Kawasaki disease in 2019—past controversies, present insights and future directions

Robert Grignani[1,2,3], Swee-Chye Quek[1,2]

[1]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore; [2]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [3]Cardiovascular Research Institute, National University Health System, Singapore

Contributions: (I) Conception and design: SC Quek; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Swee-Chye Quek, MBBS, MMed(Paed), DCH(London), MD, FRCPCH, FACC. Department of Paediatrics, NUHS Tower Block Level 12, 1E Kent Ridge Road, Singapore 119228. Email: swee_chye_quek@nuhs.edu.sg.

Abstract: Kawasaki disease (KD) is a condition that is of interest to many pediatricians. Notwithstanding possible complications to coronary arteries, there is much that is yet unknown, including the controversies which surround this vasculitis. Making a timely and accurate diagnosis is essential for appropriate treatment, and incomplete KD adds a dimension to this complexity. While there are guidelines available for diagnosis, including clinical and echocardiographic findings, there is no definitive laboratory test, given the still unclear etiology. The best treatment option for recalcitrant disease is also debatable, as are the factors for those at high risk for coronary dilation. Although scoring systems are now available to risk stratify, these have variable success. It is envisaged that with the further development of novel biomarkers and genotyping, timely identification of those at risk will be a possibility. This article discusses evolution of our knowledge in KD over 5 decades, and reviews the advances which have been made.

Keywords: Kawasaki disease (KD); echocardiography; coronary dilation; intravenous immunoglobulins (IVIG); risk scoring

Kawasaki disease (KD) is an acute medium vessel vasculitis of still unclear aetiology which typically afflicts children under 5 years (1). The peak onset is between 18 and 24 months, with an ethnic predilection for Asian populations. It is associated with long-term coronary artery abnormalities, such as coronary artery aneurysm (CAA) and ectasia in up to 15–25% of untreated children (1), and has surpassed rheumatic heart disease as the leading cause of pediatric acquired cardiac disease in the developed world (2). It has even been postulated that there is immune disequilibrium with abnormal and increased inflammatory and allergic manifestations (3,4).

History of KD

In recent times, the management and prognosis for KD has been extensively studied with a few controversies. What remains unquestioned is that as an entity, KD was first described by Dr. Kawasaki in his seminal Japanese series of 50 cases published in the "*Japanese Journal of Allergy*" (5), and subsequently in English in 1974 (6). Dr. Kawasaki himself saw his first case in 1961 (7), although KD as an unnamed disease has surely been around before that not known by an eponymous name. Reports of fatal coronary arteritis have been described in the literature in at least

Table 1 AHA versus JMH clinical diagnostic guidelines

AHA 2017 (McCrindle *et al.* 2017)
Fever for at least 5 days
And at least 4 out of 5 of the following:
Bilateral bulbar conjunctival injection without exudates
Erythema and cracking of the lips, strawberry tongue, or erythema of the oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Rash: maculopapular, diffuse erythroderma or erythema multiform like
Changes in extremities with erythema of palms and/or soles; edema of hands and/or feet in the acute phase and periungual peeling of fingers and toes in weeks 2 and 3
JMH 2013 (JCS Joint Working Group 2014)
5 of 6 of the following:
Fever for at least 5 days
Bilateral conjunctival congestion
Changes of lips and oral cavity
Acute non-purulent cervical lymphadenopathy
Polymorphous exanthema
Changes of peripheral extremities

AHA, American Heart Association; JMH, Japanese Ministry for Health.

46 cases in the Western literature and 11 cases in Japan prior to 1967 (8). Nevertheless, the likely earliest case reported was by Dr. Samuel Gee of St. Bartholomew's, London, in 1870 (8) reporting on the autopsy of a 7-year-old boy. Dr Gee described "…*consequence of scarlatinal dropsy … The heart natural in size, and the valves healthy. The coronary arteries were dilated into aneurysms at three places*".

Diagnosing KD

Diagnostic criteria for KD have been relatively unchanged in the last 50 years. Currently, two guidelines are utilized (*Table 1*) (9,10) in different parts of the world. They however both share the same 6 variables of fever for at least 5 days, conjunctivitis, oral mucosal changes, polymorphous rash, peripheral extremity swelling or peeling and cervical lymphadenopathy.

Using these criteria, some important caveats need to be considered. Firstly, more than one clinical feature may have resolved by the time of presentation. Secondly the presence of a concomitant infection in KD should not rule out KD. In general, concomitant infections have been identified in up to 33% of patients with KD (11-13). In a Korean population of 54 KD patients, Cho and colleagues (12) reported a positive multiplex real-time PCR rate of 22%, and Jordan-Villegas and colleagues (13) reported a positive direct fluorescent antibody assay in 8.8% of patients to a variety of virus in 251 KD patients in Dallas. The situation becomes especially challenging when one considers that common differentials of KD have been found as concomitant infections, including measles (14-16), scarlet fever (11,12,17-19), infectious mononucleosis (20) and adenovirus (12,13,21).

The major limitation of both guidelines is that they are based entirely on clinical criteria, with no pathognomonic laboratory test for diagnosis. Clinical acuity and acumen are key to recognising these patients. Therefore, there is a major challenge in diagnosing atypical presentation that constitutes 20–30% of cases (22). As a consequence, there are 3 major pitfalls: (I) risk of under-diagnosis, with resultant higher risk of coronary and non-coronary complication; (II) risk of over-diagnosis with side effects of medication and healthcare burden; (III) recognising incomplete or atypical forms of the condition.

Incomplete KD

Clinical judgment becomes more tedious in atypical ages such as infants, especially in those <6 months, where fever and irritability may be the only clinical manifestation. In this group, <50% of patients meet the traditional criteria (23). As a consequence, the burden of coronary artery disease is significantly higher in infants. Salgado and colleagues (24) reported >2× rate of any CAA in 43.4% in patients with KD <6 months old compared to 19.5% in those >6 months old. Furthermore, 18.6% of infants<6 months with normal echocardiogram at diagnosis, developed CAA on follow-up within 8 weeks.

It is therefore prudent to be vigilant and maintain a high index of suspicion for KD in infants <6 months with prolonged fever and any of the following: (I) irritability; (II) aseptic meningitis; (III) unexplained or culture-negative shock; (IV) cervical lymphadenitis unresponsive to antibiotic therapy; (V) retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy (9).

A similar diagnostic challenge occurs in the older patient beyond 5 years. Not only is echocardiography of the coronary vessels challenging in this group but the clinical picture is skewed, with a higher incidence in those with human immunodeficiency virus infection (25), increased rates of lymphadenopathy (93% of adult *vs.* 15% of paediatric cases) and joint involvement in (61% of adults *vs.* 24% to 38% of children) (26). To date more than 100 cases of adult onset KD have been reported in the literature (25,27-36) with the oldest diagnosed at 48 years old (36). This group, similarly to those <6 months is associated with higher risk of CAA (25,37).

There is another high-risk group in up to 5% of patients who present with the KD shock syndrome. These cases are usually diagnosed late, after they are initially treated for bacterial sepsis and septic shock (9,38,39). As a consequence, higher rates of coronary artery abnormalities, Intravenous Immunoglobulin (IVIG) resistance and myocardial dysfunction arise in this subset (40,41).

To aid in the issue of incomplete KD, current guidelines have attempted to propose pathways to tackle the issue of atypical presentation (9). Index of suspicion is raised with these pathways when 2 or 3 criteria are met with fever of at least 5 days, or in the higher risk group of infants less than 6 months with unexplained fever for 7 days. In these patients, any elevated inflammatory markers [C-reactive protein (CRP) ≥3.0 mg/dL and/or erythrocyte sedimentation rate (ESR) ≥40 mm/h] warrants further workup. A positive diagnosis is presumed if 3 or more laboratory findings are positive (anemia for age, platelet count ≥450,000 after 7th day of illness, Albumin ≤3.0 g/dL, elevated AST, WBC count ≥15,000/mm^3, urine ≥10 WBC/hpf) or if the echocardiogram is positive.

Despite these, clinical acumen is still required to recognise the potential of KD in the first place. To help identify these patients, it is prudent to evaluate supporting clinical features that are not part of the formal guidelines. Of these, reactivation of the Bacillus Calmette-Guérin injection site appears to be specific, present in up to 30.4% (42-45) of cases. Other features include extreme irritability, out of proportion to the fever (46,47), peripheral arthritis (48), perineal desquamation (49-51), aseptic meningitis (52), transient peripheral facial nerve palsy (53,54) and even sensorineural hearing loss (55). Additionally, supporting biochemical data can be useful. This includes elevated acute phase reactants and total white cell count with neutrophil predominance, low serum sodium and albumin levels (9), mild to moderate transaminases or gamma-glutamyl

transferase (GGT) in 40% to 60%, mild hyperbilirubinemia in ≈10% (56,57), sterile pyuria in up to 9% (58-60) and gallbladder hydrops (61,62).

Newer markers such as N terminal pro-B-type natriuretic peptide (63,64), IL-6 and inflammatory cytokines (65) have been promising. Beyond biochemical markers, the role of molecular modalities is gaining interest. Jaggi and colleagues (66) analysed blood transcriptional profiles and identified a classic KD bio-signature that was validated in three additional KD cohorts. They observed overexpression of inflammation, platelets, apoptosis and neutrophil genes, and under expression of T and NK cell genes. In addition, serum exosomal miR-328, miR-575, miR-134 and miR-671-5p have also been described as potential biomarkers for the diagnosis of KD (67) furthering the scope of diagnostic markers in the future.

The role of genetics in KD is another advancing area which has attracted keen recent interest, with a slew of genetics polymorphisms identified to detect those at risk. To-date, more than 62 genes have been described, associated with susceptibility and 47 associated with CAA (40,68-75). A systematic review and meta-analysis of genetic associations with KD susceptibility narrowed down the list and identified gene polymorphisms to *ACE*, *BLK*, *CASP3*, *CD40*, *FCGR2A*, *FGB*, *HLA-E*, *IL1A*, *IL6*, *ITPKC*, *LTA*, *MPO*, *PD1*, *SMAD3*, *CCL17* and *TNF* (40).

Echocardiography

The utility of echocardiography in KD is one of the few modalities that is not controversial. The diagnosis of KD remains a clinical one, and it is important to note that initial echocardiogram is usually normal in the first week of illness, and this does not rule out KD (9). Nevertheless, echocardiography should be performed at diagnosis as a baseline to evaluate early coronary status and associated cardiac involvement such as valvar regurgitation present in up to 25% of individuals (9,76-78), aortic root dilatation in up to 10% (78), myocardial dysfunction and pericardial effusions, and dilatation of the aortic root with mild aortic regurgitation (AR) which can be present in up to 4% of individuals within 1 year of follow-up (79,80).

In addition, echocardiography can help support the diagnosis of incomplete KD by identifying CAA including dilatation and aneurysm (normalized to z-score), the presence or lack of tapering of the coronary arteries and echogenicity of coronary vessels (perivascular brightness) (9,81). This brings about another long-drawn controversy,

Table 2 AHA versus JMH guidelines for coronary aneurysm

Definition	AHA 2017 (McCrindle *et al.* 2017)	JMH 2013 (JCS Joint Working Group 2014)
No involvement	z-score <2.0	–
Dilatation only	2.0< z-score <2.5	–
Small aneurysm	2.5≤ z-score <5	ID <4 mm, or if child ≥5 years ID ≤1.5 times adjacent segment
Medium aneurysm	5≤ z-score <10 and absolute <8 mm	ID >4 to ≤8 mm, or if child ≥5 years ID 1.5 to 4 times adjacent segment
Large aneurysm	z-score >10 or absolute ≥8 mm	ID >8 mm, or if child ≥5 years ID >4 times adjacent segment

AHA, American Heart Association; JMH, Japanese Ministry for Health; ID, internal diameter.

what is the definition of a CAA. Both the AHA 2017 criteria's (9) and JMH 201 (10) define aneurysm differently, either by z-score or absolute internal diameter (ID) of the coronary artery at a given age respectively (*Table 2*) (9,10).

The mode of normalization of coronary dimensions for body surface area (BSA) with the use of a z-score calculator brings up another quandary. Which formula for calculating z-score should be used? Many formulae for deriving the z-score have been described (81-89) and each uses their own methods of regression and within unique populations with regards to age, race and gender. Currently the more widely used models based on more rigorous systems are the z-score calculators by Dallaire and colleagues (86) in a Canadian population and the calculator based on a Japanese population by Kobayashi and colleagues (84). Both show good and comparable outcomes. Ogata and colleagues (90) applied the Kobayashi (84) and Dallaire (86) scoring systems on 1,082 KD patients from 2 centers in the US and 3 centers in Japan with no significant differences in outcomes for either.

Risk factors for coronary dilatation

Abnormal early echocardiogram findings, with coronary dilatation in particular, are an independent risk factor of progressive coronary dilatation (91-95). Biochemical markers such as hypoalbuminemia have also independently been associated with the occurrence of progressive coronary dilatation (91). The key may lie in molecular and genetic baselines to risk stratify our patients. Optimal therapy should be based on being able to accurately identify and manage patients according to their risk stratification, allowing for individualised tailored therapy. Kwon and colleagues identified *TIFAB* gene as a susceptibility locus for CAAs of more than 5 mm (68). Variations in *BTNL2*, *CASP3*, *FCGR2A*, *FGF23*, *FGβ*, *GRIN3A*, *HLA-E*, *IL10*, *ITPKC* and *TGFBR2* have also been identified as markers of

coronary artery involvement (40).

Management

Reducing inflammation or "putting out the fire" is key in the management of KD. This is achieved with the use of pharmacological "fire extinguishers", for which the efficacy of IVIG has been well described by Newburger and colleagues in 1986 (96). There is a strong inverse relationship between the IVIG dose and prevalence of CAA (97,98) with described improved coronary outcomes from 15–25% to 3–5% (99-101).

Current standard first-line management of KD include the use of IVIG (2 g/kg) as a single infusion plus oral Aspirin (80 to 100 mg/kg/day or 30 to 50 mg/kg/day in 4 divided doses) until 48 hours afebrile or day 14 of illness. This is followed by oral aspirin (3 to 5 mg/kg/day) for 6 to 8 weeks which can then be discontinued if no further CAA are present on follow-up.

The role and use of IVIG is not in doubt, with an optimum dosing of IVIG validated at 2 g/kg as a single infusion (97,102), preferred over the previous regime of smaller doses given over 5 days. The timing of IVIG therapy is however important, with commencement of treatment after 10 days associated with poorer outcomes with a published odds ratio (OR) 2.9 (103) and higher incidence of CAA (16% *vs.* 5%) (104). Despite this, many would consider IVIG if the patient is still febrile after 10 days, has coronary involvement or any signs of persistent inflammation (9).

Even the preparation of the IVIG is important. Being a pooled product with various manufacturing techniques, the choice of IVIG preparation may have a bearing on patient outcome with results to safety, side-effect profile and efficacy (105-109). The ideal preparation has been reported to have no B-propiolactonation, no acidification and be deplete in IVIG (106).

IVIG infusion is generally safe, although one has to be mindful of possible and potential unknown side effects. These include a Coombs-positive hemolytic anemia, especially with AB blood type (110), aseptic meningitis in 0.6–1% (111) and rare, but potentially serious transfusion-related, acute lung injury (112). In addition, the attending physician has to be aware that measles, mumps, and varicella immunisations should be deferred for 11 months after receiving high-dose IVIG (9,113).

The role and dosing of oral aspirin in the acute management remains controversial (97,114-121), with regards to IVIG resistance rates and CAA abnormalities. Although a reduction in fever duration has been reported with the use of high-dose aspirin (115,117,121), the role of CAA outcomes is not so straightforward. A limitation of most studies is the definition of CAA at 6–8 weeks with no long-term outcomes. Furthermore, clinical bias with higher rates of high-dose aspirin prescription to those with early CAA would confound the results.

Kim and colleagues (115) reported a large retrospective study including 8,456 children managed in Korea comparing IVIG with medium to high-dose aspirin versus IVIG with low-dose aspirin. They observed higher rates of IVIG resistance 10.5% vs. 16.9% (P<0.001) in those managed with low-dose aspirin. Higher rates of overall CAA were observed in those managed with IVIG and medium-high-dose Aspirin, with no differences in giant aneurysm rates. Currently, Kuo and colleagues (122) are carrying out a multi-center randomized double control trial to evaluate the efficacy of IVIG alone or IVIG with high-dose aspirin (80–100 mg/kg/day). A limitation however is that their primary endpoint is CAA at 6–8 weeks, and its value in long-term CAA sequalae will need follow-up. We nevertheless await the outcome of this trial on this controversial topic.

Regardless, the risks of aspirin include raised liver enzymes, gastrointestinal bleeding, and sensorineural hearing loss with high-dose aspirin albeit reversible (118). The risk of Reye syndrome is rare with prolonged use of high-dose aspirin only (123,124), and no association reported with low-dose aspirin. Whichever dose used, it is important for the prescribing physician to be aware of the antagonistic effect with Ibuprofen and the effect on the antiplatelet activity of aspirin (125). Furthermore, should patients require chronic aspirin therapy, annual inactivated influenza vaccine is recommended (113).

Alternatives include oral clopidogrel (0.1–1.0 mg/kg/day) for Aspirin resistance or allergy or oral dipyridamole (1–5 mg/kg/day) for patients who require ibuprofen for alternative diagnosis, aspirin resistance and allergy or at risk of Reye syndrome (9).

IVIG resistance

Despite adequate and timely therapy, the risk of IVIG resistance is documented in 9.7% to 32.2% (93,126-132) of KD children, with an up to nine-fold increased risk of CAA (133). Response to IVIG is defined as resolution of fever (T <37.5 °C) and mucocutaneous features, and may take up to 36 hours from end of IVIG infusion. (9,100). The conundrum of what next when patients don't respond to first-line standard therapy will be discussed later.

Multiple risk factors have been identified for IVIG resistance. Two meta-analysis (134,135) identified multiple risk factors including higher total bilirubin, polymorphonuclear leukocytes (PMN), pro-brain natriuretic peptide (pro-BNP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), ESR and CRP levels, with lower sodium levels, albumin level, haemoglobin, and platelet count. Even clinical variables have been associated with IVIG resistance including fever duration (136), perianal changes (137), cervical lymphadenopathy (138), changes in oral mucosa, cervical lymphadenopathy, swelling of extremities, and polymorphous rash (135).

To expand on these variables, multiple scoring systems have been proposed (126,129-132,137,139-142). These included various variables and different scoring algorithms. Cross translation of these data to different populations has however been variable in populations of different ethnic backgrounds (92,93,126,128,129,142,143,), with generally poor sensitivities. The use of four of the more commonly cited scoring methods including the Egami (131), Kobayashi (132), Sano (130) and Fukunishi (139) in our local Singaporean Chinese population had poor sensitivities resulting in 42–85% of patients with IVIG resistance missed (144). It is possible that the baseline genetic profile of the different populations would result in different risks. The different ethnic incidences of KD are already well established, being highest in Japan ~250/100,000 (145,146) followed by other Asian nations including Korea 134/100,000 (147) and Taiwan 69/100,000 (148), and lowest in Western countries including the US Mainland 17.5 to 20.8/100,000 (149,150), UK 8.4 to 9/100,000 (151,152) and Australia 8/100,000 (153). Furthermore, biochemical marker variations are observed with variable contributions of ESR, hemoglobin and platelet count in Asian and non-Asian populations (135). These differences occur even

within different Asian populations with subgroup analysis of ESR in these patients showing different outcomes (135).

Moving forward into an era of personalised medicine, a genetic risk profile could help tailor targeted therapy. Jaggi and colleagues (66) generated a genomic score that was higher at baseline in IVIG resistance (median 12,290 *vs.* 5,572 in responders, P=0.009) and independently predicted IVIG response. In addition, Kuo and colleagues (154) calculated a weighted genetic risk from 11 single nucleotide polymorphisms (SNPs) identified by genome-wide association study recognizing a significant association between weighted genetic risk score (P=4.518×10^{-3}) and the response to IVIG (P=8.224×10^{-10}).

With further work, new algorithms combining clinical, biochemical and genetic data would facilitate more accurate and population-specific risk estimations, allowing for more appropriate targeted therapy.

Alternative treatment options

Steroids were the first-line management of KD prior to the emergence of IVIG-directed therapy (155). Data on its role as first line has been controversial (156-165). As an adjuvant therapy though, this appears more promising. A meta-analysis of corticosteroid with IVIG as an initial treatment in high-risk patients demonstrated reduced coronary involvement, fever duration and inflammation in this group (166). This is supported by a recent Cochrane review (167) which included 922 participants. The studies predominantly used steroid therapy as an adjuvant to IVIG with similar outcomes of reduced CAA, shorter duration of fever and improved inflammatory markers. The limitation of the report was the short duration of follow-up with no study details beyond 24 weeks. In view of the promising early results, low-dose corticosteroids as an adjuvant to IVIG and Aspirin has been proposed in the most recent guidelines (9,157) in the management of higher risk groups. The role of monotherapy with steroids is however not indicated.

Other alternative therapies, which were evaluated, have not demonstrated conclusive evidence as yet. The use of infliximab, a TNF-alpha inhibitor, with IVIG does not decrease overall risk of CAA (168). However, its use in patients with IVIG resistance fared better, with reduced CAA in 6.3% of patients managed with IVIG and adjuvant Infliximab, compared to 20% in patients managed with IVIG alone (169). Burns and colleagues (170) similarly achieved greater defervescence rates within 48 hours in IVIG resistant patients managed with infliximab.

Methotrexate has also been tried as salvage therapy in IVIG resistance, and it has demonstrated defervescence and clinical improvement with normalization of acute phase reactants (171). There is only limited published data, and more work needs to be done. The same goes for the use of calcineurin inhibitor cyclosporine, with no significant data sets available (172). There is currently a phase III trial going on in Japan (KAICA Trial) evaluating the outcomes of cyclosporine A with IVIG versus IVIG alone (173) and we await the outcomes of this in evaluating its role in management of KD. It is likely that these additional agents may have a role as adjuvant therapy in second- or third-line treatment for IVIG resistance.

Vascular health post-KD. Risks to the post-paediatric heart

As more children with a history of KD reach adulthood, the adult cardiologists looking after these patients must therefore be mindful of the coronary sequelae of KD. They must be prepared in the distinct treatment challenges that they will face in managing this group of patients. Unfortunately, the data on this group is limited, exemplified by the fact that KD as a disease as it is known is only slightly more than half a decade old. The management of adult patients with a history of KD draws suggestions from the paediatric guidelines (9). Unfortunately, the transition from paediatric to adult cardiologists is fraught with lost follow-ups (10). It is useful to have a more seamless transition, with joint reviews by both the paediatric and adult cardiologists, especially for the complex KD to allow for a smooth transition and reduce dropout rates. It is during these visits that individual risk status should be addressed and assessed.

We know from available literature that KD has an effect on the coronary arteries, and this manifests not just only as macro changes but also micro changes. Regardless, the long-term outcomes for KD are generally good with high rates for normalisation of coronary dimensions in small to medium vessels in 45% to 91% of cases (10,174,175). In contrast, giant aneurysms, which accounts for 1–2% of CAA rarely regress (9,174-176). In our own local data 97.5% of small and moderate aneurysms regressed with regression in 25.0% of giant aneurysms (unpublished). In general, in the presence of any CAA the 10-year ischaemia event-free probability is 87.5%, for which the only independent risk factor is aneurysm severity at 1 month after onset of KD (174).

Any coronary artery damage during acute KD can also lead to calcification and stenotic lesions associated with

myointimal proliferation later in life (177,178). As such, coronary sequelae of KD are present in 5% to 9.2% of young adults evaluated by angiography for myocardial ischemia or presenting with sudden death (179,180). Tsuda and colleagues (181) in a review of 562 KD with known early coronary involvement identified 17 new or expanding aneurysms in 15 patients, all associated with localised stenosis 2 to 19 years post-KD onset. Tsuda and colleagues (182) subsequently reviewed 50 cases of acute coronary syndrome presenting as ST-segment elevation myocardial infarction (MI) in patients with a history of probably KD. The age of presentation ranged from 18 to 69 years. Of these patients, 43 had thrombotic occlusion of aneurysm with 40 patients having giant aneurysms. Of particular interest is that no aneurysms were visualised in 3 patients despite previous giant aneurysms in childhood. Notwithstanding regression of the giant aneurysms, they still had acute coronary syndrome in adulthood. Iemura and colleagues (183) reported an 86% thrombotic occlusion rate and 80% had giant aneurysms in patients with early MI at a median age of 28 years.

Patients with giant aneurysms are an important high-risk group and possess challenges. Suda and colleagues (184) reviewed 76 patients with giant aneurysm followed up for a median period of 19 years. Overall survival rates were 95%, 88%, and 88% at 10, 20, and 30 years post-KD respectively. However, high cumulative coronary intervention rates were observed with a rate of 28%, 43%, and 59% at 5, 15, and 25 years after onset respectively. Overall the reported risks associated with giant aneurysms includes a 41.6% to 64.5% risk of thrombosis or stenosis (184-186), 2.6% to 46% MI risk (175,184-187), mortality risk of 6.0% to 15.6% (184,186,187) and 30- to 35-year survival of 88% to 90% (184,187).

Despite these changes, the long-term outcome of KD remains generally favorable for patients with no coronary sequelae. Nakamura and colleagues (188) even demonstrated a lower mortality relative to the general population [standardized mortality ratios (SMR), 0.65; 95% confidence interval, 0.41–0.96].

The management and follow-up plans for patients with coronary involvement should be guided by principles established for atherosclerotic disease. Biochemical changes have been described in KD patients, with significantly elevated total cholesterol and apolipoprotein B (189). Zhang and colleagues (190) in a meta-analysis reported risk factors for atherosclerosis in 421 patients with KD and 449 controls. They identified that total cholesterol level [mean difference (MD) 3.99 mg/dL, 95% CI, 0.66–7.33, P=0.02] and low-density lipoprotein level (MD 3.42 mg/dL, CI 0.50 to 6.33, P=0.02) were significantly higher in KD patients. As such the role of statins has been proposed as a potential management strategy, in addition to aspirin, even in the paediatric guidelines (9). A phase I/IIa trial is currently underway to evaluate the use of Atorvastatin in patients with KD (191). In addition, combination use of antiplatelet and systemic anticoagulation will be required for large aneurysms long term (10,184,192,193).

Routine standard cardiovascular fitness parameters including lipid profile every 1 to 2 years are prudent, as is the evaluation and management of risk factors including diabetes, hypertensions, obesity, smoking and alcohol. Additional specific non-invasive evaluation such as transthoracic echocardiogram should be done to assess cardiac function with regional wall motion abnormalities using automated functional imaging with tissue Doppler imaging and strain assessment to evaluate for early changes. Furthermore, it is reasonable to assess for inducible myocardial ischemia [stress echocardiography, stress magnetic resonance (MR), stress nuclear medicine] every 2 to 3 years with angiographic [computed tomography (CT) and/or MR imaging (MRI)] performed every 3 to 5 years similar to the pediatric surveillance recommendations (9). Invasive angiographic catheterization should be limited to those requiring interventional procedures.

The use of MRI is a useful modality, with the benefits of no radiation exposure and possibility of repeat imaging. With the use of late gadolinium enhancement myocardial fibrosis and scarring can be detected myocardial inflammation seen on T2-weighted images (194-196). The role of CT coronary artery calcium (CAC) scoring in screening patients with previous KD and persistent coronary abnormalities has demonstrated excellent results with a sensitivity of 95% and a specificity of 100% for detecting coronary artery abnormalities (defined as CAA and/or stenosis) (197,198).

Adult patients with KD presenting with MI frequently exhibit significant thrombus, and as such the true ID may also be undersized. The role of intravascular ultrasound has been proposed to circumvent this issue (180,199). In the interventional management, high balloon filling pressures may be required during percutaneous transluminal angioplasty, although this carries a risk of neoaneurysm formation (200).

Regular routine monitoring should not be limited to those with CAA; however, one has to rationalise the timing

of further investigations including MR and CT. In patients with a history of KD and normal coronary arteries, the modality and frequency of investigations must be safe, induce minimal psychological harm and be cost effective. The Japanese Circulation Society 2013 (10) suggested non-invasive testing every 4 years with electrocardiogram (ECG) and echocardiogram, and this is a fair option. Furthermore, given the increased risk of atherosclerosis, a diagnosis of previous KD could count as a modified variable and be added into traditional risk scoring.

Being a systemic vasculitis, KD is likely to affect the systemic arterial structure with even microvascular changes of the retina observed (37). Therefore, normal macroscopic evaluation with echocardiogram or angiography (CT, MRI, invasive) does not equate to normal vascular function. Endothelial dysfunction as reflected by abnormal brachial artery reactivity and flow-mediated dilation was first reported by Dhillon and colleagues (201). Since then a variety of studies have been undertaken to evaluate the effect of KD on endothelial dysfunction including flow mediated dilation, nitroglycerin-mediated dilation and peripheral arterial tonometry; vascular thickness including stiffness index, pulse wave velocity (PWV) in both patients with and without CAA (202). In addition, the evaluation of carotid intima-media thickness (cIMT), a well-established surrogate marker of atherosclerosis (203,204) has been undertaken.

Dietz and colleagues (202) reported a systematic review and meta-analysis of 30 studies which showed important heterogeneity between studies. Most striking was the evidence for systemic arterial endothelial dysfunction in patients with CAA compared to KD in general. However, in studies of patients with no coronary involvement these were less conclusive. The data supports long-term subclinical vascular changes which affect patients with KD, afflicting primarily those with coronary artery involvement. It is interesting to note that these changes occur early with most studies performed in patients with a mean of <10 years since KD (20 of 30 studies). Only 4 studies evaluated, the vascular changes occurred with a mean time of >15 years (189,205-207).

The use of novel modalities to measure arterial stiffness such as the cardio-ankle vascular index (CAVI) could be useful to help answer these questions in a clinical setting. Developed in Japan by Fukuda Denshi, CAVI is a blood pressure-independent index of arterial stiffness (208) which correlates with the stiffness parameter β in the thoracic aorta and has a reported better reproducibility than brachial-ankle PWV (baPWV) (209,210). CAVI is increased in the presence of cerebrovascular disease (211), dementia (212), cardiovascular disease (213-215), nephrosclerosis (188), vasculitis (216,217), hypertension (218), hyperlipidemia (188), and lifestyle-related diseases including diabetes mellitus (219), smoking (220), and obesity (221), all risk factors for atherosclerosis. It also correlates with other cardiovascular risk markers, such as intimal-medial thickening and coronary atherosclerosis (222). In other forms of vasculitis, CAVI as a marker of arterial stiffness was 17% higher in the systemic lupus erythematosus (SLE) patients than in controls (7.5±0.8 *vs.* 6.4±0.7) (216). The use of CAVI in patients with KD has been reported in one recent study by Nakagawa and colleagues (223) in 201 patients with KD versus 129 healthy controls, with significantly higher aPWV in KD group. Looking into the future, CAVI potentially arms the managing cardiologist with a bedside functional vascular analysis, making it an attractive option in risk stratification.

Conclusions

KD though uncommon is a fascinating condition. Our understanding of this has come such a long way since its first description in 1967. We now know better how to detect, treat and follow up its complications. It is envisaged that with rapid advances in research and collaborative work among physicians in this field, that we will be even better equipped with knowledge to risk-stratify, diagnose and manage KD, especially the incomplete and complex variants, in achieving better outcomes.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Burns JC, Glodé MP. Kawasaki syndrome. Lancet 2004;364:533-44.
2. Taubert KA, Rowley AH, Shulman ST. Nationwide survey

of Kawasaki disease and acute rheumatic fever. J Pediatr 1991;119:279-82.

3. Liew WK, Lim CW, Tan TH, et al. The effect of Kawasaki disease on childhood allergies - a sibling control study. Pediatr Allergy Immunol 2011;22:488-93.

4. van Bever HP, Quek SC, Lim T. Aspirin, Reye syndrome, Kawasaki disease, and allergies; a reconsideration of the links. Arch Dis Child 2004;89:1178.

5. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi 1967;16:178-222.

6. Kawasaki T, Kosaki F, Okawa S, et al. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974;54:271-76.

7. Kawasaki T, Naoe S. History of Kawasaki disease. Clin Exp Nephrol 2014;18:301-4.

8. Shulman ST. Kawasaki Disease, The First 130 Years. Pediatr Res 2003;53:158.

9. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation 2017;135:e927-99.

10. JCS Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Circ J 2014;78:2521-62.

11. Benseler SM, McCrindle BW, Silverman ED, et al. Infections and Kawasaki disease: implications for coronary artery outcome. Pediatrics 2005;116:e760-6.

12. Cho EY, Eun BW, Kim NH, et al. Association between Kawasaki disease and acute respiratory viral infections. Korean J Pediatr 2009;52:1241-8.

13. Jordan-Villegas A, Chang ML, Ramilo O, et al. Concomitant respiratory viral infections in children with Kawasaki disease. Pediatr Infect Dis J 2010;29:770-2.

14. Hu P, Guan Y, Fan XC, et al. Incomplete Kawasaki disease induced by measles in a 6-month-old male infant. Int J Dermatol 2016;55:e34-6.

15. Kuijpers TW, Herweijer TJ, Schölvinck L, et al. Kawasaki disease associated with measles virus infection in a monozygotic twin. Pediatr Infect Dis J 2000;19:350-3.

16. Whitby D, Hoad JG, Tizard EJ, et al. Isolation of measles virus from child with Kawasaki disease. Lancet 1991;338:1215.

17. Hoare S, Abinun M, Cant AJ. Overlap between Kawasaki disease and group A streptococcal infection. Pediatr Infect Dis J 1997;16:633-4.

18. Anderson DG, Warner G, Barlow E. Kawasaki disease associated with streptococcal infection within a family. J Paediatr Child Health 1995;31:355-7.

19. Ryan ME, McGregor RS, Turkewitz D. Simultaneous Kawasaki Disease in Group A Streptococcal Pharyngitis. Clin Pediatr (Phila) 1993;32:510-1.

20. Barton M, Melbourne R, Morais P, et al. Kawasaki syndrome associated with group A streptococcal and Epstein-Barr virus co-infections. Ann Trop Paediatr 2002;22:257-60.

21. Fukuda S, Ito S, Fujiwara M, et al. Simultaneous development of Kawasaki disease following acute human adenovirus infection in monozygotic twins: A case report. Pediatr Rheumatol Online J 2017;15:39.

22. Liu YC, Lin MT, Wang JK, et al. State-of-the-art acute phase management of Kawasaki disease after 2017 scientific statement from the American Heart Association. Pediatr Neonatol 2018;59:543-52.

23. Chang FY, Hwang B, Chen SJ, et al. Characteristics of Kawasaki disease in infants younger than six months of age. Pediatr Infect Dis J 2006;25:241-4.

24. Salgado AP, Ashouri N, Berry EK, et al. High Risk of Coronary Artery Aneurysms in Infants Younger than 6 Months of Age with Kawasaki Disease. J Pediatr 2017;185:112-116.e1.

25. Kontopoulou T, Kontopoulos DG, Vaidakis E, et al. Adult Kawasaki disease in a European patient: a case report and review of the literature. J Med Case Rep 2015;9:75.

26. Wolff AE, Hansen KE, Zakowski L. Acute Kawasaki disease: not just for kids. J Gen Intern Med 2007;22:681-4.

27. Ataya A, Alraiyes AH, Auron M, et al. Adult Kawasaki disease. QJM 2013;106:687-8

28. Safa G, Saillard C, Darrieux L. Incomplete Kawasaki disease in an elderly man. Case Rep Dermatol 2013;5:1-3.

29. Fujimoto N, Teramura K, Tanaka T. Adult Kawasaki disease: evaluating the fluctuation of circulating lymphocytes associated with iv immunoglobulin treatment. J Dermatol 2012;39:957-8.

30. Bresson V, Bonello B, Rousset-Rouvière C, et al. Kawasaki disease in older children and young adults: 10 years of experience in Marseille, France. Arch Pediatr 2011;18:731-6.

31. Campos-Franco J, Lopez R, Alende R, et al. Adult Kawasaki disease. Intern Med 2011;50:1443-4.

32. Sève P, Lega JC. Kawasaki disease in adult patients. Rev Med Interne 2011;32:17-25.

33. Inokuchi R, Kurata H, Harada M, et al. Coronary artery aneurysms after adult-onset Kawasaki disease. Circulation 2013;127:1636-7.

34. Kanno K, Sakai H, Nakajima M, et al. An adult case of Kawasaki disease in a pregnant Japanese woman: a case report. Case Rep Dermatol 2011;3:98-102.

35. Kim JS, Chun KJ, Park YH, et al. Characteristic findings of coronary artery disease in Kawasaki disease. J Am Coll Cardiol 2011;57:884.

36. Struillou L, Magadur-Joly G, Barrier JH. Kawasaki syndrome in adults - retrospective study of 5 cases - need for a national survey. Revue De Medicine Interne 1993;14:404.

37. Chen KY, Burgner DP, Wong TY, et al. Evidence of microvascular changes in the retina following Kawasaki disease. Sci Rep 2017;7:40513.

38. Çakan M, Gemici H, Aktay-Ayaz N, et al. Kawasaki disease shock syndrome: a rare and severe complication of Kawasaki disease. Turk J Pediatr 2016;58:415-8.

39. Seaton KK, Kharbanda A. Evidence-based management of Kawasaki disease in the emergency department. Pediatr Emerg Med Pract 2015;12:1-20; quiz 21.

40. Xie X, Shi X, Liu M. The Roles of Genetic Factors in Kawasaki Disease: A Systematic Review and Meta-analysis of Genetic Association Studies. Pediatr Cardiol 2018;39:207-25.

41. Gatterre P, Oualha M, Dupic L, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. Intensive Care Med 2012;38:872-8.

42. Gamez-Gonzalez LB, Hamada H, Llamas-Guillen BA, et al. BCG and Kawasaki disease in Mexico and Japan. Hum Vaccin Immunother 2017;13:1091-3.

43. Garrido-García LM, Castillo-Moguel A, Vázquez-Rivera M, et al. Reaction of the BCG scar in the acute phase of Kawasaki disease in Mexican children. Pediatr Infect Dis J 2017;36:e237-41.

44. Kumar A, Singh S. BCG Site Reactivation in Kawasaki Disease. Arthritis Rheumatol 2016;68:2026.

45. Rezai MS, Shahmohammadi S. Erythema at BCG Inoculation Site in Kawasaki Disease Patients. Mater Sociomed 2014;26:256-60.

46. Golshevsky D, Cheung M, Burgner D. Kawasaki disease--the importance of prompt recognition and early referral. Aust Fam Physician 2013;42:473-6.

47. Thapa R, Chakrabartty S. Atypical Kawasaki disease with remarkable paucity of signs and symptoms. Rheumatol Int 2009;29:1095-6.

48. Gong GW, McCrindle BW, Ching JC, et al. Arthritis presenting during the acute phase of Kawasaki disease. J Pediatr 2006;148:800-5.

49. Isidori C, Sebastiani L, Cardellini MC, et al. Early

Desquamating Perineal Erythema in a Febrile Infant: A Characteristic Clinical Feature of Kawasaki Disease. Int J Environ Res Public Health 2017;14. doi: 10.3390/ijerph14070710.

50. Falcini F, Cimaz R, Calabri GB, et al. Kawasaki's disease in northern Italy: a multicenter retrospective study of 250 patients. Clin Exp Rheumatol 2002;20:421-6.

51. Chao SM, Phua KB. Perineal eruption as an early sign of Kawasaki disease. Ann Acad Med Singapore 1991;20:244-7.

52. Dengler LD, Capparelli EV, Bastian JF, et al. Cerebrospinal fluid profile in patients with acute Kawasaki disease. Pediatr Infect Dis J 1998;17:478-81.

53. Lim TC, Yeo WS, Loke KY, et al. Bilateral facial nerve palsy in Kawasaki disease. Ann Acad Med Singapore 2009;38:737-8.

54. Poon LK, Lun KS, Ng YM. Facial nerve palsy and Kawasaki disease. Hong Kong Med J 2000;6:224-6.

55. Alves NR, Magalhães CM, Almeida Rde F, et al. Prospective study of Kawasaki disease complications: review of 115 cases. Rev Assoc Med Bras (1992) 2011;57:295-300.

56. Tremoulet AH, Jain S, Chandrasekar D, et al. Evolution of laboratory values in patients with Kawasaki disease. Pediatr Infect Dis J 2011;30:1022-6.

57. Eladawy M, Dominguez SR, Anderson MS, et al. Abnormal liver panel in acute kawasaki disease. Pediatr Infect Dis J 2011;30:141-4.

58. Watanabe T. Pyuria in patients with Kawasaki disease. World J Clin Pediatr 2015;4:25-9.

59. Choi JY, Park SY, Choi KH, et al. Clinical characteristics of Kawasaki disease with sterile pyuria. Korean J Pediatr 2013;56:13-8.

60. Shike H, Kanegaye JT, Best BM, et al. Pyuria associated with acute Kawasaki disease and fever from other causes. Pediatr Infect Dis J 2009;28:440-3.

61. Sun Q, Zhang J, Yang Y. Gallbladder Hydrops Associated With Kawasaki Disease: A Case Report and Literature Review. Clin Pediatr (Phila) 2018;57:341-3.

62. Mathai SS, Kulkarni VB, Harsh P. Gall bladder hydrops-a rare initial presentation of Kawasaki disease. Indian J Pediatr 2013;80:616-7.

63. Reddy M, Singh S, Rawat A, et al. Pro-brain natriuretic peptide (ProBNP) levels in North Indian children with Kawasaki disease. Rheumatol Int 2016;36:551-9.

64. Cho KH, Kang SJ. Clinically useful predictors of resistance to intravenous immunoglobulin and prognosis of coronary artery lesions in patients with incomplete

Kawasaki disease. Korean Circ J 2014;44:328-35.

65. Sato S, Kawashima H, Kashiwagi Y, et al. Inflammatory cytokines as predictors of resistance to intravenous immunoglobulin therapy in Kawasaki disease patients. Int J Rheum Dis 2013;16:168-72.

66. Jaggi P, Mejias A, Xu Z, et al. Whole blood transcriptional profiles as a prognostic tool in complete and incomplete Kawasaki Disease. PLoS One 2018;13:e0197858.

67. Zhang XJ, Li S, Sun Y, et al. Disturbed ribosome-related modules were associated with Kawasaki disease. Eur Rev Med Pharmacol Sci 2018;22:6396-402.

68. Kwon YC, Kim JJ, Yu JJ, et al. Identification of the TIFAB Gene as a Susceptibility Locus for Coronary Artery Aneurysm in Patients with Kawasaki Disease. Pediatr Cardiol 2018. [Epub ahead of print].

69. Pan Y, Lu H. Angiotensin-converting enzyme insertion/ deletion polymorphism and susceptibility to Kawasaki disease: a meta-analysis. Afr Health Sci 2017;17:991-9.

70. Bae Y, Shin D, Nam J, et al. Variants in the Gene EBF2 Are Associated with Kawasaki Disease in a Korean Population. Yonsei Med J 2018;59:519-23.

71. Kim KY, Bae YS, Ji W, et al. ITPKC and SLC11A1 Gene Polymorphisms and Gene-Gene Interactions in Korean Patients with Kawasaki Disease. Yonsei Med J 2018;59:119-27.

72. Onouchi Y, Ozaki K, Burns JC, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet 2012;44:517-21.

73. Khor CC, Davila S, Shimizu C, et al. Genome-wide linkage and association mapping identify susceptibility alleles in ABCC4 for Kawasaki disease. J Med Genet 2011;48:467-72.

74. Onouchi Y. Identification of susceptibility genes for Kawasaki disease. Nihon Rinsho Meneki Gakkai Kaishi 2010;33:73-80.

75. Onouchi Y, Hata A. Susceptibility genes for Kawasaki disease. Nihon Rinsho 2008;66:272-7.

76. Altman CA. Clinical assessment of coronary arteries in Kawasaki disease: Focus on echocardiographic assessment. Congenit Heart Dis 2017;12:636-40.

77. Hashimoto I, Watanabe K. Z-score of mitral annular plane systolic excursion is a useful indicator of evaluation of left ventricular function in patients with acute-phase Kawasaki disease. Pediatr Cardiol 2017;38:1057-64.

78. Printz BF, Sleeper LA, Newburger JW, et al. Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute Kawasaki disease. J Am Coll Cardiol 2011;57:86-92.

79. Ravekes WJ, Colan SD, Gauvreau K, et al. Aortic root dilation in Kawasaki disease. Am J Cardiol 2001;87:919-22.

80. Nakano H, Nojima K, Saito A, et al. High incidence of aortic regurgitation following Kawasaki disease. J Pediatr 1985;107:59-63.

81. Manlhiot C, Millar K, Golding F, et al. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. Pediatr Cardiol 2010;31:242-9.

82. Colan SD. Normal echocardiographic values for cardiovascular structures. In: Lai WW, Mertens LL, Cohen MS, et al. editors. Echocardiography in Pediatric and Congenital Heart Disease: From Fetus to Adult. 883-901. 2016; West Sussex, UK: Wiley-Blackwell; 2009. pp. 765-85

83. Olivieri L, Arling B, Friberg M, et al. Coronary artery Z score regression equations and calculators derived from a large heterogeneous population of children undergoing echocardiography. J Am Soc Echocardiogr 2009;22:159-64.

84. Kobayashi KJ, Williams JA, Nwakanma LU, et al. EuroSCORE predicts short- and mid-term mortality in combined aortic valve replacement and coronary artery bypass patients. J Card Surg 2009;24:637-43.

85. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 2007;116:174-9.

86. Dallaire F, Dahdah N. New equations and a critical appraisal of coronary artery Z scores in healthy children. J Am Soc Echocardiogr 2011;24:60-74.

87. Tan TH, Wong KY, Cheng TK, et al. Coronary normograms and the coronary-aorta index: objective determinants of coronary artery dilatation. Pediatr Cardiol 2003;24:328-35.

88. Kurotobi S, Nagai T, Kawakami N, et al. Coronary diameter in normal infants, children and patients with Kawasaki disease. Pediatr Int 2002;44:1-4.

89. de Zorzi A, Colan SD, Gauvreau K, et al. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 1998;133:254-8.

90. Ogata S, Tremoulet AH, Sato Y, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. Int J Cardiol 2013;168:3825-8.

91. Liu MY, Liu HM, Wu CH, et al. Risk factors and implications of progressive coronary dilatation in children with Kawasaki disease. BMC Pediatr 2017;17:139.

92. Lin MT, Chang CH, Sun LC, et al. Risk factors and derived formosa score for intravenous immunoglobulin

unresponsiveness in Taiwanese children with Kawasaki disease. J Formos Med Assoc 2016;115:350-5.

93. Park HM, Lee DW, Hyun MC, et al. Predictors of nonresponse to intravenous immunoglobulin therapy in Kawasaki disease. Korean J Pediatr 2013;56:75-9.

94. Do YS, Kim KW, Chun JK, et al. 'Predicting factors for refractory Kawasaki disease. Korean Circ J 2010;40:239-42.

95. Ashouri N, Takahashi M, Dorey F, et al. Risk factors for nonresponse to therapy in Kawasaki disease. J Pediatr 2008;153:365-8.

96. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986;315:341-7.

97. Durongpisitkul K, Gururaj VJ, Park JM, et al. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics 1995;96:1057-61.

98. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr 1997;131:888-93.

99. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol 2016;67:1738-49.

100. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747-71.

101. Levin, M, Tizard EJ, Dillon MJ. Kawasaki disease: recent advances. Arch Dis Child 1991;66:1369-72.

102. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2003;(4):CD004000.

103. Qiu H, He Y, Rong X, et al. Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status. Postgrad Med 2018;130:442-7.

104. Downie ML, Manlhiot C, Collins TH, et al. Factors associated with development of coronary artery aneurysms after Kawasaki disease are similar for those treated promptly and those with delayed or no treatment. Int J Cardiol 2017;236:157-61.

105. Abolhassani H, Asgardoon MH, Rezaei N, et al. Different brands of intravenous immunoglobulin for primary immunodeficiencies: how to choose the best option for the patient? Expert Rev Clin Immunol 2015;11:1229-43.

106. Lin MC, Fu YC, Jan SL, et al. Comparative effectiveness of intravenous immunoglobulin for children with Kawasaki disease: a nationwide cohort study. PLoS One 2013;8:e63399.

107. Tsai MH, Huang YC, Yen MH, et al. Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin. J Pediatr 2006;148:38-43.

108. Rosenfeld EA, Shulman ST, Corydon KE, et al. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. J Pediatr 1995;126:1000-3.

109. Centers for Disease Control and Prevention (CDC). Outbreak of hepatitis C associated with intravenous immunoglobulin administration-United Sates Oct 1993-June 1994. MMWR Morb Mortal Wkly Rep 1994;43:505-9.

110. Luban NLC, Wong EC, Henrich Lobo R, et al. Intravenous immunoglobulin–related hemolysis in patients treated for Kawasaki disease. Transfusion 2015;55:S90-4.

111. Kemmotsu Y, Nakayama T, Matsuura H, et al. Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease. Pediatr Rheumatol Online J 2011;9:28

112. Guo Y, Tian X, Wang X, et al. Adverse effects of immunoglobulin therapy. Front Immunol 2018;9:1299.

113. Kimberlin DW, Brady MT, Jackson MA, et al. Red Book (2015): 2015 Report of the Committee on Infectious Diseases. American Academy of Pediatrics, 2015.

114. Amarilyo G, Koren Y, Brik DS, et al. High-dose aspirin for Kawasaki disease: outdated myth or effective aid? Clin Exp Rheumatol 2017;35:209-12.

115. Kim GB, Yu JJ, Yoon KL, et al. Medium- or Higher-Dose Acetylsalicylic Acid for Acute Kawasaki Disease and Patient Outcomes. J Pediatr 2017 May;184:125-129.e1.

116. Kuo HC, Lo MH, Hsieh KS, et al. High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes in Kawasaki disease. PLoS One 2015;10:e0144603.

117. Lee G, Lee SE, Hong YM, et al. Is high-dose aspirin necessary in the acute phase of kawasaki disease?. Korean Circ J 2013;43:182-6.

118. Scuccimarri R. Kawasaki disease. Pediatr Clin North Am 2012;59:425-45.

119. Lang B, Duffy CM. Controversies in the management of Kawasaki disease. Best Pract Res Clin Rheumatol 2002;16:427-42.

120. Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of

Kawasaki syndrome. Clin Pediatr (Phila) 2002;41:597-601.

121. Baumer JH, Love SJ, Gupta A, et al. Salicylate for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2006;(4):CD004175.

122. Kuo HC, Guo MM, Lo MH, et al. Effectiveness of intravenous immunoglobulin alone and intravenous immunoglobulin combined with high-dose aspirin in the acute stage of Kawasaki disease: study protocol for a randomized controlled trial. BMC Pediatr 2018;18:200.

123. Wei CM, Chen HL, Lee PI, et al. Reye's syndrome developing in an infant on treatment of Kawasaki syndrome. J Paediatr Child Health 2005;41:303-4.

124. Lee JH, Hung HY, Huang FY. Kawasaki disease with Reye syndrome: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1992;33:67-71.

125. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809-17.

126. Davies S, Sutton N, Blackstock S, et al. Predicting IVIG resistance in UK Kawasaki disease. Arch Dis Child 2015;100:366-8.

127. Seki M, Kobayashi T, Kobayashi T, et al. External validation of a risk score to predict intravenous immunoglobulin resistance in patients with Kawasaki disease. Pediatr Infect Dis J 2011;30:145-7.

128. Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. J Pediatr 2011;158:831-835.e3.

129. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr 2008;153:117-21.

130. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr 2007;166:131-7.

131. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr 2006;149:237-40.

132. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113:2606-12.

133. Campbell AJ, Burns JC. Adjunctive therapies for Kawasaki disease. J Infect 2016;72:S1-5.

134. Baek JY, Song MS. Meta-analysis of factors predicting resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. Korean J Pediatr 2016;59:80-90.

135. Li X, Chen Y, Tang Y, et al. Predictors of intravenous immunoglobulin-resistant Kawasaki disease in children: a meta-analysis of 4442 cases. Eur J Pediatr 2018;177:1279-92.

136. Ram Krishna M, Sundaram B, Dhanalakshmi K. Predictors of coronary artery aneurysms in Kawasaki disease. Clin Pediatr (Phila) 2014;53:561-5.

137. Fu PP, Du ZD, Pan YS. Novel predictors of intravenous immunoglobulin resistance in Chinese children with Kawasaki disease. Pediatr Infect Dis J 2013;32:e319-23.

138. Choi Y, Eun LY, Oh SH. Incomplete Kawasaki disease in a 12-month-old girl presenting with cardiac murmur and iron deficiency anemia. Pediatr Int 2016;58:377-9.

139. Fukunishi M, Kikkawa M, Hamana K, et al. Prediction of non-responsiveness to intravenous high-dose γ-globulin therapy in patients with Kawasaki disease at onset. J Pediatr 2000;137:172-6.

140. Yan H, Wan H, Du JB, et al. Risk factors and prediction analysis of intravenous immunoglobulin resistant Kawasaki disease. J Appl Clin Pediatr 2012;27:1637-40.

141. Choi MH, Park CS, Kim DS, et al. Prediction of intravenous immunoglobulin nonresponse Kawasaki disease in Korea. Pediatric Infection and Vaccine 2014;21:29-36.

142. Loomba RS, Raskin A, Gudausky TM, et al. Role of the Egami Score in Predicting Intravenous Immunoglobulin Resistance in Kawasaki Disease Among Different Ethnicities. Am J Ther 2016;23:e1293-9.

143. Song R, Yao W, Li X. Efficacy of four scoring Systems in Predicting Intravenous Immunoglobulin Resistance in children with Kawasaki disease in a Children's Hospital in Beijing, North China. J Pediatr 2017;184:120-4.

144. Grignani R, Rajgor DD, Leow YG, et al. A novel model for predicting non-responsiveness to IVIG in Kawasaki Disease The Singapore experience. J Paediatr Child Health 2018. [Epub ahead of print].

145. Makino N, Nakamura Y, Yashiro M, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. J Epidemiol 2015;25:239-45.

146. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. J Epidemiol 2012;22:216-21.

147. Kim GB, Han JW, Park YW, et al. Epidemiologic features of Kawasaki disease in South Korea: data from nationwide survey, 2009–2011. Pediatr Infect Dis J 2014;33:24-7.

148. Huang WC, Huang LM, Chang IS, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003–2006. Pediatrics 2009;123:e401-5.

149. Holman RC, Belay ED, Christensen KY, et al.

Hospitalizations for Kawasaki syndrome among children in the United States, 1997–2007. Pediatr Infect Dis J 2010;29:483-8.

150. Holman RC, Curns AT, Belay ED, et al. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 2003;112:495-501.

151. Harnden A, Mayon-White R, Perera R, et al. Kawasaki disease in England: ethnicity, deprivation, and respiratory pathogens. Pediatr Infect Dis J 2009;28:21-4.

152. Harnden A, Alves B, Sheikh A. Rising incidence of Kawasaki disease in England: analysis of hospital admission data. BMJ 2002;324:1424-25.

153. Saundankar J, Yim D, Itotoh B, et al. The Epidemiology and Clinical Features of Kawasaki Disease in Australia. Pediatrics 2014;133:e1009-14.

154. Kuo HC, Wong HS, Chang WP, et al. Prediction for Intravenous Immunoglobulin Resistance by Using Weighted Genetic Risk Score Identified From Genome-Wide Association Study in Kawasaki Disease. Circ Cardiovasc Genet 2017;10. doi: 10.1161/CIRCGENETICS.116.001625. Erratum in: Correction. [Circ Cardiovasc Genet 2017].

155. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984;2:1055-8.

156. Ishii M, Ogata S, Ogihara Y, et al. Clinical utility of a new strategy for preventing coronary artery lesions in refractory Kawasaki disease patients: a randomized prospective study: P-133. Pediatr Int 2012;54:104.

157. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012;379:1613-20.

158. Ogata S, Ogihara Y, Honda T, et al. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. Pediatrics 2012;129:e17-23.

159. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med 2007;356:663-75.

160. Ikeda K, Kobayashi T, Inoue Y, et al. Risk stratification and effectiveness of intravenous immunoglobulin plus prednisolone as the initial treatment of kawasaki disease. Eur J Pediatr 2006;165:38-9.

161. Inoue Y, Okada Y, Shinohara M, et al. A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome. J Pediatr 2006;149:336-41.

162. Okada Y, Shinohara M, Kobayashi T, et al. Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. J Pediatr 2003;143:363-7.

163. Sundel RP, Baker AL, Fulton DR, et al. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. J Pediatr 2003;142:611-6.

164. Sundel RP, Baker AL, Fulton DR, et al. Randomized Trial of Pulse Steroids in the Initial Treatment of Kawasaki Disease (KD). Pediatr Res 2003;53:164.

165. Kijima Y, KAMIYA T, SUZUKI A, et al. A Trial Procedure to Prevent Aneurysm Formation of the Coronary Arteries by Steroid Pulse Therapy in Kawasaki Disease: the 6th Conference on Prevention for Rheumatic Fever and Rheumatic Heart Disease. Jpn Circ J 1982;46:1239-42.

166. Chen S, Dong Y, Yin Y, et al. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. Heart 2013;99:76-82.

167. Wardle AJ, Connolly GM, Seager MJ, et al. Corticosteroids for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2017;1:CD011188.

168. Jone PN, Anderson MS, Mulvahill MJ, et al. Infliximab plus intravenous immunoglobulin (IVIG) versus IVIG alone as initial therapy in children with Kawasaki disease presenting with coronary artery lesions: is dual therapy more effective? Pediatr Infect Dis J 2018;37:976-80.

169. Mori M, Hara T, Kikuchi M, et al. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. Sci Rep 2018;8:1994.

170. Burns JC, Song Y, Bujold M, et al. Immune-monitoring in K awasaki disease patients treated with infliximab and intravenous immunoglobulin. Clin Exp Immunol 2013;174:337-44.

171. Jang H, Kim KY, Kim DS. Clinical Outcomes of Low-Dose Methotrexate Therapy as a Second-Line Drug for Intravenous Immunoglobulin-Resistant Kawasaki Disease. Yonsei Med J 2018;59:113-8.

172. Suzuki H, Terai M, Hamada H, et al. Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin. Pediatr Infect Dis J 2011;30:871-6.

173. Aoyagi R, Hamada H, Sato Y, et al. Study protocol for a phase III multicentre, randomised, open-label, blinded-end point trial to evaluate the efficacy and safety of

immunoglobulin plus cyclosporin A in patients with severe Kawasaki disease (KAICA Trial). BMJ open 2015;5:e009562.

174. Lin MT, Sun LC, Wu ET, et al. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous γ-immunoglobulin therapy. Arch Dis Child 2015;100:542-7.

175. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease: a 10-to 21-year follow-up study of 594 patients. Circulation 1996;94:1379-85.

176. Manlhiot C, Niedra E, McCrindle BW. Long-term management of Kawasaki disease: implications for the adult patient. Pediatr Neonatol 2013;54:12-21.

177. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up: myocardial and vascular complications in adulthood. J Am Coll Cardiol 2009;54:1911-20.

178. Senzaki H. Long-term outcome of Kawasaki disease. Circulation 2008;118:2763-72.

179. Rizk SR, El Said G, Daniels LB, et al. Acute myocardial ischemia in adults secondary to missed Kawasaki disease in childhood. Am J Cardiol 2015;115:423-7.

180. Daniels LB, Tjajadi MS, Walford HH, et al. Prevalence of Kawasaki disease in young adults with suspected myocardial ischemia. Circulation 2012;125:2447-53.

181. Tsuda E, Kamiya T, Ono Y, et al. Dilated coronary arterial lesions in the late period after Kawasaki disease. Heart 2005;91:177-82.

182. Tsuda E, Abe T, Tamaki W. Acute coronary syndrome in adult patients with coronary artery lesions caused by Kawasaki disease: review of case reports. Cardiol Young 2011;21:74-82.

183. Iemura M, Ishii M, Sugimura T, et al. Long term consequences of regressed coronary aneurysms after Kawasaki disease: vascular wall morphology and function. Heart 2000;83:307-11.

184. Suda K, Iemura M, Nishiono H, et al. Long-Term Prognosis of Patients With Kawasaki Disease Complicated by Giant Coronary AneurysmsClinical Perspective: A Single-Institution Experience. Circulation 2011;123:1836-42.

185. Samada K, Shiraishi H, Sato A, et al. Grown-up Kawasaki disease patients who have giant coronary aneurysms. World J Pediatr 2010;6:38-42.

186. McNeal-Davidson A, Fournier A, Scuccimarri R, et al. The fate and observed management of giant coronary artery aneurysms secondary to Kawasaki disease in the Province of Quebec: the complete series since 1976. Pediatr Cardiol 2013;34:170-8.

187. Tsuda E, Hamaoka K, Suzuki H, et al. A survey of the 3-decade outcome for patients with giant aneurysms caused by Kawasaki disease. Am Heart J 2014;167:249-58.

188. Nakamura K, Iizuka T, Takahashi M, et al. Association between cardio-ankle vascular index and serum cystatin C levels in patients with cardiovascular risk factor. J Atheroscler Thromb 2009;16:371-9.

189. Gupta-Malhotra M, Gruber D, Abraham SS, et al. Atherosclerosis in survivors of Kawasaki disease. J Pediatr 2009;155:572-7.

190. Zhang H, Xu MG, Xie LJ, et al. Meta-analysis of risk factors associated with atherosclerosis in patients with Kawasaki disease. World J Pediatr 2016;12:308-13.

191. Tremoulet AH, Jain S, Burns JC. Evaluating a novel treatment for coronary artery inflammation in acute Kawasaki disease: A Phase I/IIa trial of atorvastatin. Expert Opin Orphan Drugs 2015;3:967-70.

192. Suda K, Kudo Y, Higaki T, et al. Multicenter and retrospective case study of warfarin and aspirin combination therapy in patients with giant coronary aneurysms caused by Kawasaki disease. Circ J 2009;73:1319-23.

193. Levy DM, Silverman ED, Massicotte MP, et al. Longterm outcomes in patients with giant aneurysms secondary to Kawasaki disease. J Rheumatol 2005;32:928-34.

194. Arnold R, Ley S, Ley-Zaporozhan J, et al. Visualization of coronary arteries in patients after childhood Kawasaki syndrome: value of multidetector CT and MR imaging in comparison to conventional coronary catheterization. Pediatr Radiol 2007;37:998-1006.

195. Suzuki A, Takemura A, Inaba R, et al. Magnetic resonance coronary angiography to evaluate coronary arterial lesions in patients with Kawasaki disease. Cardiol Young 2006;16:563-71.

196. Takemura A, Suzuki A, Inaba R, et al. Utility of coronary MR angiography in children with Kawasaki disease. AJR Am J Roentgenol 2007;188:W534-9.

197. Goh YG, Ong CC, Tan G, et al. Coronary manifestations of Kawasaki Disease in computed tomography coronary angiography. J Cardiovasc Comput Tomogr 2018;12:275-80.

198. Kahn AM, Budoff MJ, Daniels LB, et al. Usefulness of calcium scoring as a screening examination in patients with a history of Kawasaki disease. Am J Cardiol 2017;119:967-71.

199. Low AF, Quek SC, Yip J. A case of myocardial infarction complicating Kawasaki disease. CMAJ 2006;174:1839.

200. Akagi T. Interventions in Kawasaki disease. Pediatr

Cardiol 2005;26:206-12.

201. Dhillon R, Clarkson P, Donald AE, et al. Endothelial dysfunction late after Kawasaki disease. Circulation 1996;94:2103-6.

202. Dietz SM, Tacke CE, Hutten BA, et al. Peripheral endothelial (dys) function, arterial stiffness and carotid intima-media thickness in patients after Kawasaki disease: a systematic review and meta-analyses. PLoS One 2015;10:e0130913.

203. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459-67.

204. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). Cerebrovasc Dis 2012;34:290-6.

205. Niboshi A, Hamaoka K, Sakata K, et al. Endothelial dysfunction in adult patients with a history of Kawasaki disease. Eur J Pediatr 2008;167:189-96.

206. Noto N, Okada T, Karasawa K, et al. Age-related acceleration of endothelial dysfunction and subclinical atherosclerosis in subjects with coronary artery lesions after Kawasaki disease. Pediatr Cardiol 2009;30:262-8.

207. Tobayama H, Takahashi K, Fukunaga H, et al. Analysis of arterial function in adults with a history of Kawasaki disease. J Cardiol 2013;61:330-5.

208. Shirai K, Utino J, Otsuka K, et al. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb 2006;13:101-7.

209. Kubozono T, Miyata M, Ueyama K, et al. Clinical significance and reproducibility of new arterial distensibility index. Circ J 2007;71:89-94.

210. Yambe M, Tomiyama H, Hirayama Y, et al. Arterial stiffening as a possible risk factor for both atherosclerosis and diastolic heart failure. Hypertens Res 2004;27:625-31.

211. Suzuki J, Sakakibara R, Tomaru T, et al. Stroke and cardio-ankle vascular stiffness index. J Stroke Cerebrovasc Dis 2013;22:171-5.

212. Yamamoto N, Yamanaka G, Ishikawa M, et al. Cardio-Ankle Vascular Index as a Predictor of Cognitive Impairment in Community-Dwelling Elderly People: Four-Year Follow-Up. Dement Geriatr Cogn Disord 2009;28:153-8.

213. Nakamura Y, Aso E, Yashiro M, et al. Mortality among persons with a history of Kawasaki disease in Japan. Circ J 2008;72:134-8.

214. Miyoshi T, Doi M, Hirohata S, et al. Cardio-ankle vascular index is independently associated with the severity of coronary atherosclerosis and left ventricular function in patients with ischemic heart disease. J Atheroscler Thromb 2010;17:249-58.

215. Horinaka S, Yabe A, Yagi H, et al. Comparison of atherosclerotic indicators between cardio ankle vascular index and brachial ankle pulse wave velocity. Angiology 2009;60:468-76.

216. Sato H, Miida T, Wada Y, et al. Atherosclerosis is accelerated in patients with long-term well-controlled systemic lupus erythematosus (SLE). Clin Chim Acta 2007;385:35-42.

217. Masugata H, Senda S, Himoto T, et al. Detection of increased arterial stiffness in a patient with early stage of large vessel vasculitis by measuring cardio-ankle vascular index. Tohoku J Exp Med 2009;219:101-5.

218. Miyashita Y, Saiki A, Endo K, et al. Effects of olmesartan, an angiotensin II receptor blocker, and amlodipine, a calcium channel blocker, on Cardio-Ankle Vascular Index (CAVI) in type 2 diabetic patients with hypertension. J Atheroscler Thromb 2009;16:621-6. Erratum in: J Atheroscler Thromb 2009;16:912. Dosage error in published abstract; MEDLINE/PubMed abstract corrected; Dosage error in article text.

219. Ibata J, Sasaki H, Kakimoto T, et al. Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pract 2008;80:265-70.

220. Noike H, Nakamura K, Sugiyama Y, et al. Changes in cardio-ankle vascular index in smoking cessation. J Atheroscler Thromb 2010;17:517-25.

221. Satoh N, Shimatsu A, Kato Y, et al. Evaluation of the cardio-ankle vascular index, a new indicator of arterial stiffness independent of blood pressure, in obesity and metabolic syndrome. Hypertens Res 2008;31:1921-30.

222. Shirai K, Hiruta N, Song M, et al. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. J Atheroscler Thromb 2011;18:924-38.

223. Nakagawa R, Kuwata S, Kurishima C, et al. Arterial stiffness in patients after Kawasaki disease without coronary artery involvement: assessment by performing brachial ankle pulse wave velocity and cardio-ankle vascular index. J Cardiol 2015;66:130-4.