation was small in the present study and the previous reports, and follow-up was short-term, the results were not always poor. Although its incidence in each group was not precisely known, the incidence of new aneurysms for second generation implantation seemed to be less than for first-generation stent implantation (Table 4). The incidence of peri-stent contrast staining in the second generation was less than that in the first generation in adults due to atherosclerosis.[24,25] The causes of the new aneurysms and peri-stent contrast staining after drug-eluting stent implantations remains unknown in this population. Their appearance may be related to the pathogenesis of coronary artery lesions caused by Kawasaki disease. Restenosis can occur due to

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Table 2. Primary coronary stent implantation in patients with acute coronary syndrome

Patient	1	2	3	4	5	6
Age (years)	37	42	32	31	48	42
Sex	Female	Male	Male	Male	Male	Male
Age at KD	Unknown	6 years	"Scarlet fever"	2 years	9 months	16 months
Management before ACS	–	Stop	–	Drop-out	Aspirin	Drop-out
Risk factor	None	Dyslipidemia	Dyslipidemia	Smoking	Dyslipidemia	Smoking
Culprit lesion	Seg 6, 7 (OC)	Seg 6 (100%)	Seg 6 (100%)	Seg 1, 2 (90%LS)	Seg 6, 7 (100%)	Seg 6 (75% LS)
Aneurysm		Regression		10 mm	11 mm	
Stent type	Promius Premier (EES)	BMS	Xience Skypoint (EES)	Xience Sierra (EES)	Synergy XD (EES)	Ultimaster (SES)
Stent size (mm)	3.0 × 8, 2.5 ×28, 2.5 x 8	3.5 × 24	4.0 × 15	2.5 × 15, 3.0 × 15	3.5 × 24, 2.5 x 38	3.5 × 28
Late period after procedure						
Follow-up (years)	4	12	2	2	3	4
Antithrombotic therapy	Clopidogrel	Warfarin	Prasgrel	Clopidogrel, Warfarin	Aspirin, Clopidogrel Warfarin	Aspirin
Outcome	slight malapposiotion	None	PSS→disappear	slight malapposition	PSS→disappear	None

ACS: acute coronary syndrome; EES: Everolimus eluting stent; BMS: bare metal stent; SES: sirolimus eluting stent; PSS: peri-stent contrast staining.

Table 3. Elective coronary stent implantation

Patient	1	2	3
Age (years)	46	35	42
Sex	Male	Male	Male
Age at KD	4 months (Propable)	2 years	16 months
Risk factor	HT, Dyslipidemia	Dyslipidemia	Smoking
	Smoking		
Previous coronary intervention	CABG,	CABG, PTCRA	Stent implantation for LAD
Culprit lesion	Seg 11 (CTO)	Seg 11 (Dissection)	Seg 1, 2 (SS)
Stent type	Xience (EES)	Synergy (EES)	Ultimaster (SES)
Stent size (mm)	3.25×33, 2.5×33	3.5×12	3.0×38
Late period			
Follow-up after stent implantation	6 years	4 years	5 years
Antithrombotic therapy	warfarin	aspirin, warfarin	aspirin
Outcome of target vessel	Patent	Unknown	Patent
Additional treatment	CRT-D	LVAD implantation	Ablation, ICD

EES: Everolimus eluting stent; CABG: coronary artery bypass grafting; HT: hypertension; PTCRA: percutaneous transluminal coronary rotational atherectomy; CTO: chronic total occlusion; SS: segmental stenosis; CRT-D: cardiac resynchronization therapy-defibrillator; LVAD: left ventricular assist device; ICD: implantable cardioverter defibrillator.

disease progression and coronary risk factors with aging. Because the pathogenesis of intimal thickening remains unknown, whether drugs can prevent intimal thickening over many years remains to be determined. When the patient is young, it is important to preserve the patency over the long-term period. On the other hand, a stentless study showed good results in patients with acute coronary syndrome caused by plaque erosion managed with aspirin and ticagrelor without stenting, in those who remained free

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Table 4. Previous reports of drug-eluting stent implantation

Procedure	Age	Sex	Branch	Lesion	Stent	Interval	Outcome	Medication	Year
Elective	12	f	RCA	90% LS	Cypher 3.0/18 mm	1 year	new AN, malapposition	DAPT	2005[14]
Elective	10	m	LAD	90% LS	Radius stent 4.0/20 mm	6 months	restenosis, new AN	DAPT	2006[15]
Elective	9	f	LAD	CTO	Cypher 2.5/18, 3.0/23 mm	2 years	OC with fracture, new AN →re-stenting		2012[16]
Elective	32	f	RCA	CTO	Liberte 3.5/24 mm	3 years	new AN, 90% stenosis		2013[17]
Elective	33	m	RCA	CTO	Tsunami 3.5/30 (2), Liberte 4.0/32 mm	8 months	OC→re-stenting		2013[17]
Elective	40	m	RCA SS	CTO	Zotarolimus 3.5/24, 2.5/24 mm	6 months	new AN, malapposition stenosis		2013[18]
Primary*	32	m	RCA	OC	Cypher 3.5/18 mm		new AN	DAPT	2015[19]
Elective	18	m	RCA	CTO	Promus Premier** 3.0/20 4.0/20 (3)	1 year	OC, new AN		2016[20]
Primary*	40	m	LAD	OC	Resolute Integrity** 3.0/34 mm	7 days	Early stent thrombosis	DAPT	2017[21]
Elective	55	m	LCX	OC	Promus Premier** 3.0/16 mm	5 months	Peri-stent contrast staining	DAPT Warfarin	2019[22]
Elective	40	m	RCA	SS	Promus Premier** 3.0/38 mm	12 months	patent		2019[23]

*Primary coronary stent implantation was treated in patients with acute coronary syndrome. **second-generation.
LS: localized stenosis; AN: aneurysm; DAPT: dual anti-platelet therapy; OC: complete occlusion; CTO: chronic total occlusion; SS: segmental stenosis.

of any major adverse cardiovascular events for <1 year.[26] Knowing the long-term efficacy and complications is important for selecting the procedure. Furthermore, outcomes of the improvements in percutaneous coronary interventions and the resolution of coronary artery lesions need to be studied in the future.

Conclusions

Acute coronary syndrome due to coronary artery lesions caused by Kawasaki disease occurs in adults, even in lesions without apparent coronary artery aneurysms. Second-generation stent implantation into coronary artery lesions with severe coronary artery calcification caused by Kawasaki disease provides acceptable short-term outcomes. Determining the long-term efficacy and complications of stent implantations will be important in the future.

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Ethical standard. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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