

ORIGINAL RESEARCH

Corticosteroids Added to Initial Intravenous Immunoglobulin Treatment for the Prevention of Coronary Artery Abnormalities in High-Risk Patients With Kawasaki Disease

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BACKGROUND: Randomized controlled trials previously provided different conclusions about the superiority of adding corticosteroids to initial intravenous immunoglobulin treatment for the prevention of coronary artery abnormalities in patients with Kawasaki disease (KD). To further assess this issue, we analyzed large-scale data from nationwide KD surveys in Japan, where combination treatment (corticosteroids added to initial standard intravenous immunoglobulin treatment) has become commonly used for patients at high risk for KD.

METHODS AND RESULTS: Standard intravenous immunoglobulin treatment and combination treatment were compared using data from time periods with and without combination treatment. Outcome measures were coronary artery abnormalities and initial intravenous immunoglobulin treatment failure. Hospitals where $\geq 20\%$ of patients received combination treatment were identified, and treatment and control groups were selected via matching by age, sex, illness day at initial treatment, and KD recurrence. Matched group selection and subsequent analyses were conducted 1000 times to minimize sampling bias and potential confounders (bootstrapping). From 115 hospitals, 1593 patients with KD in the treatment group and 1593 controls were selected for each of the 1000 sample iterations. The median proportion of patients who developed coronary artery abnormalities among the treatment group and controls were 4.6% (95% CI, 3.8%–5.8%) and 8.8% (95% CI, 7.5%–10.0%), respectively: an estimated risk ratio of 0.53 (0.41–0.67). A median of 14.1% (95% CI, 12.4%–15.9%) of the patients in the treatment group and 21.7% (95% CI, 19.8%–23.4%) in the controls had treatment failure: an estimated risk ratio of 0.65 (0.56–0.75).

CONCLUSIONS: Combination treatment reduced coronary artery abnormality risk by an estimated 47% and treatment failure by 35%. Multiple-dose corticosteroids may provide benefit in selected patients at high risk for KD.

Key Words: bootstrapping ■ coronary artery abnormality ■ corticosteroids ■ Kawasaki disease ■ treatment

See Editorial by Burns

Kawasaki disease (KD), an acute systemic vasculitis, is a disease of childhood that is more common in children <5 years of age. KD can cause significant morbidity because of associated cardiovascular complications. The most serious complications include coronary artery abnormalities (CAAs), such

as dilatations and aneurysms. KD is recognized as the leading cause of acquired heart disease among children in developed countries.^{1–3} First described in 1967,^{4,5} the etiology of KD remains largely elusive. However, evidence-based effective treatment—intravenous immunoglobulin (IVIG), typically administered

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CLINICAL PERSPECTIVE

What Is New?

- This was the largest study to date assessing the effectiveness of primary corticosteroid treatment administered in combination with standard intravenous immunoglobulin treatment for patients with Kawasaki disease.
- The combination treatment group of 1593 patients with Kawasaki disease from 115 hospitals was pair matched to the standard intravenous immunoglobulin treatment group using bootstrapping with 1000 iterations to control for sampling bias.
- Compared with standard IVIG treatment, corticosteroid combination treatment was found to reduce risk for development of coronary artery abnormalities by an estimated 47% (95% CI, 33%–59%) and nonresponsive treatment by 35% (95% CI, 25%–44%) in patients at high risk for Kawasaki disease.

What Are the Clinical Implications?

- For patients with Kawasaki disease who may be at high risk for intravenous immunoglobulin treatment nonresponse, pediatricians may consider the use of primary corticosteroid treatment in combination with intravenous immunoglobulin to reduce the risk of coronary artery abnormalities.

Nonstandard Abbreviations and Acronyms

CAA	coronary artery abnormality
IVIG	intravenous immunoglobulin
KD	Kawasaki disease

in a single infusion at a dosage of 2 g/kg—is used as a conventional standard treatment and has substantially reduced the risk of CAAs.^{1–3,6–8} An estimated 17% of patients with KD consistently fail to respond to initial IVIG treatment, increasing their risk of cardiac complications.^{2,9–12} Several scoring systems have been developed to identify high-risk patients who exhibit characteristics predictive of nonresponse to IVIG treatment.^{13–19}

Recently, clinical trials in Japan demonstrated that the use of corticosteroids in combination with the standard treatment was more effective in preventing development of CAAs among patients with predicted high-risk for nonresponse to initial standard treatment.^{20–23} In addition, several meta-analyses supported the efficacy of the combination

treatment in which corticosteroids may be administered either as a short-term, high-dose pulse treatment or as lower dosages spread over many days.^{24–26} Nevertheless, skepticism for the efficacy still remains because the studies included in these reviews used varying methodology and had small and restricted samples.²⁷ Moreover, some trials conducted in the United States have not supported therapeutic superiority of combination treatment in terms of prevention of CAAs.^{28,29}

To address the different conclusions from previous studies, we evaluated the effectiveness of corticosteroid combination treatment using an epidemiological data set obtained from nationwide surveys in Japan. The survey data include a large number of patients with KD and has the advantage of including a large number of hospitals across Japan.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Setting and Participants

We conducted a retrospective cohort study using data derived from the 21st and 24th nationwide KD surveys in Japan to compare the effectiveness of standard treatment (IVIG 2 g/kg given as a single infusion together with aspirin) and corticosteroid combination treatment (corticosteroids added to the standard treatment) in preventing CAAs in patients with KD with predicted high risk for nonresponse to initial standard treatment. In the surveys, corticosteroid use was reported as pulse treatment or low dose with prolonged administration that in the present study we refer to as “multiple-dose” corticosteroid treatment.

Data were collected on patients with KD diagnosed during January 1, 2009, to December 31, 2010, in survey 21⁹ and patients diagnosed during January 1, 2015, to December 31, 2016, in survey 24.¹² The nationwide Japanese KD survey has been conducted every 2 years since 1970, collecting information on patients with KD diagnosed during the preceding 2 years; an overview of each survey has been published previously.^{9–12} In general, survey questionnaires were sent to 2 types of medical facilities throughout Japan: (1) hospitals specializing in pediatrics and (2) hospitals with ≥100 beds and a pediatric department. During the years covered by survey 21, combination treatment use was extremely rare, whereas survey 24 covered the most recent years in which combination treatment was commonly used.^{9,12}

Inclusion Criteria

Only patients <18 years of age who met the Japanese KD definition for complete KD were included in the analysis.³⁰ Patients with complete KD were defined as patients having ≥ 5 of the following 6 principal symptoms: (1) fever persisting 5 days or more inclusive of patients in whom fever subsided before the fifth day in response to treatment; (2) bilateral conjunctival injection; (3) changes in lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa; (4) polymorphous skin rash; (5) changes in peripheral extremities: reddening of palms and soles and indurative edema in initial stage, membranous desquamation from fingertips in convalescent stage; and (6) acute nonpurulent cervical lymphadenopathy. Patients who did not receive IVIG, received IVIG ≥ 10 days from disease onset, or received

IVIG regimens other than 2 g/kg single infusion were excluded from the analysis as well as patients who were listed as responding to the initial treatment but were administered secondary treatment.

Matching and Rematching

Combination treatment was typically given to patients with KD predicted to be at high risk for standard treatment failure.^{13–15,18,21,22} We defined high-risk patients as those predicted to fail initial standard treatment based on several Japanese scoring systems, although detailed information on each specific scoring system was not available.^{13–15} A direct comparison of patients who received combination and standard treatment would have resulted in substantial confounding because of greater initial disease severity among patients receiving

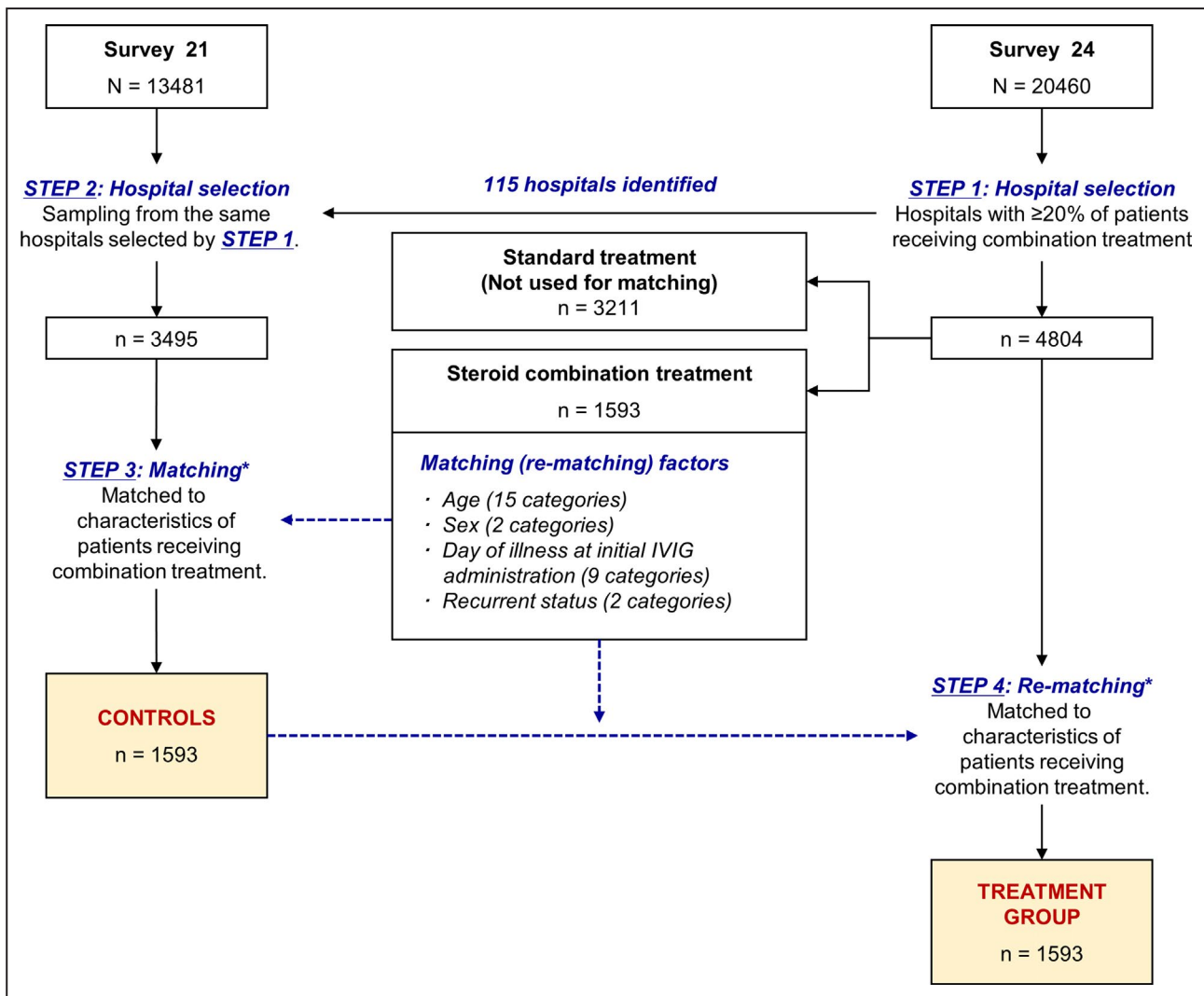


Figure 1. Flow chart for selection of patients with Kawasaki disease for the treatment group and controls.

*Separate iterations were performed for matching and rematching steps, resulting in 1000 unique sets of 1593 patients each in the treatment group and controls. IVIG indicates intravenous immunoglobulin.

combination treatment. To minimize this bias, the study was designed to compare patients receiving combination treatment in survey 24 to similar patients in survey 21. We incorporated a 4-step procedure for selecting patients from survey 21 to make sure that they were similar to those receiving combination treatment in survey 24 (Figure 1).

First, we restricted patient selection to those treated in high combination treatment use hospitals, which we defined as hospitals that (1) treated at least 10 patients with KD in survey 24, (2) administered combination treatment to $\geq 20\%$ of patients, and (3) had also treated patients with KD in survey 21 (Figure 1: step 1). Patients from survey 21 were selected from the same hospitals as survey 24 (step 2). We then identified all patients with KD who had received combination treatment in survey 24 and matched them (1:1 with replacement)

to patients with KD in survey 21 by the categories of age, sex, recurrence status, and day of illness at first IVIG administration (step 3). This matched group is similar to the patients with KD who received combination treatment in survey 24 and served as study controls. However, because the matching variables were not ideal proxies for KD severity, the matching done in step 3 can still produce patients in survey 21 who may not be representative of patients at high risk for KD. To correct this imbalance, we rematched patients who were produced from survey 21 in step 3 to patients with KD from survey 24 using the same matching variables (step 4). In this step, all patients with KD from the identified hospitals in survey 24 had the potential to be selected regardless of receipt of combination treatment. This rematched group was identified as the “treatment group.”

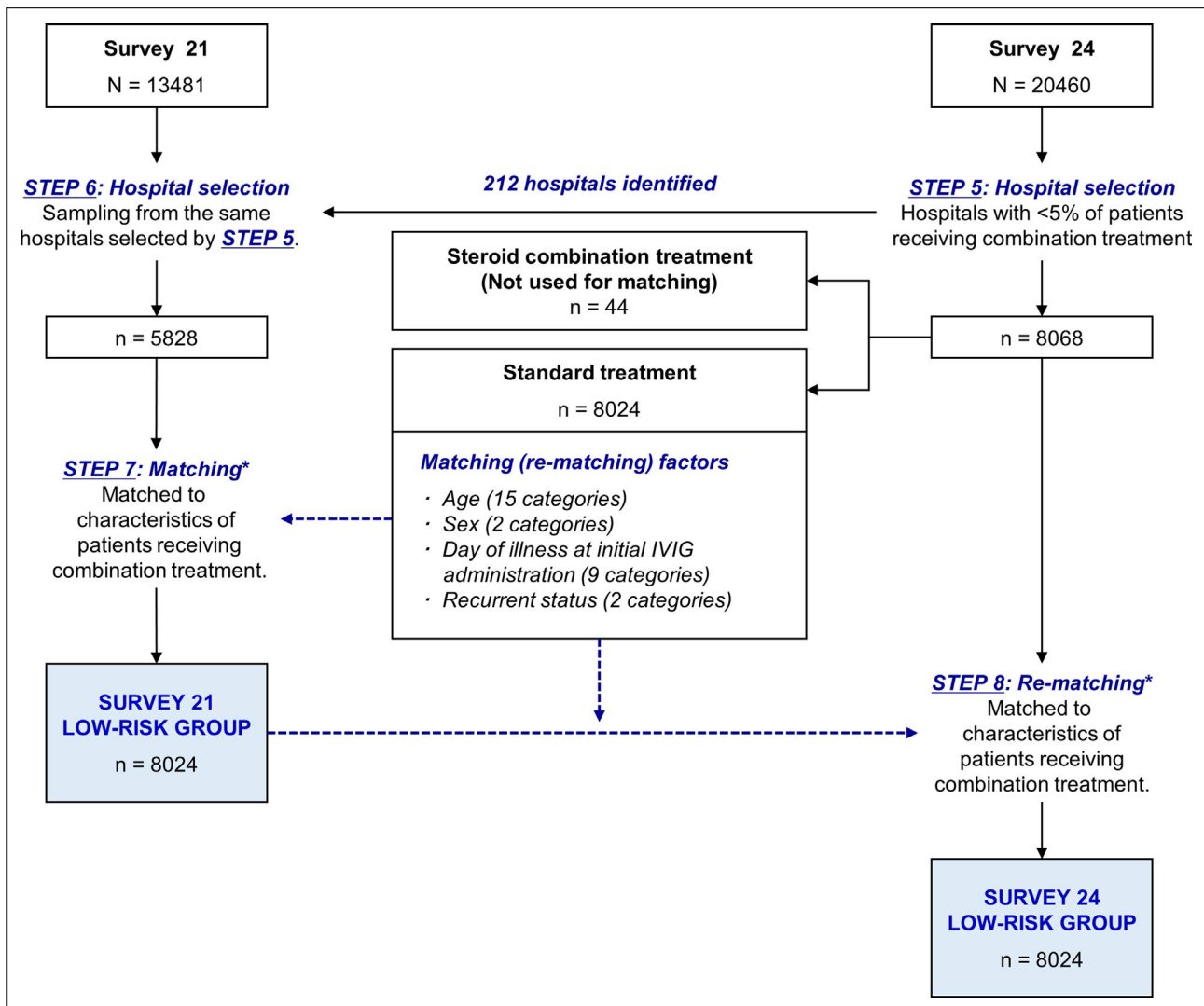


Figure 2. Flow chart for selection of patients with Kawasaki disease for low-risk groups from surveys 24 and 21.

*Separate iterations were performed for matching and re-matching steps, resulting in 1000 unique sets of 8024 patients each in the low-risk group from survey 24 and 21. IVIG indicates intravenous immunoglobulin.

Controlling for Potential Unmeasured Survey Differences

Because the treatment group and the controls are from surveys conducted in different time periods, additional unmeasured factors could affect the risk of CAAs. To control for these potential confounders, we performed a secondary analysis that included 2 additional groups matched to patients who did not receive combination treatment (Figure 2). Using the same steps 1 to 4 shown in Figure 1, we selected patients treated in low combination treatment use hospitals, which we defined as hospitals that (1) treated at least 10 patients with KD in survey 24, (2) administered combination treatment to <5% of patients, and (3) had also treated patients with KD in survey 21 (Figure 2: step 5). Patients from survey 21 were selected from the same hospitals as survey 24 (step 6). We identified all patients with KD in survey 24 who did not receive combination treatment and selected survey 21 patients matched by age, sex, recurrence status, and day of illness at first IVIG administration to create a survey 21 low-risk group (step 7). Rematching with the same variables to survey 24 patients, we produced a survey 24 low-risk group (step 8).

Statistical Analysis and Outcome Measures

In summary, we categorized patients into the following 4 different groups: (1) the treatment group from survey 24, (2) controls from survey 21, (3) survey 24 low-risk group, and (4) survey 21 low-risk group. The treatment group and controls are expected to be similar except for the treatment group largely receiving combination treatment. The comparison between these groups is intended to assess the effect of combination treatment compared with standard treatment, although there still may be unmeasured confounding attributed to the patients being from different time periods. The survey 24 and 21 low-risk groups are expected to be similar except that 1 group was selected from survey 24 and another from survey 21. The comparison between these groups would highlight any unmeasured temporal confounding. The inclusion of all 4 groups concurrently in statistical analyses was performed to isolate the effect of combination treatment while controlling for any potential confounding.

Categories used in matching and rematching were as follows: age (15 categories), sex (2 categories), recurrence status (2 categories), and day of illness at first IVIG administration (9 categories: 1–9 days of illness), which comprised a total of 540 possible matching categories. To avoid any sampling variation arising from the matching and rematching processes,

we conducted the selection and subsequent analysis 1000 separate times. For each of the 1000 iterations, we counted the number and proportion of CAAs in the treatment group and controls and reran logistic regression 1000 times to generate regression coefficients (bootstrapping). In the primary analysis, we calculated the median of these values to determine the point estimate of the effects of combination treatment. In the secondary analysis, we estimated the effect of combination treatment while adjusting for any differences between surveys as well as the difference between the low-risk and the high-risk groups. The 2.5th and 97.5th percentiles were used to express 95% CIs.

Outcome measures were (1) all CAAs, including coronary artery aneurysms and dilatations, identified based on the definition from the Japanese Ministry of Health³¹ and (2) initial treatment failure. Coronary artery dilatation was defined as a maximum absolute internal lumen diameter of ≥ 3 mm with any finding of local dilatation in children <5 years of age or a diameter of ≥ 4 mm in children ≥ 5 years of age. Coronary artery aneurysm was defined as lumen size of 4 to 8 mm or ≥ 1.5 times greater than that of an adjacent segment and giant coronary artery aneurysm as lumen size ≥ 8 mm. Multiple types of CAAs could be detected in the same patient (eg, coronary artery aneurysms with dilatations). Initial treatment failure was defined as those who developed recurrent or persistent fever ($\geq 37.5^\circ\text{C}$) at least 24 hours after the end of their initial IVIG administration. Statistical analyses were performed using R version 3.5.2 (The R Foundation for Statistical Computing). The Jichi Medical University Clinical Research Ethics Committee approved the study and waived the requirement for informed consent (receipt identification: 18-070).

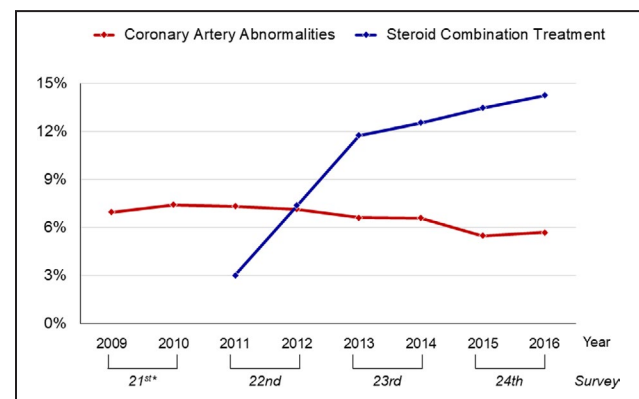


Figure 3. Temporal trends in proportion of coronary artery abnormalities and corticosteroid combination treatment.

*Information on combination treatment was unavailable for survey 21.

Table 1. Characteristics of Patients With Kawasaki Disease Identified in Surveys 21 and 24

Characteristic	Survey 21		Survey 24	
	Total, N (%)	Total, N (%)	Treatments,* N (%)	
			Standard	Combination
	N=13 481	N=20 460	n=17 825	n=2635
Sex				
Male	7669 (56.9)	11 685 (57.1)	10 162 (57.0)	1523 (57.8)
Female	5812 (43.1)	8775 (42.9)	7663 (43.0)	1112 (42.2)
Age, median (IQR), mo	25 (13–43)	27 (15–45)	26 (14–44)	33 (18–51)
Age groups				
≤1 y	6328 (46.9)	9047 (44.2)	8183 (45.9)	864 (32.8)
2–4 y	5616 (41.7)	8863 (43.3)	7529 (42.2)	1334 (50.6)
5–7 y	1327 (9.8)	2068 (10.1)	1722 (9.7)	346 (13.1)
8–17 y	210 (1.6)	482 (2.4)	391 (2.2)	91 (3.5)
Day of illness at initial treatment, median (IQR), d				
1–3 d	1041 (7.7)	2101 (10.3)	1660 (9.3)	441 (16.7)
4–6 d	10 989 (81.5)	16 373 (80.0)	14 299 (80.2)	2074 (78.7)
7–9 d	1451 (10.8)	1986 (9.7)	1866 (10.5)	120 (4.6)
Recurrence status	491 (3.6)	832 (4.1)	663 (3.7)	169 (6.4)
Corticosteroid use				
Multiple-dose treatment	NA	2298 (11.2)	NA	2298 (87.3)
Pulse treatment	NA	335 (1.6)	NA	335 (12.7)
Coronary artery abnormalities				
Total†	959 (7.1)	1114 (5.4)	923 (5.2)	191 (7.2)
Dilatations	850 (6.3)	997 (4.9)	846 (4.7)	151 (5.7)
Aneurysms	161 (1.2)	166 (0.8)	108 (0.6)	58 (2.2)
Treatment failure	2509 (18.6)	3918 (19.1)	3311 (18.6)	607 (23.0)

IQR indicates interquartile range; and NA, not applicable.

*Standard treatment is defined as intravenous immunoglobulin 2 g/kg given as a single infusion, together with aspirin. Combination treatment is defined as concurrent corticosteroids added to standard treatment.

†Some patients had both coronary artery aneurysm and dilatation.

RESULTS

A total of 13 481 and 20 460 eligible patients with KD were identified in surveys 21 (2009–2010) and 24 (2015–2016), respectively. An increasing trend in the use of combination treatment and declining trend in CAAs were observed in Japan from 2009 to 2016 (Figure 3). The demographic characteristics, recurrence status, and frequency of IVIG use were similar among patients in surveys 21 and 24 (Table 1). CAAs occurred in 7.1% of patients in survey 21 and 5.4% in survey 24, whereas treatment failure slightly increased from 18.6% in survey 21 to 19.1% in survey 24. In survey 24, 2635 (12.9%) of the 20 460 patients received combination treatment; 2298 (87.3%) of those patients received multiple-dose corticosteroid treatment as opposed to pulse treatment.

From survey 24, 115 hospitals that met the criteria for a high-combination treatment use hospital were identified (Figure 1). These hospitals treated a median of 25 patients with KD in survey 21 (range, 1–108) and a median

of 34 patients in survey 24 (range, 10–140), and the median percent of patients receiving combination treatment in survey 24 was 32% (range, 20%–73%). From these hospitals, after applying the selection criteria and the matching and rematching steps described in Figure 1, 1593 patients with KD in the treatment group and 1593 controls were selected for each of the 1000 sample iterations. For the 1000 iterations, a median of 705 (44.3%) of the 1593 patients in the treatment group received combination treatment (95% CI, 670–741 [42.1%–46.5%]).

A significantly lower proportion of patients with KD in the treatment group were reported to have CAAs compared with the controls (Table 2). The median number of patients who developed CAAs among the treatment group and controls were 74 (4.6%) (95% CI, 60–92 [3.8%–5.8%]) and 140 (8.8%) (95% CI, 120–160 [7.5%–10.0%]), respectively. The median risk ratio in the regression analysis of 1000 samples comparing the risk of CAAs between treatment group and controls was 0.53 (95% CI, 0.41–0.67), indicating that

Table 2. The Risk of Coronary Artery Abnormalities and Treatment Failure Among Patients With Kawasaki Disease in the Treatment Group and Controls Assessed Over 1000 Sampling Iterations*

Outcome	Treatment Group	Controls	Risk Ratio (95% CI)
	Survey 24; n=1593	Survey 21; n=1593	
Coronary artery abnormalities			
Total†			0.53 (0.41–0.67)
Median (%)	74 (4.6)	140 (8.8)	
95% CIs	60–92 (3.8–5.8)	120–160 (7.5–10.0)	
Dilatations			
Median (%)	64 (4.0)	125 (7.8)	
95% CIs	51–80 (3.2–5.0)	107–142 (6.7–8.9)	
Aneurysms			
Median (%)	12 (0.8)	21 (1.3)	
95% CIs	6–19 (0.4–1.2)	13–30 (0.8–1.9)	
Treatment failure			
Median (%)	225 (14.1)	345 (21.7)	0.65 (0.56–0.75)
95% CIs	198–253 (12.4–15.9)	315–373 (19.8–23.4)	

*The analysis was performed 1000 separate times, and the median values with the percentages are provided along with the 95% CIs. Not all patients in the treatment group received corticosteroid combination treatment.

†Some patients had both coronary artery aneurysm and dilatation.

combination treatment reduced the risk of CAAs by an estimated 47%. Similarly, a significantly lower proportion of patients with KD in the treatment group were reported to have treatment failure compared with controls (Table 2). A median of 225 (14.1%) (95% CI, 198–253 [12.4%–15.9%]) of the patients in the treatment group and 345 (21.7%) (95% CI, 315–373 [19.8%–23.4%]) in the controls had treatment failure. The median risk ratio comparing the risk of treatment

failure between treatment group and controls was 0.65 (95% CI, 0.56–0.75).

Table 3 shows the risk of CAAs and treatment failure among patients in low-risk groups from surveys 21 and 24. Among the identified 212 hospitals that met the criteria for a low-combination treatment use hospital, a median of 42 (0.5%) of the 8024 patients in the survey 24 low-risk group received combination treatment (95% CI, 30–55 [0.4%–0.7%]). The median risk

Table 3. The Risk of Coronary Artery Abnormalities and Treatment Failure Among Patients With Kawasaki Disease in Low-Risk Groups From Surveys 21 and 24 Assessed Over 1000 Sampling Iterations*

Outcome	Survey 24 Low-Risk Group	Survey 21 Low-Risk Group	Risk Ratio (95% CI)
	n=8024	n=8024	
Coronary artery abnormalities			
Total†			0.98 (0.88–1.11)
Median (%)	480 (6.0)	491 (6.1)	
95% CIs	442–521 (5.5–6.5)	453–531 (5.6–6.6)	
Dilatations			
Median (%)	441 (5.5)	438 (5.5)	
95% CIs	405–481 (5.0–6.0)	401–475 (5.0–5.9)	
Aneurysms			
Median (%)	52 (0.6)	72 (0.9)	
95% CIs	39–66 (0.5–0.8)	56–88 (0.7–1.1)	
Treatment failure			
Median (%)	1771 (22.1)	1638 (20.4)	1.08 (1.02–1.15)
95% CIs	1704–1844 (21.2–23.0)	1571–1705 (19.6–21.2)	

*The analysis was performed 1000 separate times, and the median values with the percentages are provided along with the 95% CIs.

†Some patients had both coronary artery aneurysm and dilatation.

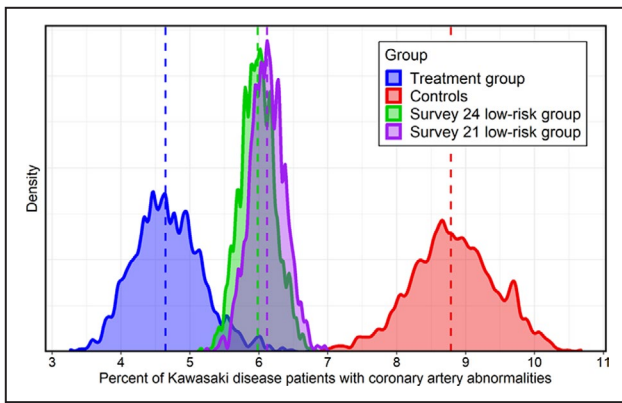


Figure 4. Risk of coronary artery abnormalities among patients with Kawasaki disease assessed over 1000 sampling iterations.

Dashed lines represent median values for each group.

ratio comparing the risk of CAAs between the survey 24 and survey 21 low-risk groups was 0.98 (95% CI, 0.88–1.11), whereas the median risk ratio comparing the risk of treatment failure between the survey 24 and survey 21 low-risk groups was 1.08 (95% CI, 1.02–1.15). The secondary analyses that controlled for potential unmeasured confounding did not substantially change the estimated effect of combination treatment on CAAs and treatment failure.

Figure 4 shows the distribution of CAA risks from all 1000 matching iterations in the treatment group, controls, and low-risk groups from surveys 21 and 24. Risk of CAAs was consistently low in the treatment group compared with the controls as well as low-risk groups. No significant difference in CAA risk was found between the low-risk groups that have not received combination treatment from surveys 21 and 24. This indicates that the substantially lower CAA risk for the treatment group compared with the controls was almost entirely attributed to the use of combination treatment. The risk for CAAs was lower in the treatment group than either

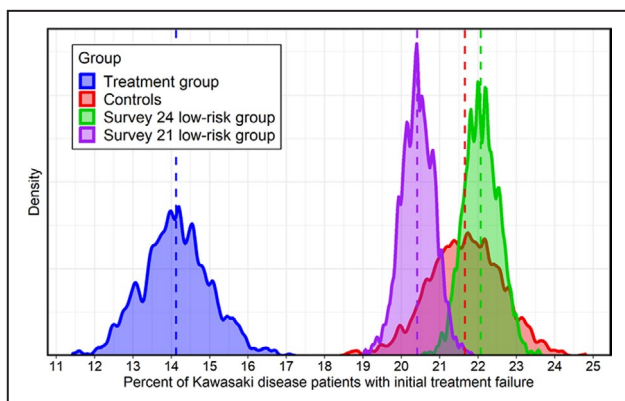


Figure 5. Risk of treatment failure among patients with Kawasaki disease assessed over 1000 sampling iterations.

Dashed lines represent median values for each group.

of the low-risk groups, highlighting the substantial protective impact of combination treatment.

The treatment group also had lower risk of treatment failure compared with all other groups (Figure 5). Risk of treatment failure increased slightly between survey 21 and survey 24 for the low-risk groups, suggesting that the observed decrease in treatment failure for the treatment group compared with the controls may be an underestimate of the true effect of combination treatment.

DISCUSSION

The findings of our study suggest that the use of corticosteroids in combination with initial standard treatment may be effective in reducing CAAs in Japanese patients with KD with high predicted risk of treatment failure. During the study period, combination treatment reduced CAAs among high-risk Japanese patients with KD by an estimated 47% (95% CI, 33%–59%). In addition, combination treatment had a significant impact on initial treatment failure, reducing the need to administer secondary treatment by an estimated 35% (95% CI, 25%–44%). In addition, after controlling for any unmeasured confounding attributed to differences between surveys 21 and 24, our results provided evidence that the improved outcomes among the treatment group are primarily attributable to corticosteroid combination treatment.

More than 87% of the patients with KD in our study who received combination treatment were treated with multiple-dose corticosteroids. The RAISE study,²¹ a prospective randomized controlled trial conducted in Japan, evaluated the use of multiple-dose corticosteroids and showed 87% reduction in CAAs among the group treated with corticosteroids compared with patients receiving standard treatment. Similarly, the Gunma University multicenter randomized trial from Japan found an 80% reduction in CAAs for patients receiving combination corticosteroid treatment.²⁰ Conversely, Newburger et al²⁹ conducted a randomized trial across 8 North American medical facilities and found no significant difference in CAA risk for patients receiving combination treatment. Another smaller randomized trial from the United States also failed to find a substantial effect of combination treatment on coronary Z scores.^{28,32} Notably, the 2 Japanese studies that showed a considerable protective effect of combination treatment assessed low-dose corticosteroid treatment administered over many days,^{20,21} whereas the 2 American studies, which showed no effect, used corticosteroid pulse treatment given within a single 3-hour period.^{28,29} Not all studies arrived at the same conclusions. Ogata et al²² reported a protective effect of initial pulse corticosteroid treatment, whereas a prospective nonrandomized multicenter cohort study (the

Post-RAISE study)²³ showed no significant protection against CAAs in patients receiving multiple-dose corticosteroids. A meta-analysis found evidence of a strong protective effect for multiple-dose, but not for pulse, corticosteroid treatment. We identified a substantial protective effect in a large population-based study predominately using multiple-dose combination treatment. Our findings suggest that supplementing standard treatment with multiple-dose corticosteroids may result in a substantial reduction in the risk of CAAs in selected patients with KD at risk of IVIG failure.

The Japanese nationwide KD surveys are a reliable source of data. Patients in Japan suspected to have KD are commonly referred to hospitals with pediatricians who have expertise with the disease. The KD surveys have been conducted in a consistent manner since 1970 with high response rates, allowing for robust comparability of epidemiological data over time.^{9–12} Compared with previous studies, including several meta-analyses,^{24–26} our study involved a large sample of patients with KD with data collected as part of a routine survey conducted throughout Japan. The primary analysis focused on 115 hospitals from across Japan involving patients routinely treated in a variety of healthcare settings. The large sample of hospitals minimizes potential bias that may be attributed to treatment practices of a single or few healthcare institutions. Careful selection of patients by matching and rematching using variables related to combination treatment use and CAAs greatly minimized any potential confounding.

One major limitation of our study is the lack of specificity about the type, dose, and duration of corticosteroid use. Initial corticosteroid treatment was recorded simply as either multiple-dose or pulse treatment. The RAISE study²¹ detailed a procedure in which 2 mg/kg per day of prednisolone was administered and slowly tapered down over 15 days, but the usage of this specific procedure among KD cases in this database is unknown. Future studies should explore the optimal dose and duration of corticosteroid treatment that would be beneficial as an adjunct to initial treatment in selected patients with KD at high risk of IVIG failure. Second, our results might underestimate the true prevalence of CAAs because information on Z scores was not available.³² Use of Z score criteria could result in increased detection of CAAs.³³ However, absence of Z score information is common to both surveys 21 and 24, and in a recent study using both Z score and Japanese criteria for CAAs, use of the different criteria did not substantially affect study findings, which showed no significant protection against CAAs.²³ Third, the assessment of echocardiogram findings was not standardized or centralized. The echocardiogram readers might have been influenced by the treatments patients received. Fourth, survey data did not capture adverse events potentially linked to corticosteroid use. Although meta-analyses^{24,25}

did not show an elevated risk of adverse events among recipients of corticosteroid combination treatment, the possibility of side effects cannot be ruled out.²³

Finally, corticosteroid combination treatment is typically administered in Japan to patients with KD determined to be at high risk for initial treatment failure based on several Japanese scoring systems.^{13–15,18} Although our analyses could minimize sampling bias as well as potential confounders, the original database did not include information on specific risk scores assessed by the systems. In addition, these scoring systems are less sensitive for patients with KD in other regions when compared with Japan.^{17,34,35} Our findings from a homogeneous Japanese population may not apply to patients in other countries. Different scoring systems have been developed in several countries to assess the risk of treatment failure.^{16–19}

CONCLUSIONS

Our study suggested a substantial protective effect of combination treatment with multiple-dose corticosteroids in a large sample of patients obtained from Japanese nationwide KD surveys. Significant reductions in CAAs and treatment failure were observed among groups of patients with KD with high usage of combination treatment. Our analyses provide evidence that combination treatment with multiple-dose corticosteroid may be effective in preventing CAAs for selected patients at high risk for KD.

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Disclosures

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