

ORIGINAL ARTICLE

Randomized Trial of Adjunctive Prednisolone for Kawasaki Disease

Siyuan Lin,¹ Y. He,² L. He,¹ Y. Liu,³ Fangjie Wang,⁴ Z. Xiong,⁵ Y. Lin,¹ L. Ye,¹ C. Chu,¹ Feng Wang,¹ L. Zhao,¹ Y. Cao,¹ Y. Zheng,¹ Q. Huang,⁶ J. Wang,¹ X. Liang,¹ Q. Zhao,¹ S. Sun,¹ Y. Dou,² W. He,² Xiaobi Huang,⁷ J. Sun,⁸ Xianmei Huang,⁹ Y. Li,¹⁰ Y. Liao,¹¹ H. Lv,¹² S. Pan,¹³ H. Zhu,¹⁴ X. An,¹⁵ X. He,¹⁶ C. Zhao,¹⁷ Xiaoyan Liu,¹⁸ Y. Hu,¹⁹ J. Piao,²⁰ L. Qin,²¹ X. Dong,²² Q. Peng,²³ C. Wang,²⁴ Shubin Lin,⁶ P. Huang,²⁵ R. Wu,²⁶ H. Peng,²⁷ Z. Li,¹³ D. Wang,²⁸ Xiaohui Liu,²⁹ W. Yan,^{2,30} F. Liu,^{1,30} and G. Huang,^{1,30} for the Chinese Kawasaki Disease Collaboration Network*

ABSTRACT

BACKGROUND

The effect of adjunctive glucocorticoids in the primary treatment of Kawasaki disease in unselected patients remains unknown.

METHODS

In this multicenter, open-label, randomized, controlled trial in China, we assigned participants with newly diagnosed Kawasaki disease in a 1:1 ratio to receive prednisolone plus standard treatment or standard treatment alone. The primary outcome was the occurrence of coronary-artery lesions at 1 month after illness onset. Prespecified key secondary outcomes, for which analyses were not controlled for multiplicity, included receipt of rescue therapy, duration of fever, change in the C-reactive protein (CRP) level, and changes in coronary-artery z scores.

RESULTS

A total of 3208 participants underwent randomization, with coronary-artery lesions detected at baseline in 870 of 3184 participants (27.3%). At 1 month, coronary-artery lesions were detected in 16.0% of the participants receiving prednisolone plus standard treatment and in 13.8% of those receiving standard treatment alone (adjusted risk difference, 1.1 percentage points; 95% confidence interval, -1.0 to 3.4; $P=0.31$). Rescue therapy was used in 4.6% of the participants receiving prednisolone plus standard therapy and in 10.1% of those receiving standard treatment alone; the median duration of fever was 8.4 hours and 13.2 hours, respectively, and the reductions in the C-reactive protein level at 72 hours were 67.5 mg per liter and 59.8 mg per liter. Decreases in coronary-artery z scores were similar in the two groups. At 3 months, the incidence of coronary-artery lesions was 12.6% with prednisolone plus standard therapy and 10.5% with standard treatment alone; the percentage of participants with progression of coronary-artery lesions was 28.6% and 28.9%, respectively, and the incidence of medium-to-giant coronary-artery aneurysms was 1.9% and 1.1%. The overall incidence of adverse events did not differ significantly between the two groups.

CONCLUSIONS

The addition of prednisolone to standard primary treatment for Kawasaki disease did not reduce the incidence of coronary-artery lesions at 1 month after illness onset. (Funded by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences and the National Natural Science Foundation of China; ClinicalTrials.gov number, NCT04078568.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Guoying Huang can be contacted at gyhuang@shmu.edu.cn or at the Pediatric Heart Center, Children's Hospital of Fudan University, 399 Wanyuan Rd., Shanghai 201102, China; Fang Liu can be contacted at liufang@fudan.edu.cn or at the Pediatric Heart Center, Children's Hospital of Fudan University, 399 Wanyuan Rd., Shanghai 201102, China; Weili Yan can be contacted at yanwl@fudan.edu.cn or at the Department of Clinical Epidemiology and Clinical Trial Unit, Children's Hospital of Fudan University, 399 Wanyuan Rd., Shanghai 201102, China; and Xiaohui Liu can be contacted at 17370026560@163.com or at the Department of Rheumatology and Immunology, Jiangxi Provincial Children's Hospital, 1666 Diezihu Ave., Nanchang, Jiangxi 330038, China.

*A full list of the investigators in the Chinese Kawasaki Disease Collaboration Network is provided in the Supplementary Appendix, available at NEJM.org.

Siyuan Lin, Yuanchen He, Lan He, Yiling Liu, Fangjie Wang, and Zhenyu Xiong contributed equally to this article.

N Engl J Med 2026;394:1480-90.

DOI: 10.1056/NEJMoa2511478

Copyright © 2026 Massachusetts Medical Society.

CME



KAWASAKI DISEASE IS AN ACUTE VASCULITIS of unclear cause that mainly affects children younger than 5 years of age.¹ Although reported worldwide, it is most prevalent in Asia, particularly Japan, with an incidence of 239.9 per 100,000 children younger than 5 years of age in 2022.² Coronary-artery lesions are the most important complication, potentially causing aneurysms, occlusion, myocardial infarction, and even death, which makes Kawasaki disease a leading cause of acquired heart disease among children in developed countries.¹

The current standard primary treatment for Kawasaki disease is high-dose intravenous immune globulin (IVIG) with aspirin.¹ However, coronary-artery lesions develop in approximately 10 to 20% of treated patients, and 8 to 25% have resistance to IVIG, which is a known risk factor for coronary-artery lesions.²⁻⁷ This situation underscores a need to improve primary treatment to reduce coronary-artery lesions.

The effect of adjunctive glucocorticoids in the primary treatment of Kawasaki disease remains controversial. A 2006 randomized, controlled trial suggested superiority of IVIG plus glucocorticoids to IVIG alone in preventing coronary-artery lesions.⁸ Subsequently, two landmark randomized, controlled trials provided conflicting evidence.^{9,10} The North American trial involving unselected patients showed no benefit from additional single-pulsed intravenous methylprednisolone in reducing coronary-artery lesions.⁹ The Randomized Controlled Trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki Disease (RAISE) focused on Japanese patients at high risk for resistance to IVIG (Kobayashi score, ≥ 5) and showed that adjunctive longer-course (for 15 days after C-reactive protein [CRP] normalization) prednisolone significantly reduced the incidence of coronary-artery lesions,¹⁰ a finding that was supported by several meta-analyses.^{11,12} On the basis of this evidence, current guidelines recommend adjunctive glucocorticoids for patients at high risk for resistance to IVIG.^{13,14}

However, critical gaps in research remain. First, the generalizability of the RAISE regimen is limited by the poor predictive performance of the Kobayashi score and other risk scores in non-Japanese populations,¹⁵⁻¹⁹ which makes identification of high-risk patients outside Japan challenging. Second, most randomized, controlled trials, including RAISE, excluded patients with early-

onset coronary-artery lesions,^{8,10,20-22} which predict poor prognosis.⁷ Retrospective studies suggested that this subgroup might benefit from adjunctive glucocorticoids.^{23,24} To resolve these gaps, we conducted a nationwide, multicenter, randomized, controlled trial to evaluate whether adjunctive glucocorticoids would reduce the occurrence of coronary-artery lesions and improve clinical outcomes in unselected patients with Kawasaki disease across China.

METHODS

TRIAL OVERSIGHT

This trial was a phase 3, multicenter, open-label, randomized, controlled trial conducted at 28 sites in China (Section 1.0 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Full details about the trial design, population, and procedures were published previously.²⁵

The trial was approved by independent ethics committees at each site. All the participants provided written informed consent. The trial steering committee designed the trial. Data were collected by the site investigators and analyzed by the Clinical Trial Unit of the leading site (Children's Hospital of Fudan University). The first two authors wrote the first draft of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org) and made the decision to submit the manuscript for publication. No confidentiality agreements exist between the sponsors and the authors. The sponsors had no role in the trial design or conduct; data collection, management, analysis, or interpretation; manuscript preparation, review, or approval; or the decision to submit the manuscript for publication.

PARTICIPANTS

Eligible patients were children 1 month of age or older who met the 2017 American Heart Association (AHA) diagnostic criteria for Kawasaki disease,¹ had received a diagnosis within 10 days after illness onset (with day 1 defined as the day of fever onset), and had not received IVIG treatment. Among the key exclusion criteria were the presence of large or giant coronary-artery aneurysms (with large or giant defined as any z score of ≥ 10 or internal diameter of ≥ 8 mm), a history



A Quick Take
is available at
NEJM.org



of Kawasaki disease, being afebrile for at least 24 hours before enrollment, and receipt of glucocorticoids or other immunosuppressive drugs within 30 days before enrollment. Details are provided in Section 2.1 in the Supplementary Appendix.

RANDOMIZATION AND BLINDING

Eligible patients were randomly assigned in a 1:1 ratio to receive prednisolone plus standard primary treatment or standard primary treatment alone. Randomization was performed in permuted blocks of four, with stratification according to trial center. Randomization sequences were generated by an independent data coordinating center and provided to site investigators in sealed, opaque, sequentially numbered envelopes containing the assigned treatments. Outcome assessors (i.e., echocardiographers) and statisticians were unaware of the trial-group assignments throughout the trial until completion of the statistical analysis.

INTERVENTIONS

In the group assigned to standard treatment alone, participants received IVIG (2 g per kilogram of body weight; maximum dose, 60 g) and oral aspirin (30 mg per kilogram per day divided into three doses). Once fever had resolved for 3 days and the CRP level had normalized, the aspirin dose was reduced to 3 to 5 mg per kilogram per day and maintained for at least 6 weeks. In the group assigned to prednisolone plus standard treatment, participants received adjunctive prednisolone (2 mg per kilogram per day; maximum dose, 60 mg) administered concurrently with the IVIG infusion. Initially, intravenous methylprednisolone at a dose of 1.6 mg per kilogram per day (equivalent to 2 mg per kilogram of prednisolone) was administered in two divided doses, with a 12-hour interval between the two infusions and each infusion completed within 30 to 60 minutes. If the participant was afebrile for 3 days after initiation of methylprednisolone, treatment was switched to oral prednisolone at a dose of 2 mg per kilogram per day. Once the CRP level had normalized, prednisolone was tapered over a period of 15 days in three 5-day steps: 2 mg per kilogram per day, 1 mg per kilogram per day, and 0.5 mg per kilogram per day. During glucocorticoid treatment, omeprazole was administered at a

dose of 0.5 mg per kilogram per day for gastroprotection. The CRP level was monitored every 3 days until normalization.

In both groups, participants with persistent or recurrent fever (axillary temperature of $\geq 37.5^{\circ}\text{C}$ or rectal temperature of $\geq 38^{\circ}\text{C}$) 36 hours after completion of the first IVIG infusion were defined as having resistance to IVIG and received rescue therapy, including retreatment with IVIG, high-dose methylprednisolone pulse therapy, a longer tapering course of prednisolone, tumor necrosis factor α inhibitors, other immunosuppressive agents, plasmapheresis, or a combination of regimens. The rescue therapy was chosen on the basis of participant conditions and physician experience. More details on concomitant treatments throughout the trial are provided in Section 2.2 in the Supplementary Appendix.

ASSESSMENTS AND OUTCOMES

Assessments included two-dimensional echocardiography, measurement of body temperature, laboratory tests, and safety assessments. All the participants received echocardiography at enrollment, 2 weeks, 1 month, and 3, 6, and 12 months after illness onset. Five coronary-artery segments — including the left main coronary artery, left anterior descending artery, left circumflex coronary artery, and proximal and middle segments of the right coronary artery — were evaluated by means of echocardiography (Fig. S2). For coronary arteries without lesions, diameters were measured as follows: left main coronary artery at midpoint; left anterior descending artery, left circumflex coronary artery, and proximal segment of the right coronary artery at 3 to 5 mm from their origin; and middle segment of the right coronary artery at the lateral atrioventricular sulcus. For coronary arteries with lesions, the diameter at the site of each lesion was recorded, and the maximum value per segment was used for analysis. Details are provided in Section 2.3.1 in the Supplementary Appendix. Designated pediatric echocardiographers at each site (all trained in a standardized fashion before trial initiation) acquired echocardiographic images and measured coronary-artery diameters. Printed protocol manuals, which were consistent with the 2017 AHA guidelines, were distributed to ensure cross-site consistency. At the time of writing, follow-up assessments at 6 and 12 months are still ongoing.

The primary outcome was the occurrence of coronary-artery lesions at 1 month after illness onset. The z score of each coronary artery was calculated from height, weight, and measured diameter, with a value of less than 2 considered to be normal.²⁶ The calculation methods are provided in Section 2.3.2 in the Supplementary Appendix. According to the 2017 AHA criteria,¹ coronary-artery lesions were defined as a z score of 2 or more in any segment. Higher z scores indicate greater dilation. Secondary outcomes included the occurrence of coronary-artery lesions at 2 weeks and 3 months, receipt of rescue therapy, duration of fever after IVIG initiation, change in the CRP level at 72 hours after IVIG completion, and changes in z scores of five coronary-artery segments at the follow-up visit. The occurrence of medium-to-giant coronary-artery aneurysms, large or giant coronary-artery aneurysms, progression of coronary-artery lesions, and changes in absolute diameters were assessed post hoc, with progression of coronary-artery lesions additionally assessed in participants with lesions at baseline. Medium-to-giant coronary-artery aneurysm was defined as a z score of 5 or more in any coronary-artery segment.¹ Progression of coronary-artery lesions was defined as a z score increment of at least 1 in any coronary-artery segment from baseline at any given time point within 3 months after illness onset.²⁴

Safety assessments included adverse events, vital-sign monitoring, and laboratory evaluations. Additional details are provided in Section 2.3 in the Supplementary Appendix.

STATISTICAL ANALYSIS

Assuming that the between-group difference in the occurrence of coronary-artery lesions at 1 month was 3.3 percentage points (9.1% with prednisolone plus standard treatment and 12.4% with standard treatment alone),²⁷ we estimated that 1390 participants in each group was required to achieve 80% power at a two-sided significance level of 5%. To allow for a dropout rate of 10%, we intended to recruit 3200 participants (1600 per group).

All analyses that are not otherwise identified were prespecified in the statistical analysis plan (available with the protocol) and were performed in the intention-to-treat population, which included all the participants who had undergone ran-

domization. Missing data for height at baseline were imputed with the use of a regression-based imputation method under the assumption that data were missing at random (see Section 2.4.1 in the Supplementary Appendix). The primary-outcome analyses were conducted with the use of generalized estimating equations to account for the correlation among repeated measures from the same participant. In the primary analysis, the model included intervention group, visit, and intervention-by-visit interaction as fixed effects and participant as a cluster effect (an exchangeable covariance structure), with the mean of five coronary-artery z scores at baseline adjusted as a covariate. The risk difference at 1 month and its 95% confidence interval were estimated with the use of a gaussian distribution with an identity link function, and P value was derived from a Wald test. Ten sensitivity analyses were conducted; these analyses are detailed in Section 2.4.2 in the Supplementary Appendix. All subgroup analyses are described in Section 2.4.3 in the Supplementary Appendix.

Repeatedly measured secondary outcomes were analyzed with the use of generalized linear mixed-effects models. Continuous data were assessed with generalized linear models, and binary outcomes were assessed with Poisson regression. Time-to-event estimates were analyzed with the Kaplan–Meier method and Cox proportional-hazards model after the Schoenfeld residuals test. Between-group risk ratios for medium-to-giant coronary-artery aneurysms, large or giant coronary-artery aneurysms, and progression of coronary-artery lesions, together with mean differences in absolute diameter changes, were estimated post hoc. Details of all secondary-outcome analyses and exploratory analyses are provided in the Supplementary Appendix. Safety analyses included all the participants who had undergone randomization and received at least one trial-related treatment dose, with comparisons using the chi-square test or Fisher's exact test as appropriate.

Two-sided analyses were conducted, and a P value of less than 0.05 for the primary outcome was considered to indicate statistical significance. For sensitivity, subgroup, and secondary-outcome analyses, confidence intervals were not formally adjusted for multiplicity, and no definitive inferences should be drawn from these findings.

Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.4.

RESULTS

PARTICIPANTS

From January 2020 through November 2024, a total of 3208 participants underwent randomization at 28 sites across China; 1604 participants were assigned to receive prednisolone plus standard treatment and 1604 to receive standard treatment alone (Fig. S3 and Table S1). Protocol violations were identified in 29 participants (1.8%) and 42 participants (2.6%) in the respective groups (Table S2). In total, 3058 participants (95.3%) completed the 1-month follow-up, and the 3-month assessment of the last participant was completed in January 2025.

The baseline characteristics of the participants were well balanced between the two groups (Table 1 and Tables S3 and S12). Overall, coronary-artery lesions were detected at baseline in 870 of 3184 participants (27.3%), including 455 of 1592 participants (28.6%) assigned to receive prednisolone plus standard treatment and 415 of 1592 participants (26.1%) assigned to receive standard treatment alone. The characteristics of the participants with missing data for height were similar to those of the overall participants (Table S4).

PRIMARY OUTCOME

At 1 month after illness onset, coronary-artery lesions were detected in 245 of 1533 participants (16.0%) receiving prednisolone plus standard treatment and in 210 of 1525 participants (13.8%) receiving standard treatment alone (adjusted risk difference, 1.1 percentage points; 95% confidence interval [CI], −1.0 to 3.4; $P=0.31$). These results remained robust after sensitivity analyses (Fig. 1). Among participants with resistance to IVIG, the incidence of coronary-artery lesions at 1 month was 45.2% (33 of 73) with prednisolone plus standard treatment and 25.6% (40 of 156) with standard treatment alone (adjusted risk difference, 13.5 percentage points; 95% CI, 2.7 to 24.3).

SECONDARY OUTCOMES

The occurrence of coronary-artery lesions at 2 weeks and 3 months did not appear to differ

substantially between the two groups (Fig. 2 and Table S6). After primary treatment, rescue therapy was used in 73 participants (4.6%) receiving prednisolone plus standard treatment and in 162 participants (10.1%) receiving standard treatment alone (risk ratio, 0.45; 95% CI, 0.34 to 0.59) (Table S5). The median duration of fever was 8.4 hours with prednisolone plus standard treatment and 13.2 hours with standard treatment alone (hazard ratio, 0.67; 95% CI, 0.61 to 0.73) (Fig. 2 and Fig. S4), with consistent findings in a sensitivity analysis (Fig. S5). The reduction in the CRP level at 72 hours after IVIG completion appeared to be greater with prednisolone plus standard treatment than with standard treatment alone (−67.5 mg per liter vs. −59.8 mg per liter; mean difference, −7.6 mg per liter; 95% CI, −10.9 to −4.3). The z scores of all coronary arteries showed similar decreases in the two groups (Fig. S6).

EXPLORATORY OUTCOMES

Among all the participants, the risk of medium-to-giant coronary-artery aneurysms at 3 months after illness onset was similar in the two groups (1.9% with prednisolone plus standard therapy and 1.1% with standard therapy alone; risk ratio, 0.98; 95% CI, 0.62 to 2.06) (Fig. 2). Similar findings were observed for progression of coronary-artery lesions (28.6% and 28.9%, respectively; risk ratio, 0.96; 95% CI, 0.89 to 1.03).

SAFETY OUTCOMES

The overall incidence of adverse events did not differ significantly between the two groups ($P=0.17$) (Table 2). Discontinuation or adjustment of the trial regimen due to adverse events was reported in 11 participants (0.7%) receiving prednisolone plus standard treatment and in 12 participants (0.7%) receiving standard treatment alone. The incidence of skin allergy was lower with prednisolone plus standard treatment than with standard treatment alone (1.1% vs. 1.9%). No deaths occurred during the trial period. Additional safety data are provided in Table S7.

DISCUSSION

In this phase 3, open-label, randomized trial, we observed that adding prednisolone to standard treatment in patients with acute Kawasaki disease did not reduce the occurrence of coronary-artery

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Prednisolone plus Standard Treatment (N = 1604)	Standard Treatment (N = 1604)
Age — yr	2.7±1.8	2.7±1.9
Male sex — no. (%)	973 (60.7)	967 (60.3)
Weight — kg	13.4±4.7	13.6±5.0
Height — cm†	91.0±16.1	91.2±16.8
Duration of illness at enrollment‡	6.4±1.5	6.5±1.5
Incomplete Kawasaki disease — no. (%)§	298 (18.6)	308 (19.2)
Diameter of coronary arteries — mm¶		
Left main coronary artery	2.3 (2.1–2.6)	2.3 (2.0–2.6)
z Score	0.9±1.2	0.8±1.1
Left anterior descending artery	1.9 (1.7–2.1)	1.9 (1.7–2.1)
z Score	1.1±1.2	1.0±1.2
Left circumflex coronary artery	1.5 (1.4–1.8)	1.5 (1.4–1.7)
z Score	0.2±0.9	0.2±0.9
Proximal segment of right coronary artery	2.0 (1.8–2.3)	2.0 (1.8–2.3)
z Score	0.8±1.1	0.8±1.1
Middle segment of right coronary artery	1.8 (1.6–2.1)	1.8 (1.6–2.0)
z Score	1.0±1.2	0.9±1.1
Coronary-artery lesion detected at baseline — no./total no. (%)¶	455/1592 (28.6)	415/1592 (26.1)
No. of coronary-artery segments with lesion — no./total no. (%)¶		
1	208/1592 (13.1)	199/1592 (12.5)
2	114/1592 (7.2)	102/1592 (6.4)
3	61/1592 (3.8)	56/1592 (3.5)
4	52/1592 (3.3)	38/1592 (2.4)
5	20/1592 (1.3)	20/1592 (1.3)
Classification of coronary-artery lesion — no./total no. (%)		
Large or giant aneurysm	1/1592 (0.1)	3/1592 (0.2)
Medium aneurysm	39/1592 (2.4)	17/1592 (1.1)
Small aneurysm	235/1592 (14.8)	224/1592 (14.1)
Dilation only	180/1592 (11.3)	171/1592 (10.7)
Any z score of ≥2.5 — no./total no. (%)	275/1592 (17.3)	244/1592 (15.3)

* Plus-minus values are means ±SD.

† Data on height were missing for 12 participants in each of the two groups.

‡ Days of illness were defined as days from first calendar day of fever to first calendar day of intravenous immune globulin infusion.

§ Complete or incomplete Kawasaki disease was defined according to the diagnostic criteria for Kawasaki disease published by the American Heart Association (AHA) in 2017.

¶ Data were missing as follows: for left main coronary artery, 2 participants assigned to receive prednisolone plus standard treatment and 7 participants assigned to receive standard treatment alone; for left anterior descending artery, 14 participants and 24 participants, respectively; for left circumflex coronary artery, 19 participants and 31 participants; for the proximal segment of the right coronary artery, 2 participants and 8 participants; and for the middle segment of the right coronary artery, 60 participants and 76 participants. The z score of each coronary artery was calculated on the basis of height, weight, and measured absolute diameter of the coronary artery according to the Dallaire formula. The z score of each coronary artery could not be calculated for 12 participants in each of the two groups.

|| The classification of coronary-artery lesions was based on the maximum z score and followed the 2017 AHA guideline: z score of 2 to less than 2.5 (dilation only); z score of 2.5 to less than 5 (small aneurysm); z score of 5 to less than 10 and all absolute dimensions of less than 8 mm (medium aneurysm); and z score of 10 or more or any absolute dimension of 8 mm or more (large or giant aneurysm).

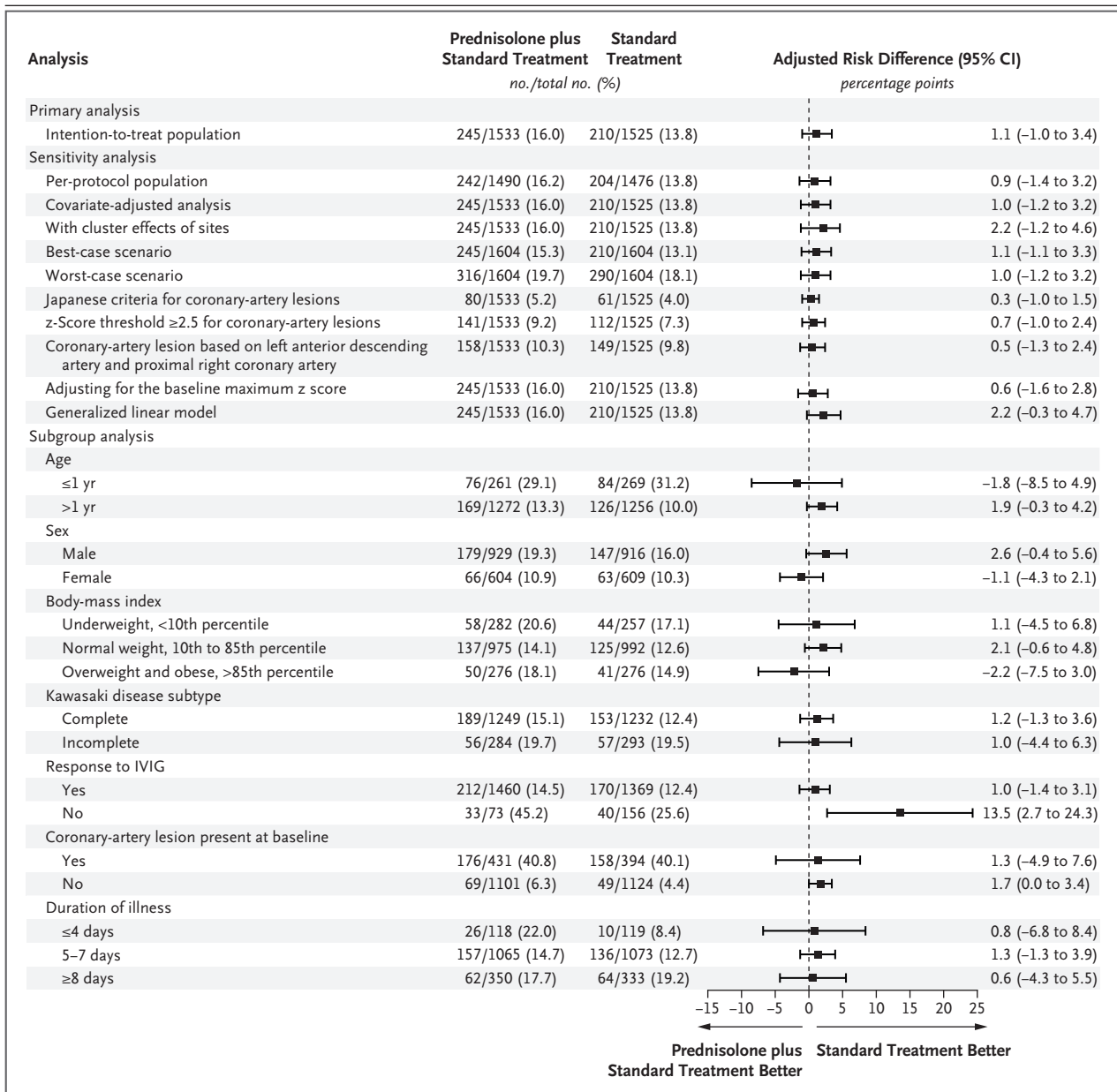


Figure 1. Primary, Sensitivity, and Subgroup Analyses of the Primary Outcome.

Risk differences and 95% confidence intervals for the primary outcome (coronary-artery lesions detected at 1 month after illness onset) were calculated in the primary analysis (intention-to-treat population, including all the participants who had undergone randomization), two prespecified sensitivity analyses (per-protocol [including all the participants who had undergone randomization and received at least one dose of trial-related treatment] and covariate-adjusted), eight post hoc sensitivity analyses, and subgroup analyses. Prespecified subgroups included age group, sex, category of body-mass index (weight in kilograms divided by square of height in meters), complete or incomplete Kawasaki disease, response or nonresponse to intravenous immune globulin (IVIG response), and presence or absence of coronary-artery lesion at baseline. Another post hoc subgroup analysis involved duration of illness. In the subgroup with coronary-artery lesions detected at baseline, 24 participants receiving prednisolone plus standard treatment and 21 receiving standard treatment alone did not complete the 1-month follow-up. At 1 month, data regarding coronary-artery segments with lesions were as follows: in the group receiving prednisolone plus standard treatment, one segment in 138 participants, two segments in 59 participants, three segments in 22 participants, four segments in 15 participants, and five segments in 11 participants; in the group receiving standard treatment alone, one segment in 112 participants, two segments in 47 participants, three segments in 24 participants, four segments in 14 participants, and five segments in 13 participants (Table S12). Confidence intervals for sensitivity and subgroup analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

Table 2. Adverse Events.*

Safety Outcome	Prednisolone plus Standard Treatment (N = 1604)	Standard Treatment (N = 1602)	P Value
	<i>no. of participants (%)</i>		
Any adverse event†	33 (2.1)	45 (2.8)	0.17
Any adverse event leading to discontinuation or adjustment of treatment dose	11 (0.7)	12 (0.7)	
Types of adverse events			
Skin allergy	18 (1.1)	30 (1.9)	
Nasal hemorrhage	5 (0.3)	6 (0.4)	
Hematochezia	2 (0.1)	0	
Liver-enzyme elevation	5 (0.3)	11 (0.7)	
Hemolytic anemia	3 (0.2)	0	
Aseptic meningitis	1 (<0.1)	0	

* Safety outcomes were based on the safety analysis population, including all the participants who had undergone randomization and received at least one dose of trial-related treatment.

† In the group receiving prednisolone plus standard treatment, one participant had two adverse events: skin allergy and nasal hemorrhage. In the group receiving standard treatment alone, two participants had two adverse events: skin allergy and liver-enzyme elevation.

lesions at 1 month after illness onset (16.0% with prednisolone plus standard treatment and 13.8% with standard treatment alone). The two groups also had clinically similar use of rescue therapy, reductions in CRP levels, duration of fever, and 3-month progression of coronary-artery lesions or occurrence of medium-to-giant aneurysms.

Our primary finding aligns with that of the North American trial but contrasts with that of RAISE.^{9,10} Discrepancies in trial populations may partially explain the contradiction: RAISE enrolled participants at high risk for resistance to IVIG without coronary-artery lesions at baseline, whereas our trial included participants irrespective of risk of IVIG resistance or coronary-artery status. In this trial, the percentages of participants with coronary-artery lesions at baseline (27.3% with a z score of ≥ 2.0 and 16.2% with a z score of ≥ 2.5) are similar to those in several cohorts using similar definitions.^{6,7} Results were consistent in the prespecified subgroup without coronary-artery lesions at baseline. In addition, given that different definitions of coronary-artery lesions between trials potentially hindered comparison of the incidence at 1 month, we adopted the Japanese criteria used in RAISE for a sensitivity analysis and detected similar between-group differences.²⁸ Our trial shows that use of an adjunctive glucocorticoid, an antiinflammatory agent, was not superior to the standard treatment in reducing coronary-

artery lesions in unselected patients. This dissociation between antiinflammatory and coronary benefits, also reported with other interventions such as high-dose aspirin,²⁹ highlights the unclear link between suppressing inflammation and preventing coronary-artery lesions. The higher risk of coronary-artery lesions among participants with resistance to IVIG who received prednisolone plus standard treatment than among those who received standard treatment alone requires cautious interpretation owing to the small sample size and baseline imbalance (Table S8).

The large sample size of this trial offers adequate statistical power and reliable estimates of the primary outcome. Our trial recruited patients with broad characteristics from 28 hospitals across diverse Chinese geographic regions, yielding a representative sample of Chinese patients with Kawasaki disease (Table S13). These factors enhance generalizability within China. Other strengths include high follow-up rate for the primary outcome, and the collection of comprehensive data on the acute phase of Kawasaki disease.

Our trial has certain limitations. First, information bias in outcome measurements exists from being conducted at each site rather than in a core laboratory, although adherence to standardized protocols and block randomization according to site should help minimize this risk. Second, trial enrollment during the coronavirus disease

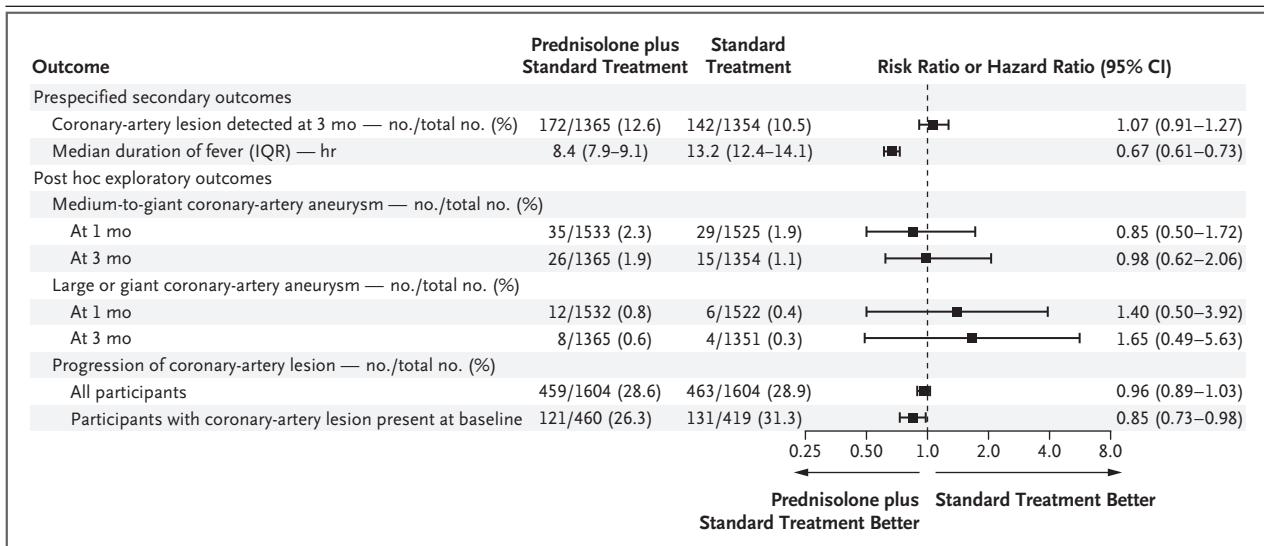


Figure 2. Secondary and Exploratory Outcomes.

Shown are results of prespecified secondary outcomes and post hoc exploratory outcomes. Unless otherwise specified, analyses were conducted in the intention-to-treat population. Risk ratios and 95% confidence intervals are reported for coronary-artery lesions detected at 3 months, medium-to-giant coronary-artery aneurysm, large or giant coronary-artery aneurysm, and progression of coronary-artery lesions; hazard ratio and 95% confidence interval are reported for duration of fever. No adjustment for multiplicity was made, so 95% confidence intervals should not be used for hypothesis testing. Duration of fever was recorded from initiation of initial IVIG to 96 hours thereafter. Progression of coronary-artery lesions was defined as a z score increment of at least 1 in any coronary artery within 3 months after illness onset. Classification of coronary-artery lesions followed the 2017 American Heart Association guideline.

2019 pandemic was below expectations, with the dropout rate exceeding the initial estimate of 5%. The estimate was subsequently revised to 10%, and final sample size met the target, which suggests minimal effect on the results. Third, participants not meeting eligibility criteria were included in the primary analysis. Given the small proportion of such participants and the consistent results in the per-protocol population (which included participants who had undergone randomization, received the assigned treatment, and adhered to the protocol), the overall findings appear to be tenable. Fourth, subgroup and exploratory analyses were underpowered, thereby warranting confirmation by future studies. Fifth, because follow-up is still ongoing, the protocol-specified 6-month and 1-year data are not included in the current analysis.

In our trial, the administration of glucocorticoids in addition to standard primary treatment did not reduce the incidence of coronary-artery lesions at 1 month among Chinese children with Kawasaki disease. Future studies are needed to better assess longer treatment and follow-up dura-

tion of glucocorticoids or other immunomodulating therapies to reduce the burden of coronary artery disease in patients with Kawasaki disease.

Supported by a grant (2019-I2M-5-002) from the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences and grants (82070513 and 82100524) from the National Natural Science Foundation of China.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants, their families, and the research staff at the participating trial sites for their contributions to the current trial and Drs. Hongyan Chen and Guangan Dai for their assistance in manuscript preparation.

AUTHOR INFORMATION

Siyuan Lin, M.D.,¹ Yuanchen He, M.Sc.,² Lan He, M.D.,¹ Yiling Liu, M.D.,³ Fangjie Wang, M.D.,⁴ Zhenyu Xiong, M.D.,⁵ Yixiang Lin, M.D.,¹ Lan Ye, R.N., B.D.,¹ Chen Chu, M.D.,¹ Feng Wang, M.D.,¹ Lu Zhao, M.D.,¹ Yinyin Cao, M.D.,¹ Yuanzheng Zheng, M.D.,¹ Qin Huang, M.D.,⁶ Jie Wang, M.D.,¹ Xuecun Liang, M.D.,¹ Quming Zhao, M.D.,¹ Shuna Sun, M.D.,¹ Yalan Dou, Ph.D.,² Wennan He, M.S.,² Xiaobi Huang, M.D.,⁷ Jingwei Sun, M.D.,⁸ Xianmei Huang, M.D.,⁹ Yan Li, M.D.,¹⁰ Yanling Liao, M.D.,¹¹ Haitao Lv, M.D.,¹² Silin Pan, M.D.,¹³ Hua Zhu, M.D.,¹⁴ Xinjiang An, M.D.,¹⁵ Xuehua He, M.D.,¹⁶ Cuifen Zhao, M.D.,¹⁷ Xiaoyan Liu, M.D.,¹⁸ Yaoifei Hu, M.D.,¹⁹ Jinhua Piao, M.D.,²⁰ Lijun Qin, M.D.,²¹ Xiangyu Dong, M.D.,²² Qian Peng, M.D.,²³ Ce Wang,

M.D.,²⁴ Shubin Lin, M.D.,⁶ Ping Huang, M.D.,²⁵ Rongzhou Wu, M.D.,²⁶ Hua Peng, M.D.,²⁷ Zipu Li, M.D.,¹³ Duolao Wang, M.D.,²⁸ Xiaohui Liu, M.D.,²⁹ Weili Yan, Ph.D.,^{2,30} Fang Liu, M.D.,^{1,30} and Guoying Huang, M.D.^{1,30}

¹Pediatric Heart Center, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai; ²Department of Clinical Epidemiology and Clinical Trial Unit, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai; ³Department of Pediatric Cardiology, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; ⁴Department of Cardiology, Children's Hospital Affiliated of Zhengzhou University, Zhengzhou, China; ⁵Department of Cardiology, Kaifeng Children's Hospital, Kaifeng, China; ⁶Department of Cardiology, Children's Hospital of Fudan University (Xiamen Branch), Xiamen, China; ⁷Department of Pediatric Cardiology, Anhui Provincial Children's Hospital (Children's Hospital of Anhui Medical University), Hefei, China; ⁸Pediatrics Department, Bengbu First People's Hospital, Bengbu, China; ⁹Department of Pediatrics, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou, China; ¹⁰Department of Pediatrics, Third Affiliated Hospital of Zhengzhou University, Zhengzhou, China; ¹¹Department of Pediatrics, Liuzhou Maternity and Child Health Hospital, Liuzhou, China; ¹²Department of Cardiology, Children's Hospital of Soochow University, Suzhou, China; ¹³Heart Center, Women and Children's Hospital, Qingdao University, Qingdao, China; ¹⁴Department of Pediatrics, Inner Mongolia Autonomous Region People's Hospital, Hohhot, China; ¹⁵Department of Cardiovascular Medicine, Xuzhou Children's Hospital Affiliated to Xuzhou Medical University, Xuzhou, China; ¹⁶Department of Pediatric Cardiology, Hunan

Provincial People's Hospital, First Affiliated Hospital of Hunan Normal University, Changsha, China; ¹⁷Department of Pediatrics, Qilu Hospital of Shandong University, Jinan, China; ¹⁸Department of Cardiovascular Medicine, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Structural Birth Defect and Reconstruction, Chongqing, China; ¹⁹Department of Pediatrics, Taihe Hospital, Hubei University of Medicine, Shiyan, China; ²⁰Department of Pediatric Cardiovascular, Children's Medical Center, First Hospital of Jilin University, Changchun, China; ²¹Department of Pediatrics, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; ²²Department of Pediatrics, Lanzhou University Second Hospital, Lanzhou, China; ²³Department of Pediatrics, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, China; ²⁴Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, China; ²⁵Department of Cardiology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China; ²⁶Department of Pediatric Cardiology, Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China; ²⁷Pediatric Department, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; ²⁸Global Health Trials Unit, Liverpool School of Tropical Medicine, Liverpool, United Kingdom; ²⁹Department of Rheumatology and Immunology, Jiangxi Provincial Children's Hospital, Nanchang, China; ³⁰Research Unit of Early Intervention of Genetically Related Childhood Cardiovascular Diseases (2018RU002), Chinese Academy of Medical Sciences, Shanghai.

REFERENCES

- 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(17):e927-e999.
- Nakamura Y, Yashiro M, Yanagawa H. Epidemiology of Kawasaki disease in Japan in 2021-2022: results of the 27th nationwide survey. *Pediatr Int* 2025;67(1):e70007.
- Xie L-P, Yan W-L, Huang M, et al. Epidemiologic features of Kawasaki disease in Shanghai from 2013 through 2017. *J Epidemiol* 2020;30:429-35.
- Kim GB, Eun LY, Han JW, et al. Epidemiology of Kawasaki disease in South Korea: a nationwide survey 2015-2017. *Pediatr Infect Dis J* 2020;39:1012-6.
- Vasudeva R, Poku FA, Thommana M, et al. Trends and resource utilization in Kawasaki disease hospitalizations in the United States, 2008-2017. *Hosp Pediatr* 2022;12:257-66.
- Tulloch RMR, Mayon-White R, Harnaden A, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child* 2019;104:640-6.
- Narayan HK, Lizcano A, Lam-Hine T, et al. Clinical presentation and outcomes of Kawasaki disease in children from Latin America: a multicenter observational study from the REKAMLATINA Network. *J Pediatr* 2023;263:113346.
- 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.
- 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.
- 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.
- Chen S, Dong Y, Kiuchi MG, et al. Coronary artery complication in Kawasaki disease and the importance of early intervention: a systematic review and meta-analysis. *JAMA Pediatr* 2016;170:1156-63.
- Green J, Wardle AJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2022;5:CD011188.
- Jone P-N, Tremoulet A, Choueier N, et al. Update on diagnosis and management of Kawasaki disease: a scientific statement from the American Heart Association. *Circulation* 2024;150(23):e481-e500.
- Miura M, Ayusawa M, Fukazawa R, et al. Guidelines for medical treatment of acute Kawasaki disease (2020 revised version). *J Pediatr Cardiol Card Surg* 2021;5:41-73 (https://www.jstage.jst.go.jp/article/jpccs/5/1/5_0501G1/_pdf).
- Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr* 2011;158(5):831-835.e3.
- Davies S, Sutton N, Blackstock S, et al. Predicting IVIG resistance in UK Kawasaki disease. *Arch Dis Child* 2015;100:366-8.
- Shin J, Lee H, Eun L. Verification of current risk scores for Kawasaki disease in Korean children. *J Korean Med Sci* 2017;32:1991-6.
- Xie LP, Gong J, Fu Y, et al. Questioning the establishment of clinical prediction model for intravenous immunoglobulin

- resistance in children with Kawasaki disease. *Chin J Evid Based Pediatr* 2019;14:169-75.
19. Tan X-H, Zhang X-W, Wang X-Y, et al. A new model for predicting intravenous immunoglobulin-resistant Kawasaki disease in Chongqing: a retrospective study on 5277 patients. *Sci Rep* 2019;9:1722.
20. Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003;142:611-6.
21. Ogata S, Ogihara Y, Honda T, Kon S, Akiyama K, Ishii M. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. *Pediatrics* 2012;129(1):e17-e23.
22. Eleftheriou D, Moraes YC, Purvis C, et al. Multi-centre, randomised, open-label, blinded endpoint assessed, trial of corticosteroids plus intravenous immunoglobulin (IVIG) and aspirin, versus IVIG and aspirin for prevention of coronary artery aneurysms (CAA) in Kawasaki disease (KD): the KD CAA prevention (KD-CAAP) trial protocol. *Trials* 2023;24:60.
23. Friedman KG, Gauvreau K, Baker A, et al. Primary adjunctive corticosteroid therapy is associated with improved outcomes for patients with Kawasaki disease with coronary artery aneurysms at diagnosis. *Arch Dis Child* 2021;106:247-52.
24. Dionne A, Burns JC, Dahdah N, et al. Treatment intensification in patients with Kawasaki disease and coronary aneurysm at diagnosis. *Pediatrics* 2019;143(6):e20183341.
25. Lin S-Y, He L, Xie L-P, et al. Effects of immunoglobulin plus prednisolone in reducing coronary artery lesions in patients with Kawasaki disease: study protocol for a phase III multicenter, open-label, blinded-endpoints randomized controlled trial. *Trials* 2021;22:898.
26. 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.
27. Zhu B-H, Lv H-T, Sun L, et al. A meta-analysis on the effect of corticosteroid therapy in Kawasaki disease. *Eur J Pediatr* 2012;171:571-8.
28. Research Committee on Kawasaki Disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo: Ministry of Health and Welfare, 1984. (In Japanese.)
29. Kuo H-C, Lin M-C, Kao C-C, et al. Intravenous immunoglobulin alone for coronary artery lesion treatment of Kawasaki disease: a randomized clinical trial. *JAMA Netw Open* 2025;8(4):e253063.

Copyright © 2026 Massachusetts Medical Society.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* website at [NEJM.org](https://www.nejm.org). At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.