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REVIEW ARTICLE

Long-term Management of Kawasaki Disease: Implications for the Adult Patient

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Coronary artery complications from Kawasaki disease (KD) range from no involvement to giant coronary artery aneurysms (CAA). Current long-term management protocols are calibrated to the degree of maximal and current coronary artery involvement reflecting the known likelihood of severe long-term cardiac complications. It has recently been suggested that all KD patients may be at potential risk of severe long-term cardiac complications. If this assertion was to be confirmed, current follow-up protocols would need to be extensively modified, with important implications both for the growing adult population with a previous history of KD and for the healthcare system. Based on the available evidence, patients with multiple large and/or giant CAA are at substantial risk of severe long-term cardiac complications and should have regular specialized follow-up. Patients with transient or no CAA have not been reported to be at risk of severe long-term cardiac complications. The influence of KD on the atherosclerotic process remains suboptimally defined, and should be the focus of future studies. Heightened cardiovascular risk factor surveillance and management is recommended regardless of coronary artery involvement. Based on the currently available evidence, existing long-term management protocols seem to be appropriately calibrated to the level of risk. Revised long-term management protocols should incorporate newer, noninvasive imaging methods and intensive management of atherosclerotic risk. There is insufficient evidence at this time to mandate long-term specialized follow-up and invasive testing for patients who have not had CAA.

1. Introduction

Long-term cardiovascular complications of persistent coronary artery aneurysms (CAA) secondary to Kawasaki disease (KD) are well documented. These patients require life-long

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clinical follow-up and management. Conversely, it is generally accepted that patients with no or transient coronary artery dilation during acute KD, comprising ~95% of individuals diagnosed with KD in the past 25 years,[1] live with long-term cardiovascular health comparable to the general population and are usually discharged from specialized care within 2 years of diagnosis. An intermediate group of patients, those with small to medium sized CAA that may or may not have regressed, have an unclear long-term prognosis and, hence, may receive suboptimal follow-up.

Recently, it has been suggested that previously unrecognized long-term cardiovascular adverse effects may be associated with a previous history of KD, regardless of history of coronary artery involvement.[2] These late effects, including both arterial and myocardial abnormalities, have recently been the topic of much review and debate.[1] It is important that the controversies and questions on these matters are properly clarified through systematic research, to not only identify and properly manage patients at potentially unrecognized long-term cardiovascular risk, but also to avoid mislabeling a majority of individuals as high-risk adult patients, burdening them with unnecessary testing, follow-up, and emotional uncertainties regarding their long-term prognosis.

2. CAA

Three pathological processes that characterize KD, including CAA formation, have been identified. The first of these, an acute, self-limited necrotizing arteritis, may result in saccular aneurysm formation in the first 2 weeks of illness. Next, a subacute/chronic vasculitis causes variable, persistent inflammation of the arteries, potentially resulting in both fusiform and saccular aneurysms. Finally, subacute/chronic vasculitis may promote luminal myofibroblastic proliferation, where smooth muscle cell-derived myofibroblasts and their matrix products result in gradual stenosis of the vessel lumen.[3] These processes involve three critical pathophysiologic steps, including inflammatory T-cell infiltration and proliferation, tumor necrosis factor-α production, and upregulation of matrix metalloproteinase-9.[4] Consequently, the destruction of the internal elastic lamina, as well as smooth muscle cell death, lead to coronary artery aneurysms.[5]

CAA are the most serious consequences of KD, and are the major cause of morbidity and mortality related to the disease.[6] Less frequently, KD may also result in other acute cardiac sequelae, including endocarditis, valvulitis, and conduction system abnormalities.[7] In the absence of acute treatment, the incidence of CAA in KD patients is 15–25%[8–10]; standard treatment with high dose intravenous immunoglobulin (IVIG) at 2 mg/kg, given within 10 days of onset of fever, decreases this incidence to ~5%.[8] Risk factors for CAA development include low serum albumin, longer duration of fever during the acute phase of disease, and age <1 year or >9 years.[11–14] Resistance to initial IVIG treatment (persistence or recurrence of fever) is seen in 13–21% of KD patients, and is associated with an increased risk of CAA.[15] Risk of CAA is also increased by delayed diagnosis and late treatment with IVIG, which remains an ongoing issue in clinical practice.[16]

CAA resulting from KD occur preferentially in the proximal segments of the major coronary arteries,[12] and vary in terms of size and arterial involvement as defined by luminal dimensions.[6] Cardiac complications and outcomes for KD patients are associated with the extent and severity of coronary artery involvement. Recently, it was shown that CAA can be optimally classified using only z-scores[17] and those CAA with z-scores ≥10 are at substantial risk of medium-term complications (stenosis, thrombosis, or myocardial infarct) regardless of absolute coronary artery size (Figure 1), while those ≥2.5 to <10.0 were not.[17]

Over time, smaller CAA may also remodel and regress by a process involving intimal thickening and angiogenesis.[18] There is some controversy as to whether or not these regressed CAA are healed coronary arteries, or continue to undergo long-term pathological changes; however, current consensus suggests minimal long-term risk in such cases.[10,19] The mechanism and prognosis associated with transient coronary artery dilation, which normalizes within 30 days to 8 weeks of illness onset, remains controversial.[6,20] Crystal et al found coronary artery z-score regression in patients with normal acute-phase coronary arteries,[21] suggesting that dilation is a common and spontaneously resolving characteristic of acute illness. As such, dilation is an acute-phase phenomenon of endothelial dysfunction and coronary artery dysregulation, resulting in no permanent changes to the vasculature.[10] In contrast, transient dilation could represent pathological changes with long-term consequences for coronary artery health. While this issue must be investigated further, there is currently a lack of evidence for increased long-term risk in such patients.

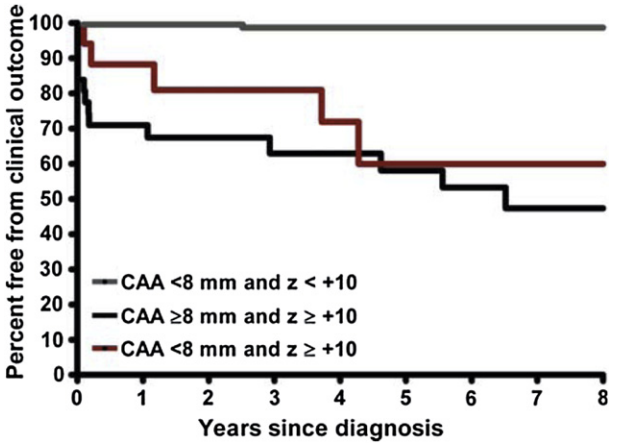

Figure 1 Freedom from clinical complications based on maximum coronary artery aneurysms (CAA) absolute diameters and coronary artery z-score. CAA with z-scores ≥10 are at substantial risk or medium-term complication (stenosis, thrombosis or myocardial infarct) regardless of absolute coronary artery size while CAA ≥2.5 to <10.0 were not at substantial medium-term risk of complications. Reprinted with permission from: Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol* 2010;**31**:242–9.

3. Long-term Fate and Complications of Giant CAA

Although rare, giant CAA ($\geq$8 mm or z-score $\geq$10) are highly unlikely to resolve[6,10,22]; they are associated with the most severe long-term complications, including progression to stenosis or occlusion[6,22] resulting in ischemic heart disease. Stenosis of persistent and regressed CAA may occur as a result of myointimal proliferation, an intrinsic process of postacute KD[23] in which smooth muscle cells migrate from the media to the intima, producing large amounts of extracellular matrix and fibrosis.[24] This process may further result in calcification of the aneurysm site by a mechanism similar to arteriosclerosis,[25] which may be accelerated with persistent inflammation in some patients.[26] Calcification occurs primarily at the media-intimal or the subendothelial surface.[24] Calcification is a prevalent and unique characteristic of giant CAA; affecting 12% at 5 years, 44% at 10 years, and 94% at 20 years after diagnosis.[27] Finally, occlusion of the coronary arteries at the site of giant CAA may also be caused by thrombosis.[6,22,24] Thrombotic occlusion may also progress to calcification after the organization and recanalization of a nonocclusive mural thrombus.[28] Myocardial infarction is the major cause of death from KD,[6,22] resulting either from sudden thrombotic occlusion of a vessel, or gradual stenotic occlusion.[28] Risk of ischemia-related ventricular dysfunction, ventricular dysrhythmias, and sudden death is persistent in patients with giant CAA, although it is mitigated for some patients who develop an extensive network of collateral vessels, particularly in young children.[5,29] These patients almost universally required thromboprophylaxis with anticoagulant and/or antiplatelet agents and may eventually require revascularization.[30,31] Because of the persistent high-risk of potentially severe complications, patients with giant CAA are closely and consistently monitored throughout their lifetime.

4. Long-term Fate and Complications of Nongiant CAA

Most CAA resulting from KD are small- to medium-sized; 50–67% of these have been shown to regress to normal luminal diameter within 1–2 years of illness,[6] by a process of localized intimal proliferation.[12] Factors associated with increased likelihood of regression include age $<$1 year at disease onset, fusiform rather than saccular aneurysm shape, and location of the aneurysm in a distal coronary artery segment.[12] Smaller maximum aneurysm size is among the most important factors associated with regression.[10]

Regressed CAA appear to be at limited risk of major sequelae compared to persistent giant CAA. However, several lines of evidence suggest that regressed CAA may be at risk for some long-term complications, particularly accelerated atherosclerotic disease. First, the vasculitis of KD tends to target the same sites along the coronary arteries that are often affected by atherosclerosis in adulthood.[32] Second, the intrinsic healing process after vasculitis involves fibrosis and the proliferation of smooth muscle cells at the site of a regressed lesion, processes that may contribute to atherosclerosis.[19] Finally, persistent abnormal vascular wall morphology and dysfunction indicate the presence of a premature atherosclerotic process in patients with regressed CAA in the long-term.[19] A 10-year follow-up study investigating atherosclerotic markers in KD patients with regressed CAA found that, although such patients showed no stenosis or other major arterial irregularities, intravascular ultrasound imaging detected various degrees of intimal thickening at the sites of regressed CAA.[19] Endothelial dysfunction was also apparent in patients with regressed CAA, in the form of increased constriction upon stimulation with acetylcholine and poor dilation upon stimulation with isosorbide dinitrate. These results are supported by other studies; marked intimal thickening with or without calcification has been seen elsewhere in patients with regressed CAA,[10] while a decreased fibrinolytic response to venous occlusion and other measures of endothelial dysfunction have been demonstrated long-term in KD patients with varying degrees of coronary involvement.[33–35] Several studies have reported alterations in myocardial blood flow reserve in KD patients with CAA, a further marker of atherosclerosis.[36–38] Despite these long-term atherosclerotic findings in KD patients, the extent and true nature of accelerated atherosclerosis post-KD is still unclear.

5. Long-term Coronary Artery Health After KD Not Complicated by CAA

Individuals with no coronary artery involvement after KD, or transient dilation that resolves within the acute phase of illness, appear to be free of major cardiac complications into adulthood. A long-term study by Kato et al found that patients with normal coronary arteries at a first, acute-phase angiogram had no cardiac symptoms or abnormal findings throughout a 10-year follow-up period.[10] Similarly, patients who showed transient dilation during the acute phase of illness did not have any long-term ischemic findings.[10] As a result of such findings, individuals without coronary artery abnormalities after KD are generally considered to have the same cardiovascular risk as the general population into adulthood.[1] However, it is important to note the possibility that subclinical inflammation and dilation of the coronary arteries occur in a majority of patients during acute illness,[21] leading to some concern that acute-phase inflammation, even in the absence of CAA development, may have as yet undetected effects on long-term cardiovascular health.[6]

6. Interplay of Traditional Cardiovascular Factors and Previous History of Kawasaki Disease

Several studies have recently found greater long-term incidence of traditional cardiovascular risk factors in KD patients. Newburger et al first demonstrated that KD patients, particularly those with persistent coronary abnormalities, have decreased high-density lipoprotein cholesterol levels long after acute illness.[39] Cheung et al, in their follow-up of KD patients at a mean of 7 years after

illness, found that patients with CAA had not only reduced high-density lipoprotein cholesterol, but also low apolipoprotein A and elevated apolipoprotein B, all risk factors for cardiovascular disease; these patients also demonstrated increased peripheral conduit arterial stiffness, indicating that they have suboptimal cardiovascular health.[40] In comparison, KD patients without CAA demonstrated slightly improved lipid profiles, but were still found to have elevated apolipoprotein B, as well as increased brachio-radial arterial stiffness. After acute illness, KD patients were found to perform significantly less physical activity than their healthy peers[41]; this may have resulted from parental concerns surrounding the long-term prognosis of KD,[42] which may adversely affect perceived physical functioning.[41] Importantly, KD patients as an overall cohort may be predisposed to a decreased fibrinolytic response after acute illness, which is not only a marker of accelerated atherosclerosis, but may also present elevated long-term risk for ischemic heart disease.[34] Other indicators of increased cardiovascular risk seen to be prevalent in KD patients, regardless of coronary artery involvement, include increased inflammatory markers, dyslipidemia, blood pressure abnormalities, and oxidative stress, although this has not been definitively established.[5,35,43] A previous study investigating the long-term presence and effects of early atherosclerotic markers after KD found no significant systemic endothelial dysfunction in KD patients.[35] Another small study found that, although KD patients demonstrated signs of subclinical atherosclerosis, autonomic function was normal compared to controls, particularly in terms of short-term blood pressure regulation.[44] The effects of traditional cardiovascular risk factors on all subsets of KD patients may have an important impact on long-term outcomes and follow-up strategies. Therefore, clarifying the contradictions in current evidence on this topic should be a focus of further research.

7. Potential Evidence for As Yet Unrecognized Long-term Adverse Effects Associated with a Previous History of KD Regardless of CAA Involvement

It has been recently proposed that the overall KD population, regardless of CAA, may be at significant risk of increased cardiovascular complications into adulthood, including myocarditis and myocardial fibrosis, valvulitis and subsequent valvular incompetence, late-onset ventricular arrhythmia, and ventricular dysfunction.[2] Clarifying the risk of such long-term complications in the overall KD population is important given that current follow-up protocols primarily aim to capture the risks associated with CAA. Here, we address the evidence supporting risk of several major cardiovascular outcomes, which may be prevalent in the aging KD population, independent of CAA.

Valvulitis, primarily of the aortic and mitral valves, may occur in up to 2% of patients during acute KD, presenting a possible long-term risk of valvular incompetence.[2] While valvular dysfunction may not be rare after KD, the current evidence preferentially supports valvular disease, particularly mitral valve incompetence, as a correlate and consequence of giant CAA after KD, rather than a long-term clinical risk for all KD patients (Table 1).

Mild aortic root dilatation has been found to have a 4% incidence 1 year after KD diagnosis, indicating that dilatation may be common and persistent among patients with KD,[45] with a potential to result in aortic valve regurgitation. However, clinically significant aortic valve regurgitation is rare in adult KD patients, and the relationship between early valvulitis and aortic root dilatation and long-term aortic valve regurgitation is unknown.[45] Importantly, current evidence suggests that aortic valve regurgitation may be associated with CAA severity (Table 1).[46]

A single study has shown a high incidence of persistent myocarditis and fibrosis in the general KD patient population, regardless of CAA[47]; these data, from the era before the adoption of IVIG for acute treatment, seem to suggest that myocardial damage is not infrequent after acute illness. This evidence is supported by findings of myocardial fibrosis from a handful of case reports.[48–50] However, these case reports show that, although myocardial damage may occur with KD, it may not result in clinically significant long-term effects, and may only occur in patients with severe, persistent CAA (Table 1). Abnormal regional wall motion, myocyte hypertrophy, degeneration and disarray have also been found to varying degrees in postacute KD patients. However, evidence shows that these phenomena are associated with CAA (Table 1).

Systolic and diastolic ventricular dysfunction, secondary to diffuse myocarditis, have also been suspected as possible long-term outcomes in an unspecified subset of KD patients.[2] Tissue Doppler studies have found abnormalities reflecting systolic and diastolic ventricular dysfunction subsequent to KD; however, these were acute-phase data, and may not reflect long-term outcomes.[51] Small case series of adults with a presumed history of KD have found rare occurrences of long-term cardiac dysfunction, however this cannot be conclusively said to be independent of CAA (Table 1). Similarly, ischemic complications from severe CAA cannot be ruled out as a cause for death from ventricular dysfunction and presumed arrhythmia after KD (Table 1).[2,52]

Based on the current evidence, it is unlikely that ventricular dysfunction or other cardiac pathologies are significant, independent long-term risks in the general KD population, or in an unspecified subset of patients other than KD patients with severe, persistent CAA.

8. Current Long-term Follow-up Protocols for KD Patients into Adulthood

Long-term follow-up of KD patients recommended by both the American Heart Association (AHA) and the Japanese Ministry of Health (JMH) is tailored to the current presence and severity of CAA.[6,20] For patients with giant CAA, or multiple, complex or persistent large CAA $\geq$6 mm, the AHA recommends a very thorough follow-up regime (Table 2). The JMH guidelines similarly recommend imaging follow-up every 3–6 months for the highest risk group (patients with persistent, stenotic CAA, with or without ischemia); however, the precise management plan is to be tailored by the individual physician (Table 3). The JMH guidelines also

Table 1 Long-term risk of cardiovascular complications of Kawasaki disease (KD) other than thrombosis and myocardial infarction.

Complication	Group at long-term risk	Summary
Mitral valve regurgitation	Patients with giant CAA	Observed cases of persistent mitral valvular disease may be secondary to ischemia of the papillary muscles.[59]
Aortic valve regurgitation	Patients with giant CAA	Observed rarely in the long-term after KD; higher incidence only observed in patients with CAA and/or myocardial infarction.[46]
Myocardial abnormalities	Patients with CAA	Abnormal regional wall motion twice as frequent in patients with CAA; myocyte hypertrophy, degeneration and disarray primarily seen in conjunction with CAA.[60]
Myocarditis/fibrosis	Patients with giant CAA	Rarely observed in the IVIG era; in observed cases, cause of death is complications from severe CAA, with fibrosis often attributable to previous myocardial infarction.[48–50]
Systolic and diastolic ventricular dysfunction	Unclear; probably patients with giant CAA	Only seen in adults with presumed antecedent KD; all patients studied had severe, long-term CAA.[61,62]
Ventricular dysfunction/arrhythmia	Unclear; probably patients with giant CAA	All observed cases had history of myocardial infarction, a known cause of ventricular abnormalities.[2,52,63]

CAA = coronary artery aneurysms; IVIG = intravenous immunoglobulin.

distinguish between follow-up for patients with persistent CAA and those with persistent, stenotic lesions, with the former recommended similar, but less frequent, testing (Table 3). Because of the severity of complications in this patient group, current guidelines result in reduced loss to follow-up during transition to adult care, and thorough documentation of the long-term outcomes and cardiovascular health in this population.

For patients whose CAA regress, the AHA recommends follow-up as long as the lesion persists, including annual assessments and biennial stress tests for patients aged >10 years (Table 2). Although the Japanese guidelines also suggest that such patients be followed with annual cardiology testing until elementary school age is reached, only three, age-specific follow-up visits are recommended thereafter (Table 3). Because rigorous follow-up of this patient group is only conducted until CAA regress, many patients may be lost to follow-up as adults, and few data are available on long-term outcomes and cardiovascular risk in this population.[1]

According to both the AHA and JMH, patients whose coronary artery dilatation resolves shortly after acute illness and those with no coronary artery involvement are considered to be at comparably low long-term risk of cardiac complications (Tables 2 and 3). The AHA does not recommend any specialized assessment or follow-up beyond the initial 6–8 week period (Table 2). Despite the lack of supporting data, the Japanese guidelines recommend a slightly more thorough, although still minimal, follow-up, with ECG and echocardiography at 6 months, 1 year, and 5 years after initial illness (Table 3). While evidence supporting these guidelines are available, the long-term cardiovascular risk in this population, and thus the validity of this management strategy, remains to be confirmed.

Counseling on lifestyle factors affecting cardiovascular health including dyslipidemia, hypertension, smoking, and obesity,[20] is an important aspect of long-term risk management in all patients with a previous history of KD. Both the Japanese and the AHA guidelines recommend healthy lifestyle counseling and cardiovascular risk assessment through primary health care for all KD patients every 5 years as minimal follow-up (Tables 2 and 3). Because the effects of lifestyle-related cardiovascular risk factors on long-term prognosis are uncertain, healthy lifestyle should be strongly promoted for all KD patients until research further clarifies its utility to specific patient subsets. Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) may prove to be a key tool in the long-term management of KD. Although statins are traditionally prescribed to reduce cholesterol levels, they have other pleiotropic effects, including immunosuppression and attenuation of vascular remodeling and thrombosis.[53–55] As chronic inflammation and endothelial dysfunction persist long after KD,[56] particularly in patients with CAA, statins may be able to reduce long-term vascular damage and adverse events. Animal research has shown that statins inhibit key inflammatory steps in the formation of CAA,[4] whereas a pilot study of statins in children with CAA after KD found improvements in vascular inflammation and

Table 2 American Heart Association follow-up recommendations for patients with a previous history of Kawasaki disease.

Risk level	Pharmacological therapy	Physical activity	Follow-up and diagnostic testing	Invasive testing
I (no coronary artery changes at any stage of illness)	None beyond 1st 6—8 weeks	No restrictions beyond 1 st 6—8 weeks	Cardiovascular risk assessment, counseling at 5-y intervals	None recommended
II (transient coronary artery ectasia disappears within 1st 6—8 weeks)	None beyond 1st 6—8 weeks	No restrictions beyond 1st 6—8 weeks	Cardiovascular risk assessment, counseling at 3- to 5-y intervals	None recommended
III (1 small-medium coronary artery aneurysm/major coronary artery)	Low-dose aspirin (3—5 mg/kg aspirin/d), at least until aneurysm regression documented	For patients <11 y old, no restriction beyond 1st 6—8 weeks; patients 11—20 y old, physical activity guided by biennial stress test, evaluation of myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents	Annual cardiology follow-up with echocardiogram + ECG, combined with cardiovascular risk assessment, counseling; biennial stress test/ evaluation of myocardial perfusion scan	Angiography, if noninvasive test suggests ischemia
IV (≥1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without obstruction)	Long-term antiplatelet therapy and warfarin (target INR 2.0—2.5) or low-molecular-weight heparin (target: antifactor Xa level 0.5 —1.0 U/mL) should be combined in giant aneurysms	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/ evaluation of myocardial perfusion scan outcome	Biannual follow-up with echocardiogram + ECG; annual stress test/ evaluation of myocardial perfusion scan	1st angiography at 6—12 mo or sooner if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances (see text)
V (coronary artery obstruction)	Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of β-blockers to reduce myocardial O_2 consumption	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/ myocardial perfusion scan outcome	Biannual follow-up with echocardiogram and ECG; annual stress test/ evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options

ECG = electrocardiogram; INR = international normalized ratio.

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endothelial dysfunction.[56] Clinical trials assessing the safety and efficacy of statins in KD patients are needed.

Magnetic resonance imaging (MRI) has recently emerged as a possibly important diagnostic tool for CAA and an alternative to invasive testing.[57,58] Coronary angiography is currently recommended as a major adjunctive imaging modality, secondary to echocardiography, in the characterization of CAA.[6,20] However, the invasiveness of angiography and its associated risks give it low acceptability to patients. MRI, in contrast, may provide clear 3D imaging of the coronary arteries,[20] while also being noninvasive and free of sedation and radiation exposure. However, MRI use in KD follow-up is currently limited by its ineffectiveness in detecting arterial stenoses, for which

Table 3 Japanese Ministry of Health follow-up recommendations for patients with a previous history of Kawasaki disease.

Risk level	Pharmacological therapy	Physical activity	Follow-up and diagnostic testing	Invasive testing
I (no dilatation at any stage of illness)	None beyond first 3 mo	No restrictions	Follow-up for 5 y, at 30 d, 60 d, 6 mo, 1 y and 5 y, with ECG and echocardiogram (and chest X-ray if necessary); exercise ECG at final follow-up is desirable	None recommended
II (transient dilatation during the acute phase, subsiding within 30 d of onset)	None beyond first 3 mo	No restrictions	Follow-up for 5 y, at 30 d, 60 d, 6 mo, 1 y and 5 y, with ECG + echocardiogram (+chest X-ray if necessary); exercise ECG at final follow-up is desirable	None recommended
III (regression)	Antiplatelet therapy until aneurysm regresses	No restrictions	Annual follow-up with ECG, echocardiogram and chest X-ray until age 6–7 (entry into elementary school); same follow-up + exercise ECG at age 9–10 (4^{th} grade), age 12–13 (entry into junior high school) and age 15–16 (entry into senior high school); for patients who had aneurysms with large internal diameter during the acute phase, with an appropriate combination of echocardiogram, stress echocardiogram, stress myocardial scintigraphy, MRI, MRA, and/or MDCT.	For patients who had aneurysms with large internal diameter during the acute phase, selective CAG and/or IVUS, as appropriate
IV (remaining coronary aneurysms)	Antiplatelet therapy (ex. aspirin); anticoagulants for patients with giant aneurysms or thrombi in coronary aneurysms	No restrictions, unless giant aneurysms; patients with giant aneurysms allowed moderate exercise, but prohibited from school sport club activities (if no changes noted after one year, intense exercise may be allowed)	Follow-up with exercise ECG and an appropriate combination of echocardiogram, stress echocardiogram, stress myocardial scintigraphy, MRI, MRA, and/or MDCT; for patients with giant aneurysms or a large internal diameter during the acute phase, stress myocardial scintigraphy every 2–5 y to monitor progression to stenotic lesions	Selective CAG and/or IVUS, as appropriate
V-a (coronary stenotic lesions, no findings of ischemia)	Antiplatelet therapy (ex. aspirin); calcium channel blockers, nitrates, β-blockers	No restrictions, unless giant aneurysms; patients with giant aneurysms allowed moderate	Lifelong follow-up tailored to the individual, generally every 3–6 mo; follow-up must include	Selective CAG and/or IVUS, as appropriate

	and angiotensin receptor II blockers to prevent ischemic attacks and heart failure	exercise, but prohibited from school sport club activities (if no changes noted after one year, intense exercise may be allowed)	exercise ECG and an appropriate combination of echocardiogram, stress echocardiogram, stress myocardial scintigraphy, MRI, MRA, and/or MDCT	
V-b (coronary stenotic lesions with findings of ischemia)	Antiplatelet therapy (ex. aspirin); calcium channel blockers, nitrates, β-blockers and angiotensin receptor II blockers to prevent ischemic attacks and heart failure	School sport club activities prohibited; exercise restricted to home/hospital treatment, school attendance but no exercise, mild exercise or moderate exercise, according to findings of exercise testing and extent of ischemia.	Lifelong follow-up tailored to the individual, generally every 3 −6 mo; follow-up must include exercise ECG and an appropriate combination of echocardiogram, stress echocardiogram, stress myocardial scintigraphy, MRI, MRA, and/or MDCT	Selective CAG and/or IVUS, as appropriate

CAG = coronary angiography; ECG = electrocardiogram; IVUS = intravascular ultrasound; MRA = magnetic resonance angiography; MDCT = multi-row detector computed tomography; MRI = magnetic resonance imaging.

Adapted with permission from Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)—digest version. *Circ J* 2012;**74**:1989—2020.

coronary angiography is required. Systematic studies are, therefore, currently warranted to determine the efficacy of MRI as a stand-alone assessment tool in KD.

9. Conclusions

Based on current evidence on the long-term risks after KD, it appears that current follow-up strategies are adequately poised to address long-term cardiovascular consequences for specific patient subgroups. Currently, there is no indication that patients without CAA after the acute disease episode are in need of any specialized care in the long term, but should have their cardiovascular risk effectively managed at the primary care level. Patients whose CAA have regressed represent a challenge to long-term management, as the true long-term risks and outcomes for such patients are unknown. The prognosis for such patients must be clarified through prevention of loss to follow-up and large-scale, long-term studies of cardiovascular risk. Until then, clinicians must execute caution in managing patients with regressed CAA, monitoring for complications into adulthood without burdening individuals with unnecessary follow-up. The need for very long-term follow-up of patients with giant CAA is well established, and will require extensive cooperation and coordination between pediatric KD experts and adult cardiologists as this patient group transitions into adulthood. Adult cardiologists specializing in ischemic heart disease should be aware of the care requirements and potential complications of adult KD patients with persistent and regressed CAA, as well as being aware that some young patients with myocardial infarction may have coronary artery complications related to an undocumented or forgotten childhood episode of KD, requiring a different management algorithm.

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