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Corticosteroids for the treatment of Kawasaki disease in children (Review)

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TABLE OF CONTENTS

[Intervention Review]

Corticosteroids for the treatment of Kawasaki disease in children

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ABSTRACT

Background

Kawasaki disease (KD), or mucocutaneous syndrome, is the leading cause of childhood-acquired heart disease in the developed world. There is much controversy on how best to treat children with KD and in particular who may benefit from additional treatment beyond the standard intravenous immunoglobulin (IVIG) and aspirin, such as the addition of corticosteroids.

Objectives

To assess the impact of corticosteroid use on the incidence of coronary artery abnormalities in KD as either first-line or second-line treatment. Corticosteroids may be given alone or in conjunction with other accepted KD treatments. Secondary objectives include the effect of steroids on mortality, the time taken for laboratory parameters to normalise, the duration of acute symptoms (such as fever), the long-term impact of steroid use and evaluating their safety in KD and their efficacy in relevant population subgroups.

Search methods

The Cochrane Vascular Information Specialist searched Cochrane Vascular's Specialised Register (25 November 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) in the Cochrane Library (searched 25 November 2016). Trial registries were also searched for details of ongoing or unpublished studies.

Selection criteria

We selected randomised trials involving children with all severities of KD who were treated with corticosteroids, including different types of corticosteroid and different durations of treatment.

Data collection and analysis

MJS and GMC independently selected studies, assessed evidence quality and extracted data. This process was overseen by AJW.

Main results

Seven trials consisting of 922 participants were included in this analysis. Trials ranged from 32 to 242 participants. On pooled analysis, corticosteroids reduced the subsequent occurrence of coronary artery abnormalities (odds ratio (OR) 0.29, 95% confidence interval (CI) 0.18 to 0.46; 907 participants; 7 studies; I^2 = 55%) without resultant serious adverse events (no events, 737 participants) and mortality (no events, 915 participants). In addition, corticosteroids reduced the duration of fever (mean difference (MD) −1.65 days, 95% CI −3.31 to 0.00; 210 participants; 2 studies; I^2 = 88%), time for laboratory parameters (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) to normalise (MD −2.80 days, 95% CI −4.38 to −1.22; 178 participants; 1 study) and length of hospital stay (MD −1.41 days, 95% CI −2.36 to

−0.46; 39 participants; 1 study). No studies detailed outcomes beyond 24 weeks. Subgroup analysis showed some potential groups that may benefit more than others; however, further randomised controlled trials are required before this can be the basis for clinical action.

Evidence quality was graded according to the GRADE system. Evidence was considered high quality for the incidence of serious adverse events, mortality and time for laboratory parameters to normalise. Evidence was considered moderate for the incidence of coronary artery abnormalities due to potential inconsistencies in data geography and patient benefits according to grouping. Evidence was moderate for duration of clinical symptoms (fever, rash) due to potential subjectivity in measurement. Evidence was moderate for length of hospital stay as only one study recorded this outcome. This means that we are reasonably confident that the true effect is close to that estimated in this work.

Authors' conclusions

Moderate-quality evidence shows that use of steroids in the acute phase of KD can be associated with improved coronary artery abnormalities, shorter duration of hospital stay and a decreased duration of clinical symptoms. High-quality evidence shows reduced inflammatory marker levels. There were insufficient data available regarding incidence of adverse effects attributable to steroids, mortality and long-term (> 1 year) coronary morbidity. Certain groups, including those based in Asia, those with higher risk scores, and those receiving longer steroid treatment may have greater benefit from steroid use, especially with decreasing rates of heart problems, but more tests are needed to answer these questions. Evidence presented in this study suggests that treatment with a long course of steroids should be considered for all children diagnosed with KD until further studies are performed.

PLAIN LANGUAGE SUMMARY

Using steroids to treat Kawasaki disease

Review question

We reviewed the use of a set of drugs known as steroids in children affected by Kawasaki disease for the reduction in the chance of future heart problems as well as the effect on the duration of fever, signs of infection in the blood and the number of days spent in hospital.

Background

We currently have a limited understanding of Kawasaki disease and how best to manage it. This is important as one of the long-term consequences can involve the heart, putting the child at higher risk of life-shortening outcomes.

Study characteristics

Evidence is current to November 2016. Male and female children diagnosed with Kawasaki disease were included in this review. We selected only randomised clinical trials. Trials compared the use of steroids against not using steroids. This review involves seven trials and 922 participants.

Key results

Steroids appear to reduce the risk of heart problems after Kawasaki disease without causing any important side effects. They also reduce the length of symptoms (fever and rash), length of hospital stay, and blood markers associated with being unwell. Certain groups, including those based in Asia, those with higher risk scores, and those receiving longer steroid treatment, may have greater benefit from steroid use, especially with decreasing rates of heart problems, but more tests are needed to answer these questions. More tests are also needed to obtain a more accurate marker of the risk of serious side effects and to determine if there is a lower chance of death when using steroids. Evidence presented in this review suggests that treatment with a long course of steroids should be considered for all children diagnosed with Kawasaki disease until further studies are performed.

Quality of the evidence

Evidence quality was graded according to the GRADE system. Evidence was considered high quality for serious adverse events, mortality and time for laboratory parameters to normalise. Evidence was considered moderate quality for the risk of future heart problems, duration of clinical symptoms (fever, rash) and length of hospital stay. This means that we are reasonably confident that the true effect is close to that estimated in this work.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table: Corticosteroids versus no corticosteroid use for treatment if Kawasaki disease in children

Corticosteroids versus no steroid use for the treatment of Kawasaki disease in children

Patient or population: children diagnosed with Kawasaki disease
Setting: hospital-based
Intervention: corticosteroids
Comparison: no corticosteroid use

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no corticosteroid use	Risk with corticosteroids				
Incidence of coronary artery abnormalities Duration: 2 to 6 weeks	Study population		OR 0.29 (0.18 to 0.46)	907 (7 RCTs)	⊕⊕⊕⊖ MODERATE[1, 2]	
	168 per 1000	56 per 1000 (35 to 85)				
	Moderate					
	114 per 1000	36 per 1000 (23 to 56)				
Incidence of serious adverse effects attributable to steroid use Duration: 2 to 6 weeks	Study population		not estimable	737 (6 RCTs)	⊕⊕⊕⊕ HIGH	No cases of adverse events attributable to steroids use are recorded by the included studies
	see comments					
Mortality (all-cause) Duration: 2 to 6 weeks	Study population		not estimable	915 (7 RCTs)	⊕⊕⊕⊕ HIGH	No deaths are recorded by the included studies
	see comments					
Duration of clinical symptoms: fever, rash (days) Duration: N/A	-	The mean duration of clinical symptoms (fever, rash) in the intervention group was 0.97 days fewer (1.2 fewer to 0.74 fewer)	-	210 (2 RCTs)	⊕⊕⊕⊖ MODERATE[3]	

Time for laboratory parameters to normalise: CRP, ESR (days) Duration: N/A	-	The mean time for laboratory parameters (CRP, ESR) to normalise in the intervention group was 2.8 days fewer (4.38 fewer to 1.22 fewer)	-	178 (1 RCT)	⊕⊕⊕⊕ HIGH	
Length of hospital stay (days) Duration: N/A	-	The mean length of hospital stay in the intervention group was 1.41 days fewer (2.36 fewer to 0.46 fewer)	-	39 (1 RCT)	⊕⊕⊕⊖ MODERATE[4]	
Longer-term (> 1 year post disease onset) coronary morbidity (non-aneurysmal) Duration: N/A	see comment		see comment	see comment	see comment	None of the included studies included data on outcomes (including coronary morbidity (non-aneurysmal) > 1 year after study enrolment

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **OR:** Odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Further investigation to reduce potential confounding required to explain inconsistencies in data (i.e. geographical variation), however overall effect unlikely to change (likely beneficial)
[2] Downgraded by one level: large group and effect size, however subgroup analysis suggests that those with low-risk scores or receiving single-dose treatment may not benefit
[3] Downgraded by one level: significant heterogeneity within the data, likely due to the subjective nature of the included outcome (i.e. rash)
[4] Downgraded by one level: length of hospital stay measured in one small study only (n = 39)

BACKGROUND

Description of the condition

Kawasaki disease (KD), or mucocutaneous syndrome, is the leading cause of childhood-acquired heart disease in the developed world (Kato 1996). Originally described by Kawasaki 1967, it is a medium vessel vasculitis of unclear aetiology that has been linked with an abnormal host response to an infectious trigger. Generally affecting children less than five years old, peak onset is between 18 and 24 months. The incidence in those aged under 5 years varies widely throughout the world, including 8.4 per 100,000 in the UK, 17.5 per 100,000 to 20.8 per 100,000 in the USA, and 239.6 per 100,000 in Japan (Gardner-Medwin 2002; Harnden 2002; Holman 2003; Nakamura 2012; Singh 2015). Rate of recurrence is approximately 3600 per 100,000, whilst acute mortality occurred in just one of the 23,730 cases Nakamura analysed in the 2009 to 2010 period (Nakamura 2012). Such varied epidemiology has strengthened theories linking KD with genetics and one or more infectious agents (Wood 2009).

KD is a multisystem vasculitis but its most important complication involves the predisposition for coronary artery vasculitis leading to aneurysms in up to 25% of untreated patients (Burns 1996). Such complications render the coronary vessels vulnerable to stenoses and thromboses, with subsequent risk of myocardial infarction and death (Daniels 2012). Furthermore, these thromboses act as focus for accelerated KD vasculopathy, increasing cardiovascular risk.

There is no diagnostic test for KD but laboratory findings typically show a raised white cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Diagnosis is generally based on clinical symptoms from one of two major sets of criteria. The Diagnostic Guidelines of the Japan KD Research Committee require any five from (1) fever longer than five days, (2) conjunctivitis, (3) lymphadenopathy, (4) polymorphous rash, (5) oral and perioral changes, and (6) changes in the extremities (Ayusawa 2005). The American Heart Association guidelines are similar, requiring a total of five of the aforementioned six but also stipulating that fever must feature (Newburger 2004). Diagnosis is complicated by these symptoms being prevalent in various common childhood viral exanthems. Symptoms may also occur sequentially rather than simultaneously. This variability leads to the idea of 'incomplete' KD, where KD is suspected but only three of five diagnostic criteria are satisfied.

Description of the intervention

It is thought that the prompt and effective treatment of KD can decrease the incidence of its cardiac sequelae. Accepted and proven initial pharmacological management involves intravenous immunoglobulin (IVIG) at a dose of 2 g/kg in a single 12-hour infusion alongside 30 to 50 mg/kg of aspirin in four divided doses (Eleftheriou 2013). This has been shown to limit the duration of the acute phase of KD as well as reduce the long-term coronary sequelae from 25% to 4.7% (Levin 1991). Both medications have already been subject to Cochrane Reviews (Baumer 2006; Oates-Whitehead 2003). Plasma exchange is also used in certain institutions (Hokosaki 2012).

Patients do not always respond to the above regimen. A subset of KD patients, approximately 20%, have clinical symptoms that are resistant to the first dose of IVIG and aspirin after 48 hours. This group has been proven to be at higher risk for cardiac sequelae (Brogan 2002). Various systems for identifying this group have been formulated, including the Kobayashi score; however, while specific, these have shown poor sensitivity in Western populations compared with the Japanese groups in which they were devised (Kobayashi 2008; Sleeper 2011). Currently accepted identifiers for this high-risk group include the following (Eleftheriou 2013).

1. Resistance to IVIG.
2. Very young age of onset (< 12 months).
3. Severe inflammatory markers.
4. Clinical features of shock.
5. Existing arterial aneurysms.
6. Kobayashi score greater than or equal to five.

These high-risk patients have a higher prevalence of coronary aneurysms, especially giant aneurysms (> 8 mm), and have associated greater long-term cardiovascular morbidity and mortality (Tatara 1987). Current consensus on management recommends a repeat dose of IVIG which facilitates disease defervescence in approximately half of the patients (Hashino 2001b). Measures to improve the success rate have been reviewed and the utility of intravenous steroids (IVS) with or without infliximab has shown mixed results. Current data on infliximab are insufficiently powered to draw conclusions (Davies 2013). IVS have long been used in vasculitides similar to KD; however, their use in KD has been subject to long-standing controversy due to earlier works showing a deleterious effect (Levin 2013). That stated, it is now widely believed that these studies were subject to significant selection bias, with only the most severe cases, bearing the greatest probability of a poor outcome, given steroids (Kato 1979).

There have been recent gains in knowledge regarding the use of corticosteroids in KD. The early use of steroids has been advocated, but only in high-risk patients (as defined above). This acknowledged, it remains unclear how best to use corticosteroids (Chen 2013). A recent editorial has highlighted some of the critical issues with current meta-analyses in this area (Levin 2013). Problems include varying inclusion criteria and populations, differing methodologies of included works and an overall lack of power with respect to data on side effects. It is not currently known which demographic groups show the greatest benefit with respect to coronary sequelae, or if there is the potential for complications with IVS treatment. Furthermore, the most effective types, frequencies and doses of steroid have not yet been clarified, nor whether steroids should be administered alongside IVIG, aspirin or infliximab (Levin 2013).

How the intervention might work

Steroid treatment is already utilised in a broad range of vasculitides to great effect. Furthermore, steroids were a key part of KD treatment prior to the advent of IVIG. Research into the exact pathological mechanisms is ongoing and current theories of KD pathogenesis implicate immunological responses to infectious agents (Eleftheriou 2013). Such reactions are thought to be controllable via steroid administration due to a reduction in inflammatory mediator transcription. In the context of KD, this may mean a reduction in fever as well as lower levels of inflammation, leading to a reduction in the formation of coronary abnormalities and subsequent incidence of future cardiovascular sequelae (Levin

2013). It therefore remains important to ascertain the utility of IVS in KD.

Why it is important to do this review

There is much controversy regarding how best to identify the high-risk patients who may benefit from additional treatment beyond the standard IVIG and aspirin. Furthermore, this situation is complicated by early reports of harmful effects of steroids in KD, although these conclusions are now considered to be the result of selection bias as only the sickest patients were investigated (Kato 1979). Current markers used to indicate resistance to IVIG include very young age of onset (< 12 months), high inflammatory markers, clinical features of shock, existing arterial aneurysms, or a Kobayashi score greater than or equal to five. The utility of corticosteroids in KD as a whole remains unclear despite several meta-analyses and we seek to use this work to clarify the situation through a more targeted approach to analysis. In addition, it is unclear how best to define the patients that may benefit from corticosteroids the most, for example whether ethnic origin, severity of KD or pre-steroid treatment status may help define the optimum population. It is hoped that the whole group and subgroup analyses of this work will cast greater light on this issue.

OBJECTIVES

To assess the impact of corticosteroid use on the incidence of coronary artery abnormalities in KD as either first-line or second-line treatment. Corticosteroids may be given alone or in conjunction with other accepted KD treatments. Secondary objectives assess the effect of steroids on mortality, the time taken for laboratory parameters to normalise, the duration of acute symptoms (such as fever), the long-term impact of steroid use and evaluating their safety in KD and their efficacy in relevant population subgroups.

METHODS

Criteria for considering studies for this review

Types of studies

We searched all randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation methods are not completely random, for example using alternation). Cross-over trials were not included as the response to steroid intervention may depend on timing and previous treatment state. We excluded all studies not conforming to the RCT format.

Types of participants

We included all children (less than 19 years old) diagnosed with KD worldwide in the analysis. The diagnosis of KD had to fulfil the Diagnostic Guidelines of the Japan KD Research Committee. This requires any five of the following (Ayusawa 2005).

1. Fever for more than five days, non-responsive to anti-pyrexial agents.
2. Conjunctivitis: bilateral bulbar, non-suppurative.
3. Lymphadenopathy: cervical, generally more than 1.5 cm.
4. Polymorphous exanthem, no crusts or vesicles.
5. Oral and perioral changes: strawberry tongue, cracked erythematous lips, diffuse oropharyngeal erythema.
6. Changes in the extremities, either acute (< 2 weeks): erythema and oedema of the palms and soles; or convalescent: desquamation at the fingertips.

An accepted exception to the above for a positive KD diagnosis exists if only four criteria are fulfilled but cardiac complications are found at echocardiography or angiography. We also accepted American Heart Association guideline definitions (Newburger 2004). These are similar, requiring a total of five of the above six, but stipulating that fever must feature. Therefore fulfilment of the American criteria automatically fulfils the Japanese criteria.

Corticosteroids could be part of the initial treatment for KD or form part of the second-line treatment after failure of first-line treatment that did not include steroids. The comparison group had to be in parallel. Cross–over trials were not eligible for inclusion.

Participants with positive blood cultures were excluded.

Types of interventions

All forms of corticosteroid therapy in conjunction with any combination of no treatment, placebo, immunoglobulin, aspirin or infliximab for the treatment of KD were considered the intervention of interest. That stated, the use of corticosteroids had to be the only difference in management between trial arms.

Comparator groups included any of:

1. placebo;
2. immunoglobulin only;
3. aspirin only;
4. immunoglobulin and aspirin;
5. infliximab only;
6. infliximab and immunoglobulin;
7. infliximab, immunoglobulin and aspirin.

Types of outcome measures

Primary outcomes

- The incidence of coronary artery abnormalities (measured via diameter or z-scores; Boston scores (de Zorzi 1998)) per study group found at either cardiac angiography or echocardiography within three months of KD diagnosis. Coronary abnormality was defined using either the de Zorzi criteria (a coronary dimension that is ≥ 2.5 standard deviations (SDs) above the mean for body surface area) (de Zorzi 1998); or the Japanese Ministry of Health criteria (Research Committee on Kawasaki Disease 1984), as follows.
  a. Lumen > 3 mm in children < 5 years old;
  b. Lumen > 4 mm in children > 5 years old;
  c. Internal diameter of a segment measuring ≥ 1.5 times that of an adjacent segment.
- The incidence of any serious adverse effects per study group that is attributable to the administration of steroids at any point after treatment initiation. Known side effects of steroids in other diseases include, for example, immunosuppression with resultant opportunistic infection and avascular necrosis of the femoral head.

Secondary outcomes

1. Mortality (all-cause).
2. Duration of clinical symptoms: fever and rash.
3. Time for laboratory parameters to normalise: CRP and ESR.
4. Length of hospital stay.
5. Longer-term (greater than one-year post-disease onset) coronary morbidity (non-aneurysmal).

Search methods for identification of studies

We included studies reported as full-text or published as abstract only.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials:

- The Cochrane Vascular Specialised Register (searched 25 November 2016);
- The Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) in the Cochrane Library (searched 25 November 2016).

See Appendix 1 for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trial registries for details of ongoing and unpublished studies;

- ClinicalTrials.gov (www.ClinicalTrials.gov).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).
- ISRCTN Register (www.isrctn.com/).

See Appendix 2 for details of the search strategies used.

Searching other resources

We contacted the authors of trials that met the eligibility criteria identified by the searches as ongoing or unpublished trials. We also searched reference lists of relevant trials for further publications.

Data collection and analysis

Selection of studies

Two review authors (MJS and GMC) independently applied the selection criteria to the studies identified by the search strategy. This included independently assessing whether the studies fulfilled the inclusion and exclusion criteria. If insufficient information was available to decide whether a study was truly eligible we contacted the study authors to request further information. A third review author (AJW) resolved disagreements.

Data extraction and management

Two review authors (MJS and GMC) independently extracted data using a modified version of the Cochrane Vascular standard data extraction form. These data were then brought together and monitored for discrepancies by a third review author (AJW), before being entered into Review Manager 5 software (RevMan 2014). We contacted study authors for any required information that was not included in the published works. The key information gathered in the data collection form included the following.

1. General study information: publication type.
2. Fulfilment of eligibility criteria: study type, interventions, outcomes measured and reasons for exclusion.
3. Study methods: allocations methods, study dates, duration, ethical approval and statistical methods.
4. Participants: methods of recruitment, consent, total number, treatment groups, age, sex, race, KD severity, subgroup analyses reported and eligibility criteria.
5. Intervention (steroids): number of participants, dosing, frequency, duration, delivery method, providers, compliance and concomitant treatment.
6. Outcomes: coronary diameters (acute), coronary diameter z-scores (acute), coronary abnormality (long term), duration of clinical symptoms (e.g. fever), adverse effects, duration of laboratory parameter abnormality (e.g. CRP) and duration of hospital stay.

Assessment of risk of bias in included studies

Risk of bias was assessed using the recommended Cochrane tool as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (MJS and GMC) performed this independently, and resolved any disagreements by discussion with a third review author (AJW). The domains assessed included:

1. sequence generation (selection bias);
2. allocation sequence concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);
7. other bias.

Measures of treatment effect

The effect measure of choice for dichotomous data was the odds ratio (OR) with a 95% confidence interval (CI). This is a ratio between the corticosteroid intervention group and its parallel comparator group.

We managed continuous data, including time-to-event data, using mean differences (MD) and 95% CIs. If necessary, we planned to use a standardised mean difference (SMD) for studies that measured the same outcome but used different methods.

Unit of analysis issues

The unit of analysis was each participant recruited into a trial.

Dealing with missing data

We accounted for all missing data due to dropouts via an intention-to-treat (ITT) analysis. We reported if the individual trials carried this out. If they did not then we have endeavoured to apply an ITT analysis. In the event that we have been unable to do this then we utilised a per protocol analysis. We have explained all post-allocation dropouts. We have followed up any data missing from the published document with the study's original authors. If data still remain absent then we have considered this in the 'Risk of bias' assessments.

Assessment of heterogeneity

We took heterogeneity into account using the I^2 statistic for quantification of variability (< 40% = likely low heterogeneity; 40% to 60% = possible moderate heterogeneity; > 60% = possible significant heterogeneity). We also used the Chi^2 test (limit = degrees of freedom) and P values (10% significance threshold). Where heterogeneity exceeded generally accepted limits (> 60% heterogeneity) we subgrouped the analysis in a logical manner to explain these differences and reduce remaining heterogeneity. These methods were reinforced by visual recognition on forest plots to assess for overlapping CIs.

Assessment of reporting biases

Had there been more than eight trials, we planned to screen for publication and reporting bias using funnel plot asymmetry and measure using tests as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For smaller studies, we took into account 'the small-study effect', where smaller studies can show larger treatment effects due to poor methodology, heterogeneity, selection bias, chance or artefact. We also tried to find eligible studies that have been registered and should have been completed, but are without available published data. It should be noted that the 'Risk of bias' assessment has taken into account selective outcome reporting.

Data synthesis

Statistical analysis took place using a fixed-effect model if there was low heterogeneity, and a random-effects model if there was significant heterogeneity (I^2 > 60%). We undertook outcome analyses using an ITT model. Two-sided P values less than or equal to 0.05 were considered significant and all analyses were undertaken using Review Manager 5 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses (data permitting) included:

1. type of steroid used;
2. steroid dosing;
3. steroid treatment frequency;
4. total steroid treatment duration;
5. steroid route of administration;
6. first-line versus second-line management;
7. geographical distribution of trial participants, ethnicity;
8. KD severity (non-high risk versus high risk as detailed earlier);
9. recognised concomitant treatments for KD (as detailed earlier in the text).

We also looked at employing further subgroup analyses if heterogeneity remained significant (I^2 > 60%). These subgroups were tested using a Chi^2 P value threshold of 0.05.

Sensitivity analysis

We planned to perform a sensitivity analysis to explore causes of heterogeneity and the robustness of the results if there were sufficient data available. We planned to include the following factors in the sensitivity analysis.

1. Type of study design (RCT versus quasi-RCT).
2. Low risk of bias trials versus high risk of bias trials.
3. Rates of dropouts for each treatment group.

Summary of findings

We presented the main findings of the review results concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the outcomes (Types of outcome measures) in a 'Summary of findings' table, according to the GRADE principles as described by Higgins 2011 and Atkins 2004. We used the GRADEpro (GRADEproGDT) software (www.guidelinedevelopment.org/) to assist in the preparation of the 'Summary of findings' table.

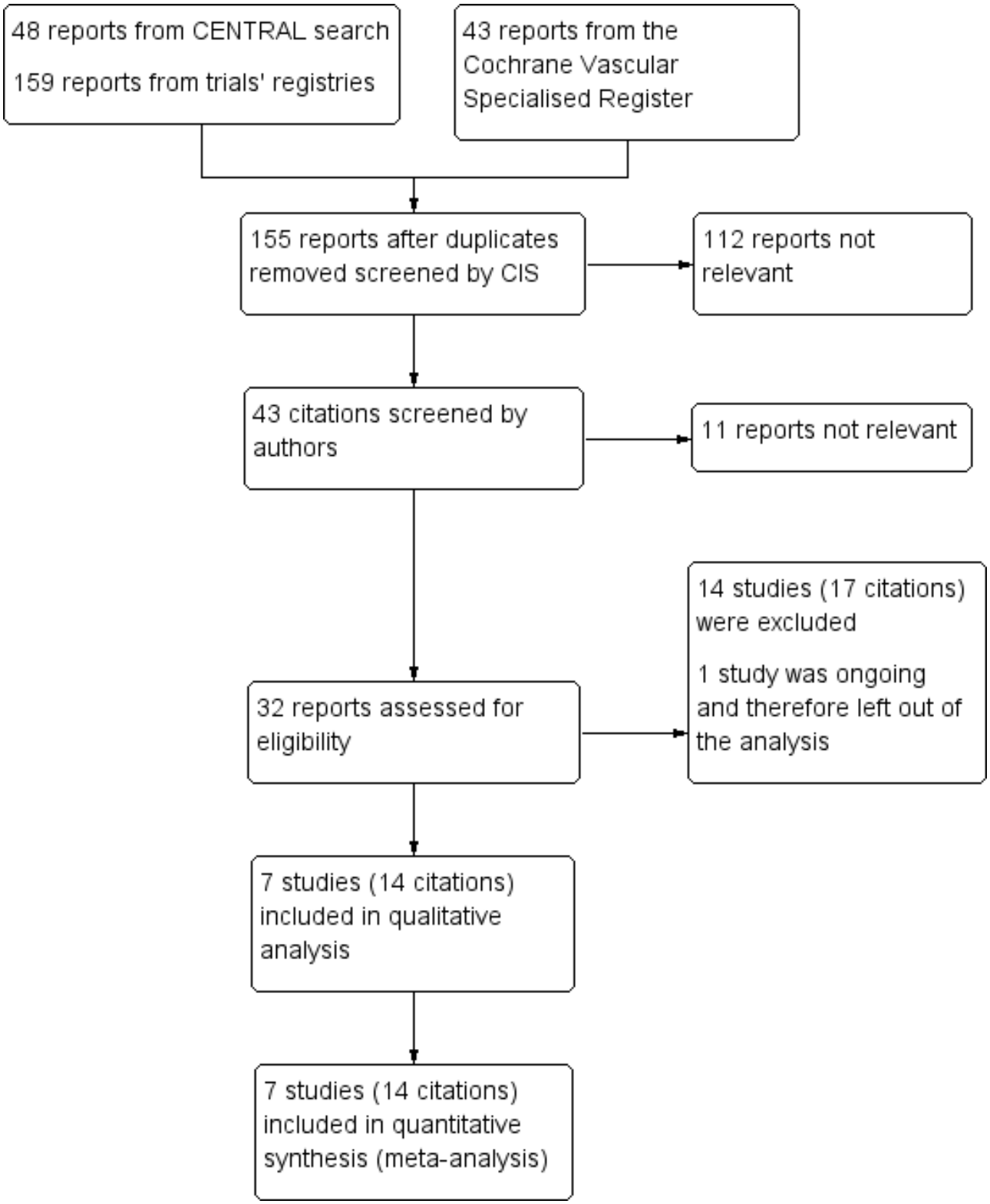
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

After applying the aforementioned inclusion and exclusion criteria, we identified seven trials (14 reports) suitable for inclusion within this review (Ikeda 2006; Inoue 2006; Kobayashi 2012; Newburger 2007; Ogata 2012; Okada 2003; Sundel 2003). This process is summarised in a flow diagram (Figure 1). Full-text publications

were obtained from the websites of the original source of publication. When studies had multiple publications, data were combined in order to give as complete an interpretation of available data as possible.

Two trials were conducted in North America (Newburger 2007; Sundel 2003); and five in Japan (Ikeda 2006; Inoue 2006; Kobayashi 2012; Ogata 2012; Okada 2003). Three trials were single centre (Ikeda 2006; Ogata 2012; Sundel 2003); and four trials were multicentre (Inoue 2006; Kobayashi 2012; Newburger 2007; Okada 2003).

The seven trials consisted of 922 participants and ranged from 32 to 242 participants. Three studies segmented high-risk participants using criteria as set out in Table 1 (Ikeda 2006; Kobayashi 2012; Ogata 2012).

Coronary artery abnormality was the primary outcome in four studies (Ikeda 2006; Inoue 2006; Kobayashi 2012; Newburger 2007). Duration of fever was the primary outcome in two studies (Ogata 2012; Sundel 2003). Cytokine levels was the primary outcome in one study (Okada 2003).

Further details including dosing and baseline characteristics can be found in Characteristics of included studies.

Excluded studies

See Characteristics of excluded studies.

Fourteen studies (17 reports) were excluded from the review (Asai 1985; Hashino 2001; ISRCTN74427627; Jibiki 2005; Kato 1979; Kusakawa 1983; Miura 2008; Nakamura 1985; Nonaka 1995; Ogata 2009; Sekine 2012; Seto 1983; Xu 2002; Yuan 2000).

Six studies did not assess the outcomes of this review (Jibiki 2005; Miura 2008; Nakamura 1985; Ogata 2009; Sekine 2012; Yuan 2000). Attempts were made to contact the study authors without success. For four studies, study outcome data were not available and again study authors were contacted without success (ISRCTN74427627; Kato 1979; Kusakawa 1983; Nonaka 1995). Hashino 2001 was excluded due to trial design affecting the comparability of results with the included works. Two studies combined steroids with an additional intervention meaning steroids were not the only differential factor between the trial arms (Asai 1985; Xu 2002).

One trial is ongoing and there are currently no suitable data available for review (JPRN-UMIN000009524).

Risk of bias in included studies

All included studies were assessed for bias as illustrated in Figure 2 and Figure 3 and Characteristics of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

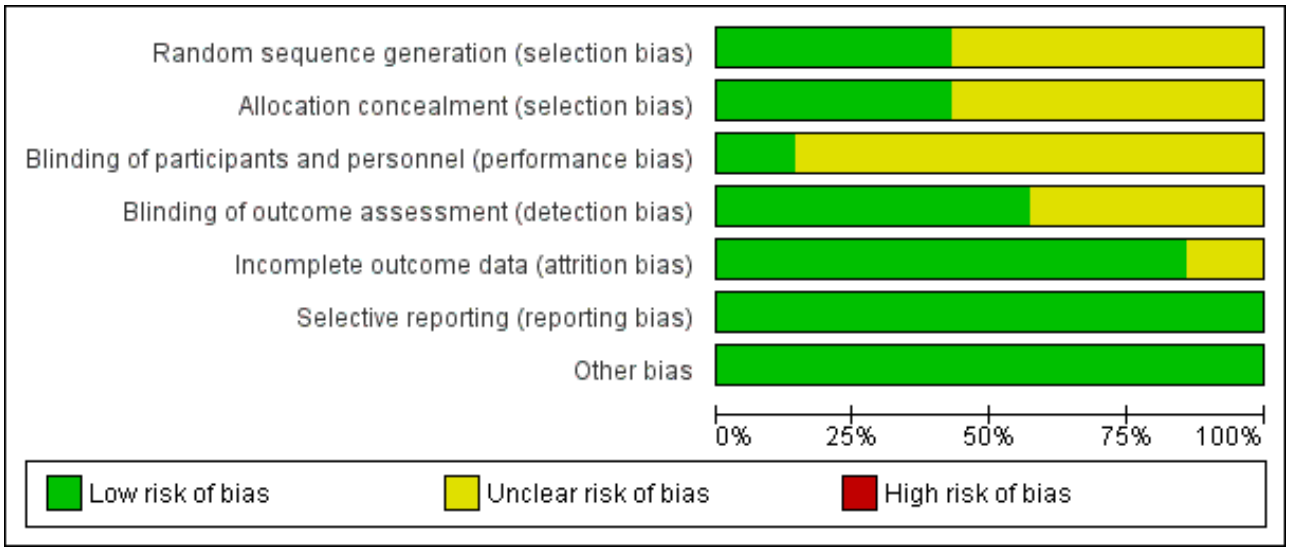
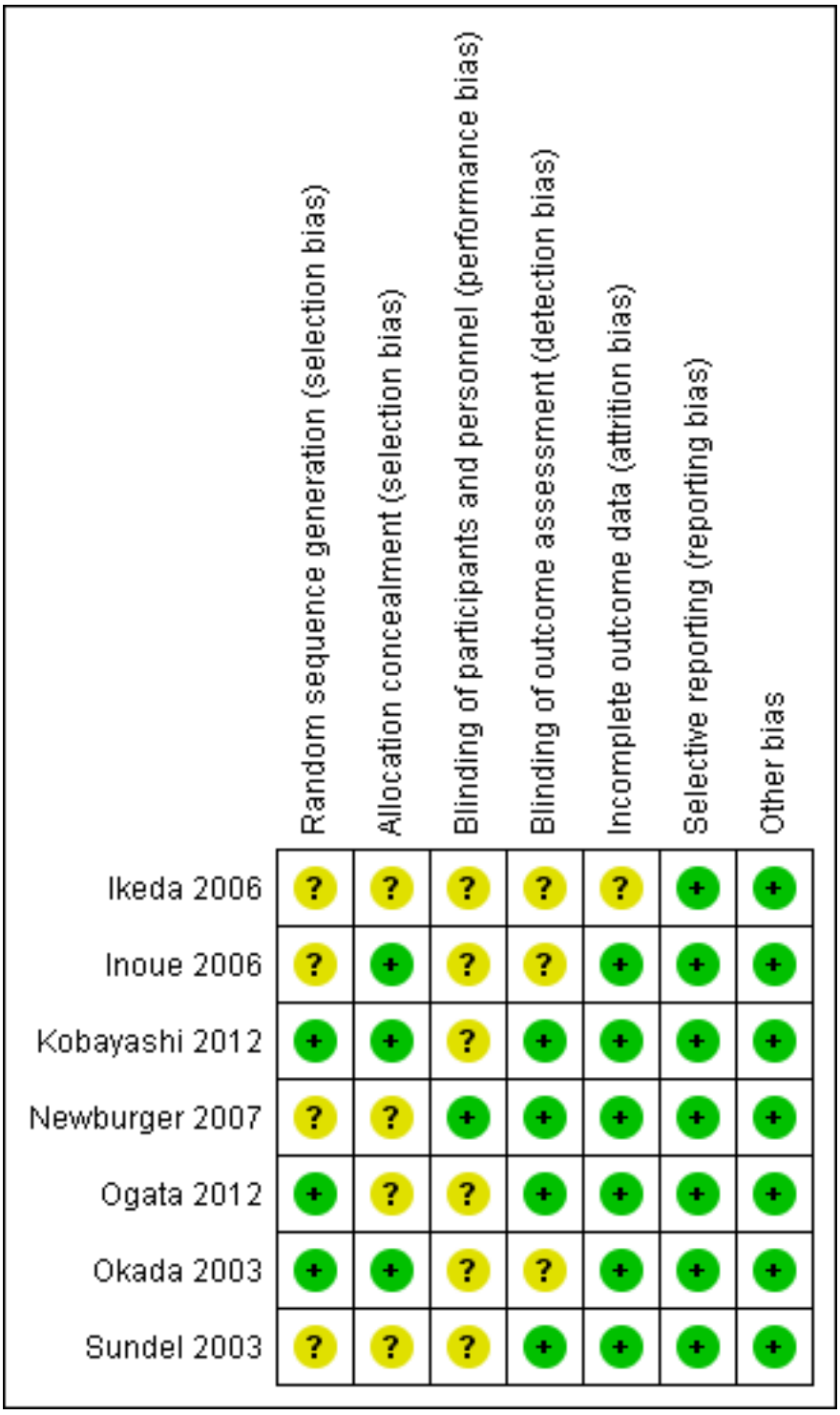


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All included studies are randomised controlled trials (Ikeda 2006; Inoue 2006; Kobayashi 2012; Newburger 2007; Ogata 2012; Okada 2003; Sundel 2003).

Random sequence generation

Three studies were deemed to be of low risk of bias from random sequence generation due to the use of recognised and accepted approaches to this step (e.g. use of computer generation) (Kobayashi 2012; Ogata 2012; Okada 2003). Four studies were deemed to be of unclear risk of bias because although the use of random allocation was stated, there was no detail regarding the

exact approach (Ikeda 2006; Inoue 2006; Newburger 2007; Sundel 2003).

Allocation concealment

Four studies were deemed of unclear bias for allocation concealment due to inadequate detail being published (Ikeda 2006; Newburger 2007; Ogata 2012; Sundel 2003). Three were regarded as low risk of allocation disclosure due to the use of centrally held databases (Inoue 2006; Kobayashi 2012; Ogata 2012).

Blinding

Five trials were non-blinded (Inoue 2006; Kobayashi 2012; Ogata 2012; Okada 2003; Sundel 2003); one trial was double blinded (Newburger 2007); and one trial did not state whether participants or investigators were blinded (Ikeda 2006). Therefore six studies were deemed at unclear risk of performance bias (Ikeda 2006; Inoue 2006; Kobayashi 2012; Ogata 2012; Okada 2003; Sundel 2003), and one study was deemed at low risk of performance bias (Newburger 2007).

Four studies had blinded outcome reporters and are coded as low risk of bias (Kobayashi 2012; Newburger 2007; Ogata 2012; Sundel 2003); one study had non-blinded outcome reporters (Inoue 2006); and two studies did not mention if outcome reporters were blinded and was therefore judged as 'unclear' for detection bias (Ikeda 2006; Okada 2003).

Incomplete outcome data

Intention-to-treat analysis was mentioned in two studies (Kobayashi 2012; Newburger 2007). Inoue 2006 reported key outcome variables as per protocol analysis with an intention-to-treat analysis also performed. Three further studies were able to account for all or most of the data (Ogata 2012; Okada 2003; Sundel 2003). These were all judged to be of low risk of bias. One study did not state how data were handled and was therefore coded as unclear risk of bias (Ikeda 2006).

All trials had a relatively short follow-up period, up to five weeks, so there was limited loss to follow-up, which is consistent throughout the studies. No study had a dropout rate exceeding 20%.

Selective reporting

The protocol for one study was published before initiation of the trial (Newburger 2007). The published methodology including outcome measures reported by the remainder of the trials was consistent with that reported in the respective results section (Ikeda 2006; Inoue 2006; Kobayashi 2012; Ogata 2012; Okada 2003; Sundel 2003). The risk of selective reporting bias for these studies has therefore been coded as low.

Other potential sources of bias

None noted.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table: Corticosteroids versus no corticosteroid use for treatment if Kawasaki disease in children

Primary outcomes

Incidence of coronary artery abnormality

Seven trials on 907 participants assessed incidence of coronary artery abnormality (Ikeda 2006; Inoue 2006; Kobayashi 2012; Newburger 2007; Ogata 2012; Okada 2003; Sundel 2003). The pooled data of steroid use versus no steroid use demonstrate an OR of 0.29 (95% CI 0.18 to 0.46, P < 0.00001) (Analysis 1.1). There was possible moderate heterogeneity of 55% and this was reduced in subgroup analysis (see below).

Incidence of serious adverse events attributable to steroid use

From six trials with 737 participants, no serious adverse events attributable to corticosteroid use were noted and the effects were deemed not estimable (Analysis 1.2) (Inoue 2006; Kobayashi 2012; Newburger 2007; Ogata 2012; Okada 2003; Sundel 2003). Ikeda 2006 did not disclose sufficient information for inclusion despite attempts to contact the authors.

Secondary outcomes

Mortality (all cause)

From the seven trials with 915 participants no deaths were recorded within the observed study period (Analysis 1.3) (Ikeda 2006; Inoue 2006; Kobayashi 2012; Newburger 2007; Ogata 2012; Okada 2003; Sundel 2003).

Duration of clinical symptoms: fever, rash

Two studies reported data on the duration of clinical symptoms (days), showing a significant reduction in time (MD −1.65 days, 95% CI −3.31 to 0.00; participants = 210; studies = 2; I^2 = 88%; P = 0.05) (Inoue 2006; Okada 2003). There was possible significant heterogeneity at 88% which was not explained by subgroup analysis for high- and low-risk scores (Analysis 4.2). In both studies a child was considered afebrile if their temperature was below 37.5 °C for more than 24 hours; Inoue 2006 measured axillary temperature and Okada 2003 simply measured "body temperature", but does not state the site. This may account for the heterogeneity as body temperature can vary depending on measurement site.

Time for laboratory parameters to normalise: CRP, ESR

One study involving 178 participants directly measured the time for laboratory parameters to normalise (Inoue 2006). Analysis showed a MD of −2.80 days (95% CI −4.38 to −1.22; P = 0.0005) in the steroid group versus the non-steroid group (Analysis 1.5).

Length of hospital stay

One study reported on the length of hospital stay with steroid use versus non-steroid use and demonstrated a reduction in days stayed in hospital (MD −1.41 days, 95% CI −2.36 to −0.46; participants = 39; P = 0.004) (Analysis 1.6) (Sundel 2003).

Longer-term (> 1 year post disease onset) coronary morbidity

None of the included studies included data on outcomes (including coronary morbidity (non-aneurysmal) more than 1 year after study enrolment.

Subgroup analysis

Planned subgroup analyses are listed below with comments on the ability for them to be performed.

1. Type of steroid used: this subgroup analysis was performed for the outcome coronary artery abnormalities in six of the included studies (Inoue 2006; Kobayashi 2012; Newburger 2007; Ogata 2012; Okada 2003; Sundel 2003), where the type and duration of steroid used was stated. When looking at the use of steroids as a single intravenous (IV) dose there was no evidence of effect with regards to coronary artery abnormalities (OR 0.56, 95% CI 0.29 to 1.08; participants = 277; studies = 3; I^2 = 36%) (Newburger 2007; Okada 2003; Sundel 2003). When this was followed with an oral course of steroids fewer coronary artery abnormalities were identified in the corticosteroid group (OR 0.13, 95% CI 0.05 to 0.32; participants = 452; studies = 3; I^2 = 0%) (Inoue 2006; Kobayashi 2012; Okada 2003). The P value for the test for subgroup differences is 0.009. Subgroupings explained the heterogeneity identified for the combined analysis (Analysis 2.1).
2. Steroid dosing: this subgroup analysis was not applicable as steroid dosing was broadly classed into one-off IV methylprednisolone, or a longer tapering course of prednisolone, and the subgroup analysis for this was performed in the subgroup analysis 1 above.
3. Steroid treatment frequency: this subgroup analysis was not applicable as steroid dosing was broadly classed into one-off IV methylprednisolone, or a longer tapering course of prednisolone, and the subgroup analysis for this was performed in the subgroup analysis 1 above.
4. Total steroid treatment duration: this subgroup analysis was not applicable as steroid dosing was broadly classed into one-off IV methylprednisolone, or a longer tapering course of prednisolone, and the subgroup analysis for this was performed in the subgroup analysis 1 above.
5. Steroid route of administration: this subgroup analysis was not applicable as steroid dosing was broadly classed into one-off IV methylprednisolone, or a longer tapering course of prednisolone. All steroids in the initial phase were given intravenously, and the subgroup analysis for this was performed in the subgroup analysis 1 above.
6. First-line versus second-line management: there were insufficient data to perform this subgroup analysis.
7. Geographical distribution of trial participants, ethnicity: this subgroup analysis found that the use of steroids appears to have an increased beneficial effect on coronary artery abnormalities in the studies conducted in Japan (Ikeda 2006; Inoue 2006; Kobayashi 2012; Ogata 2012; Okada 2003; OR 0.14, 95% CI 0.07 to 0.29, 678 participants) versus no evidence of benefit in North America (Newburger 2007; Sundel 2003; OR 0.77, 95% CI 0.37 to 1.59, 229 participants). The P value for test for subgroup differences is 0.001; however it is important to note that this analysis is vulnerable to confounding as most participants who received a one-off dose of steroid were from the North American cohorts (Analysis 3.1).
8. KD severity (non-high risk versus high risk as detailed earlier): on analysis of high-risk participants only there is strong evidence of effect (OR 0.13, 95% CI 0.06 to 0.29; participants = 377; studies = 3; I^2 = 0%) (Ikeda 2006; Kobayashi 2012; Ogata 2012). When looking at low-risk participants alone the benefit was weaker and potentially lost (OR 0.53, 95% CI 0.29 to 1.00; participants = 530; studies = 5; I^2 = 6%) (Ikeda 2006; Inoue 2006; Newburger 2007; Okada 2003; Sundel 2003). These groups proved to be significantly different (P = 0.007). In both subgroups heterogeneity was reduced to negligible levels (Analysis 4.1).
9. Recognised concomitant treatments for KD (as detailed earlier in the text): there were insufficient data to perform this subgroup analysis.

Sensitivity analysis and reporting bias

A sensitivity analysis was not required for this review as all studies were randomised controlled trials, no studies were found to have a significant risk of bias and dropout rates were not significantly different between studies.

As there were only seven trials included in this Cochrane Review, we have not screened for publication and reporting bias by assessing funnel plot asymmetry using tests as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

DISCUSSION

Summary of main results

Pooled data show that the use of steroids in the acute phase of KD in children can lead to reduced incidence of coronary artery aneurysms, duration of clinical symptoms (fever, rash), time for laboratory parameters to normalise (CRP, ESR) and length of hospital stay. There were insufficient data available regarding incidence of adverse effects attributable to steroids, mortality and long-term (> 1 year) coronary morbidity.

Subgroup analysis demonstrated that with respect to coronary abnormality:

- the greatest benefit was in children in Japan versus those in North America, but the use of different regimens may have contributed to the different outcomes in Japanese and American studies;
- the greatest benefit was in children with high-risk scores versus those with low-risk scores, although both display benefit;
- there is a benefit of steroids if taken over a prolonged course versus the potential for no benefit if steroids are given as a one-off dose.

However, potential confounding of the subgroup analyses must be noted here – those studies completed in North America are both considered part of the lower-risk group and employed single-dose regimens (Newburger 2007; Sundel 2003).

Subgroup analysis demonstrated that with respect to duration of clinical symptoms both groups with high- and low-risk scores benefit from steroid treatment, with the greatest benefit in those with high-risk scores although the numbers of studies and participants on which this is based are small.

Overall completeness and applicability of evidence

All studies in this review collected data on the stated primary outcomes of this review: coronary artery abnormalities and serious adverse events attributable to steroids use. All relevant participants, interventions and outcomes have been investigated. Overall, the evidence collected is highly applicable to this review. The evidence demonstrates that steroids have some benefit in the acute treatment of KD in the populations studied in this review.

That stated, further data looking at different ethnicity subgroups, disease risk scores, and duration of steroid use are required for a more complete guide. In particular, an investigation outside Japan employing risk stratification and IV steroid treatment followed by oral doses would be beneficial.

None of the studies demonstrated any serious adverse events during their follow-up periods due to the use of steroids.

Difficulties remain with the application of the results of this review to Western populations, where there is no comparable severity risk score. The identification of groups who might gain the greatest benefit from steroids will remain problematic until a reliable risk stratification score is developed for this group.

Overall the results of this review are applicable to the majority of children worldwide diagnosed with KD, and should serve as a guide to the treating clinician.

Quality of the evidence

See Summary of findings for the main comparison

All studies included in this meta-analysis were randomised trials, with variable incidence in the blinding of participants and outcome assessors. However, we do not believe the risks of bias identified in this work would affect the direction of the reported outcome variables. Trials reported data using a mixture of per protocol and intention-to-treat analyses. The overall quality of the current evidence can be considered moderate. This is represented by several inconsistencies in the different findings incorporated within this review.

We graded evidence quality according to the GRADE system. We considered evidence was high quality for the incidence of adverse events, mortality and time for laboratory parameters to normalise. We considered evidence was moderate for the incidence of coronary artery abnormalities, duration of clinical symptoms (fever, rash) and length of hospital stay. We downgraded coronary artery abnormality evidence as subgroup analysis suggests that those with low-risk scores or receiving single-dose treatment may not have benefit. We downgraded 'duration of clinical symptoms' due to the large heterogeneity. We downgraded 'length of hospital stay' as only one very small study recorded this outcome. Subgroup analysis suggests that those with low-risk scores or receiving single-dose treatment may not have benefit.

Overall, this means that we are reasonably confident that the true effect is close to that estimated in this work.

Potential biases in the review process

There are no known biases to disclose in the implementation of this review. There were no limitations within the search and this study followed the predefined protocol following Cochrane guidelines.

Agreements and disagreements with other studies or reviews

The results of this review reflect the shifting paradigm regarding the use of steroids in KD and show that steroids are beneficial in the treatment of KD, fitting with their use in other vasculitic diseases. The included studies suggest that steroids enhance the resolution of fever and inflammatory markers and are associated with improved coronary artery outcomes. This is thought to be due to suppression of the inflammatory reaction in KD that causes the coronary artery abnormalities (influx of neutrophils, large mononuclear cells and lymphocytes which destroy the internal elastic lamina, followed by myofibroblast proliferation causing a coronary aneurysm (Eleftheriou 2013)). In addition, other recent systematic reviews on this question have come to similar conclusions on the efficacy of steroids for KD (Chen 2013; Zhu 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-quality evidence shows that use of steroids in the acute phase of KD can be associated with improved coronary artery abnormalities, shorter duration of hospital stay and a decreased duration of clinical symptoms. High-quality evidence shows improved rates of reduced inflammatory markers with the use of steroids. There were insufficient data available regarding incidence of adverse effects attributable to steroids, mortality and long-term (> 1 year) coronary morbidity during the study periods included in this analysis.

There appears to be an increased benefit to patients of Japanese origin, higher risk score and receiving a prolonged course of steroids. That stated, there is a risk of confounding in these conclusions. Therefore more tests are needed to answer these questions. Evidence presented in this study suggests that treatment with a long course of steroids should be considered for all children diagnosed with KD until further studies are performed.

Implications for research

This meta-analysis partially answers the question of the utility of steroids in the treatment of the acute phase of KD. However, the follow-up periods were generally short and data are lacking to ascertain the long-term benefit for patients.

Further trials and increased follow-up of previous trials is required to evaluate the longer-term implications of steroid use in KD. More trials outside Japan of appropriate steroid use and treatment duration are also required.

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Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Archives of Disease in Childhood* 2015;**100**(11):1084-8.

Sleeper 2011

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Tatara 1987

Tatara K, Kusakawa S. Long-term prognosis of giant coronary aneurysm in Kawasaki disease: an angiographic study. *Journal of Pediatrics* 1987;**111**(5):705-10.

Wood 2009

Wood LE, Tulloh RM. Kawasaki disease in children. *Heart* 2009;**95**(10):787-92.

Zhu 2012

Zhu BH, LV HT, Sun L, Zhang JM, Cao L, Jia HL, et al. A meta-analysis on the effect of corticosteroid therapy in Kawasaki disease. *European Journal of Pediatrics* 2012;**171**(3):571-8.

References to other published versions of this review

Wardle 2014

Wardle AJ, Kiddy HC, Seager MJ, Tulloh RMR, Levin M. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database of Systematic Reviews* 2014, Issue 8. [DOI: 10.1002/14651858.CD011188]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ikeda 2006

Methods	Participants "randomly assigned" and stratified into high- or low-risk groups Unclear how many centres
Participants	178 with a diagnosis of KD were randomly assigned No statement of baseline characteristics at enrolment between groups 90 assigned to steroid, 88 to control and they were divided as follows: Low risk: • Steroid = 45 participants • Control = 46 participants High risk: • Steroid = 45 participants • Control = 42 participants
Interventions	Participants given control (IVIG) or treatment (IVIG + prednisolone) No information on route, duration or dose of steroid used
Outcomes	Coronary artery abnormalities Unclear at what time point outcome measure assessed
Notes	No statement of blinding participants or researchers No clear dose, route or duration of steroid use Uncear source of funding No clear definition of "coronary artery abnormalities" No indication of when measurements were taken after treatment Undertaken at Gunma Children's Medical Centre, Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly assigned"

Ikeda 2006 *(Continued)*

		Comment: unclear how this was done
Allocation concealment (selection bias)	Unclear risk	Not stated Comment: impossible to know if participants or physicians were blinded to the allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated Comment: impossible to know if participants or physicians were blinded to the study treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated Comment: impossible to know if there was any blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All data present
Selective reporting (reporting bias)	Low risk	Published methodology consistent with that reported in published results
Other bias	Low risk	None identified

Inoue 2006

Methods	Mulitcenter (12 centres in Gunma and Saitama, Japan) prospective non-blinded randomised. September 2000 to March 2005.
Participants	588 children referred to the medical institutions. 410 found to be ineligible (389 because parents decided against participation, 17 because of a previous diagnosis of KD, and 4 because a coronary artery abnormality was present before randomisation) 178 participants who were all diagnosed with KD (had at least 5 of the following: fever (> 38 °C), non-exudative conjunctival injection, changes in the oropharynx (including mucosal erythema; dry, cracked lips; and "strawberry tongue"), changes in the extremities (including palmar and plantar erythema), oedema of the hands and feet or periungual desquamination, rash and cervical lymphadenopathy Groups well balanced in respect of baseline demographic and clinical characteristics, alongside risk score. All participants followed up for at least 2 months (range 2 to 50 months). Control: 88 Steroid: 90
Interventions	Control: • IVIG 1 g/kg/day for 2 days given over 12 h • Aspirin 30 mg/kg/day decreased to 5 mg/kg/day once CRP resolved Treatment: • IVIG 1 g/kg/day for 2 days given over 12 h • Aspirin 30 mg/kg/day decreased to 5 mg/kg/day once CRP resolved • Prednisolone sodium succinate 2 mg/kg/day in 3 divided doses, intravenous until fever resolved, then given orally until CRP normalised. Once CRP normalised prednisolone was given orally in tapering

Inoue 2006 *(Continued)*

	doses over 15 days in 5-day steps (2 mg/kg/day for 5 days, 1 mg/kg/day for 5 days, then 0.5 mg/kg/day for 5 days). If there was difficulty with oral delivery, doses were given IV Excluding 1 participant whose steroid treatment was discontinued at the discretion of the treating physician, duration of steroid treatment 18 to 100 days (median 23 days). Total dose of prednisolone ranged from 23.5 to 90 mg/kg (median 32 mg/kg)
Outcomes	Primary: • Detection of coronary artery abnormality (luminal diameter > 3.0 mm in a child < 5 yrs, or > 4.0 mm in a child > 5 yrs, when the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or when a luminal contour was clearly irregular) Secondary: • Duration of fever after initial treatment • Time to normalisation of CRP level (< 5 mg/dL) • Incidence of treatment failure and recurrence
Notes	Study terminated on 31 March 2005 by data monitoring committee at the time of the deadline despite a lower enrolment rate than expected Unclear source of funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "centre randomly assigned the patient" Comment: no clear statement of mechanism for random assignment
Allocation concealment (selection bias)	Low risk	Quote: "Centrally maintained table of random numbers" Comment: likely adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Non-blinded Comment: unclear how this would have influenced results
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Echocardioraphy operators were non-blinded Quote: "findings reviewed in a non blinded manner" Unclear if laboratory team processing blood samples were blinded Comment: unclear how this would have influenced results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Key outcome variables are reported as per protocol analysis with intention-to-treat analysis variable performed
Selective reporting (reporting bias)	Low risk	Published methodology consistent with that reported in published results
Other bias	Low risk	None identified

Kobayashi 2012

Methods	Multicentre (74 hospitals in Japan), prospective, randomised, blinded end points 29 September 2008 to 2 December 2010
Participants	Eligible participants had a diagnosis of KD (Japanese diagnostic guidelines) and a risk score of 5 points or higher, which emphasised the positive predictive value of no response to initial treatment with IVIG (2 points for each of the following: blood sodium < 133, < 4 days of fever at diagnosis, AST > 100, neutrophils > 80% of total WCC; 1 point for each of the following: platelet count < 30 x 10^4, CRP > 100, age < 12 months) Excluded were children with a history of KD, those diagnosed on or after day 9 of fever, those with coronary artery abnormalities prior to enrolment, those who were afebrile prior to enrolment, those who had received steroids in the previous 30 days before the study, those who had received IVIG in the previous 180 days before the study, those with concomitant severe medical disorders, or those with suspected infectious disease 2014 children assessed for eligibility. 1547 did not meet inclusion criteria (1436 had low risk scores, 44 had previous diagnosis of KD, 24 had defervescence, 16 had suspected infectious disease, 12 had presence of coronary artery abnormality at diagnosis, 10 had illness for > 9 days, 3 had pre-existing severe disease, 1 had a history of IVIG use, 1 had history of steroid use, 219 declined to participate. 248 participants randomly assigned. Steroid group: 125 (4 excluded: 1 withdrew consent, 2 had presence of coronary artery abnormality, 1 had misdiagnosis of KD) Control group: 123 (2 excluded: 1 had presence of coronary artery abnormalities at enrolment, 1 did not receive IVIG) No significant differences between groups at baseline
Interventions	Control: • IVIG 2 g/kg over 24 h • Aspirin 30 mg/kg/day until afebrile, then 3 to 5 mg/kg/day for at least 28 days from fever onset Steroid group: • IVIG 2 g/kg over 24 h • Aspirin 30 mg/kg/day until afebrile, then 3 to 5 mg/kg/day for at least 28 days from fever onset • IV prednisolone 2 mg/kg/day in 3 divided doses for 5 days, or until fever resolved, if longer. When CRP normalised (< 5mg/L) prednisolone doses were tapered in 5 day steps over 15 days, from 2 mg/kg/day, to 1 mg/kg/day to 0.5 mg/kg/day • 0.5 mg/kg/day H2 blocker famotidine whilst on prednisolone
Outcomes	Primary end point: • Detection of coronary artery abnormality during study period (luminal diameter > 3.0 mm in a child < 5 years, or > 4.0 mm in a child > 5 yrs, when the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or when a luminal contour was clearly irregular) Secondary end point: • Incidence of coronary artery abnormality at week 4 after enrolment • Incidence of need for additional rescue treatment • CRP concentrations at 1 and 2 weeks after enrolment • Incidence of serious adverse events
Notes	Funding source: Japanese Ministry of Health, Labour and Welfare – had no role in study design, data collection, data analysis, data interpretation or writing of the report

Kobayashi 2012 *(Continued)*

RASIE study. Registered with University Hospital Medical Information Network clinical trials registry, number UMIN000000940

Pre-planned interim analysis after enrolment of the 200th participant in June 2010 demonstrated significance difference in the incidence of coronary artery abnormalities between the 2 treatment groups ($P < 0.0001$), therefore independent data and safety monitoring committee recommended termination of the study. Study terminated on 2 December 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated randomisation sequence" Comment: likely adequate and performed
Allocation concealment (selection bias)	Low risk	Quote: "Centrally maintained table of random numbers" Comment: likely adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Participant and treating physician non-blinded" Comment: unclear how this would have influenced results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded end point" Echocardiography assessors blinded Comment: appears adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Intention to treat analysis used" Comment: appears adequate
Selective reporting (reporting bias)	Low risk	Published methodology consistent with that reported in published results
Other bias	Low risk	None identified

Newburger 2007

Methods	Multicentre (8 centres in North America), randomised, double-blind, placebo-controlled trial. December 2002 to December 2004
Participants	All participants between day 4 and day 10 of illness Inclusion criteria: • Child met > 4 of principal clinical criteria. • Coronary artery z-score of > 2.5 (RCA or LAD) and met 2 principal clinical criteria if < 6 months, 3 criteria if > 6 months • Presence of a coronary artery aneurysm and met at least 1 clinical criterion Exclusion criteria: • Previous treatment with IVIG

Newburger 2007 *(Continued)*

- Oral steroid use in preceding 2 weeks
- Presence of a disease known to mimic KD
- Contraindications to steroid use
- Allergy to aspirin

589 children identified. 276 were ineligible (185 met at least 1 exclusion criterion. 95 did not meet inclusion criteria)

313 considered eligible, of these 199 parents granted consent

199 children randomised

Treatment: 101 participants

Control: 98 participants

No significant differences between groups at baseline randomisation

Interventions	Control: • 1 mg/kg diphenhydramine • IVIG 2 g/kg over 10 h • Aspirin 80 to 100 mg/kg/day until they were afebrile for 48 h, then 3 to 5 mg/kg/day aspirin until study completion Treatment: • One-off dose of 30mg/kg intravenous methyl prednisolone • 1 mg/kg diphenhydramine • IVIG 2 g/kg over 10 h • Aspirin 80 to 100 mg/kg/day until they were afebrile for 48 h, then 3 to 5 mg/kg/day aspirin until study completion If children had recurrent fever > 36 h after the initial infusion (and no alternative source was found) then a further dose of IVIG 2 mg/kg, then if they remained pyrexial after a further 36 h another dose of IVIG 2 mg/kg was administered
Outcomes	Primary outcome: • Detection of coronary artery abnormality during study period (luminal diameter > 3.0 mm in a child < 5 yrs, or > 4.0 mm in a child > 5 yrs, when the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or when a luminal contour was clearly irregular, of a z-score of > 2.5) Secondary outcomes: • Duration of fever • Number of days spent in hospital until first discharge • Number of total days spent in hospital during study period • Number of episodes of re-treatment with IVIG • Incidence of adverse events • Laboratory data at week 1 and 5 after randomisation
Notes	ClinicalTrials.gov number: NCT00132080 Funding: National Institutes of Health and Higgins Family Cardiology Research Fund No relevant potential conflict of interest reported
Risk of bias	

Newburger 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly assigned" with use of "dynamic balancing" at each centre Comment: no information of what "dynamic balancing" entailed
Allocation concealment (selection bias)	Unclear risk	Not stated Comment: impossible to know if participants or physicians were blinded to the allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind" Comment: appears adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind" Comment: appears adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Interim analysis reviewed by an independent data and safety monitoring board." Data excluded for "6 patients who were discovered to have met an exclusion criteria, for 2 patients who did not receive IV steroid despite randomisation into this group, and 8 patients who were enrolled because they had coronary abnormalities but did not meet the classic criteria for KD."
Selective reporting (reporting bias)	Low risk	Pre-trial protocol published on ClinicalTrials.gov and consistent with methodology and results published
Other bias	Low risk	None identified

Ogata 2012

Methods	Single centre in Japan (Kitasato University Hospital), unblinded with stratification of participants into high- and low-risk groups. Participants were then randomly assigned to each treatment group April 2007 to November 2010
Participants	Incluson criteria: • 5 of 6 clinical criteria for KD Exclusion criteria: • Previous diagnosis of KD • Presence of a coronary artery abnormality before treatment • Use of steroid treatment before recruitment 122 participants enrolled into the study - all Japanese 100% consent rate for parents High-risk group (Egami score > 3): aspirin + IVIG = 26, aspirin + IVIG + steroid = 22 Low-risk group (Egami score < 2; Table 1): aspirin alone = 6, aspirin + IVIG = 62

Ogata 2012 *(Continued)*

	No significant differences at baseline between groups in the high-risk group
Interventions	**Low risk group:** Treatment: • Aspirin 30 mg/kg 3 times daily until afebrile for 36 h, then 5 mg/kg/day • IVIG 2 g/kg over 24 h Control: • Aspirin 30 mg/kg 3 times daily until afebrile for 36 h, then 5 mg/kg/day **High risk group:** Treatment: • Aspirin 30 mg/kg 3 times daily until afebrile for 36 h, then 5 mg/kg/day • IVIG 2 g/kg over 24 h • One-off dose of intravenous methyl prednisolone 30mg/kg over 2 h Control: • Aspirin 30 mg/kg 3 times daily until afebrile for 36 h, then 5 mg/kg/day • IVIG 2 g/kg over 24 h
Outcomes	Primary outcome: • Treatment resistance (temperature > 37.5 °C) at 36 h Secondary outcomes: • Duration of fever • Laboratory markers of vasculitic markers • Z-scores of coronary arteries
Notes	Trial number: UMIN000005021 No conflict of interest reported Grant-in-aid for scientific research from Ministry of Education, Culture, Sports, Science and Technology; a Parents' Association Grant at Kitasato University School of Medicine, and a grant-in-aid from the Kawasaki Disease Research Centre in Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Randomly assigned using a "random number list" Comment: appears adequate
Allocation concealment (selection bias)	Unclear risk	Not stated Comment: impossible to know if participants or physicians were blinded to the allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Non-blinded Comment: unclear how this would have influenced results

Ogata 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blinded" Comment: appears adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data included in analysis
Selective reporting (reporting bias)	Low risk	Published methodology consistent with that reported in published results
Other bias	Low risk	None identified

Okada 2003

Methods	Multicentre (9 centres in Gunma Prefecture, Japan), prospective, randomised. Once participants identified, randomised into treatment groups June 2001 to May 2002
Participants	Inclusion criteria: • At least 5 of the following: fever (> 38 °C), non-exudative conjunctival injection, changes in the oropharynx (including mucosal erythema; dry, cracked lips; and strawberry tongue), changes in extremities (palmar and plantar erythema, oedema of the hands and feet, or periungual desquamation in subacute phase of the disease), rash, cervical lymphadenopathy • Enrolled within 9 days of onset of fever 32 participants recruited: • Steroid treatment group: 14 • Control: 18 Age, sex distribution, and severity score were similar in the 2 groups
Interventions	Control: • IVIG 1 g/kg for 2 days • Aspirin 30 mg/kg per day throughout the study period • Dipyridamole 2 mg/kg throughout the study period Treatment: • IVIG 1 g/kg/day for 2 days • Prednisolone intravenous 2 mg/kg 3 times daily until resolution of fever, then oral prednisolone 2 mg/kg 3 times daily until CRP normalised, then a reducing regime of prednisolone was used, 1 mg/kg 2 times daily for 5 days, then 0.5 mg/kg once daily for 5 days • Aspirin 30 mg/kg per day throughout the study period • Dipyridamole 2 mg/kg throughout the study period
Outcomes	Primary outcome: • Cytokine levels pre-treatment, post IVIG dose, day 7 and day 14 Secondary outcomes: • Average duration of fever • Time to normalisation of CRP

Okada 2003 *(Continued)*

- Coronary artery abnormality (luminal diameter > 3.0 mm in a child < 5 yrs, or > 4.0 mm in a child > 5 yrs, when the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or when a luminal contour was clearly irregular)
- Adverse effects

Notes	Unclear source of funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomised via a controller in the registration centre" Comment: appears adequate
Allocation concealment (selection bias)	Low risk	Quote: "Controller in the registration centre" Comment: efforts made to separate randomisation from the study trial, reducing chance of information spread
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Non-blinded Comment: unclear how this would have influenced results
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if blinded Comment: unclear how this would have influenced results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants appears in analysis
Selective reporting (reporting bias)	Low risk	Published methodology consistent with that reported in published results
Other bias	Low risk	None identified

Sundel 2003

Methods	Single centre (Boston, North America). Prospective randomised trial. Once recruited participants were randomised to each treatment group February 1998 to November 2000
Participants	Inclusion criteria: • Fever < 10 days • 4 out of 5 clinical criteria Exclusion criteria: • Previous diagnosis of KD • Presence of coronary artery aneurysm • Possible infection • Known hypersensitivity to IVIG • Contra-indications to steroid therapy

Sundel 2003 *(Continued)*

	71 met eligibility criteria. 10 declined consent. 20 not enrolled due to insufficient time prior to IVIG infusion. 2 excluded due to coronary artery abnormalities 39 participants recruited: • Control = 21 • Treatment = 18 No significant differences in demographic data at enrolment
Interventions	Control: • IVIG 2 g/kg over 10 h • Aspirin 20 to 25 mg/kg every 6 h until afebrile for 48 h, then 3 to 5 mg/kg/day for the duration of the study • Diphenhydramine pretreatment prior to IVIG Treatment: • IVIG 2 g/kg over 10 h • Aspirin 20 to 25 mg/kg every 6 h until afebrile for 48 h, then 3 to 5 mg/kg/day for the duration of the study • Diphenhydramine pretreatment prior to IVIG • One-off dose of IV methyl prednisolone 30 mg/kg (max dose 1.5 g) 3 h before IVIG
Outcomes	Primary outcome: • Duration of fever Secondary outcomes: • Length of hospital stay • Inflammatory markers at 6 weeks • Coronary artery abnormalities • Incidence of adverse events
Notes	Unclear funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly assigned" Comment: unclear how this was done
Allocation concealment (selection bias)	Unclear risk	Not stated Comment: impossible to know if participants or physicians were blinded to the allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Participants and investigators were not blinded to treatment assignment" Comment: unclear risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Outcome markers were generally measured objectively (e.g. temp, laboratory values), or were read by blinded observers unaware of patients' treatment status (echocardiograms)."

Sundel 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	95% of children had ECHO at 2 weeks 93% of children had ECHO at 6 weeks (1 in treatment group, 2 in control group)
Selective reporting (reporting bias)	Low risk	Published methodology consistent with that reported in published results
Other bias	Low risk	None identified

AST: aspartate aminotransferase
CRP: C-reactive protein
ECHO: cardiac echocardiogram
IV: intravenous
IVIG: intravenous immunoglobulin
KD: Kawasaki disease
LAD: left anterior descending
RCA: right coronary artery
WCC: white cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Asai 1985	Intervention included dipyridamole as well as prednisolone as the difference between the groups. Effect of steroids therefore not ascertainable. Furthermore primary outcome— arterial changes — poorly defined
Hashino 2001	Steroids only used if children were non-responders to 2 treatments with IVIG. These IVIG non-responsive children were then divided into groups allocated to receiving steroid (9 children) and those who received another dose of IVIG (8 children). This caused a significant delay in the administration of any steroids Due to the steroid treatment group being classed as non-responders to IVIG, and the delay in receiving treatment, this study was not included as it is not comparable to any of the other studies used in this review
ISRCTN74427627	Study outcome data not available despite attempts to contact author
Jibiki 2005	Outcome not as per inclusion criteria of the review. Investigators assessed the laboratory mechanism of action of IVIG and steroid therapy in KD
Kato 1979	Study outcome data not available despite attempts to contact author. Available outcome information does not provide objective data but categorises into aneurysm vs no aneurysm with inadequate detail on exact approach
Kusakawa 1983	Study outcome data not available despite attempts to contact author. Available outcome information does not provide objective data but categorises into aneurysm versus no aneurysm with inadequate detail on exact approach
Miura 2008	Outcome not as per inclusion criteria. Investigators assessed the laboratory mechanism of action of IVIG and steroid therapy in KD
Nakamura 1985	Outcome not as per inclusion criteria of the review. The outcome of this study was regarding platelet laboratory processes, which was not an outcome measure of this review

Study	Reason for exclusion
Nonaka 1995	Study outcome data not available despite attempts to contact author. Available outcome information does not provide objective data but categorises into aneurysm vs no aneurysm with inadequate detail on exact approach
Ogata 2009	Outcome not as per inclusion criteria of the review. Investigators assessed the molecular mechanism of action of IVIG and steroid therapy in KD
Sekine 2012	Outcome not as per inclusion criteria of the review. The outcome of this study was oxidative stress, which was not an outcome measure of this review
Seto 1983	Inadequate information on methodology for validation, specifically no evidence of randomisation
Xu 2002	Interventions included immunoglobulin versus steroids, meaning steroids were not the only differential factor between the groups and therefore their effect cannot be clearly defined. Inadequate information on methodology, specifically around randomisation, despite contacting authors
Yuan 2000	Outcome not as per inclusion criteria of the review. Study does not clearly define coronary aneurysm or how this was measured

IVIG: intravenous immunoglobulin

Characteristics of ongoing studies *[ordered by study ID]*

JPRN-UMIN000009524

Trial name or title	A prospective randomised controlled trial of immunoglobulin plus prednisolone for KD patients with high risk for coronary abnormalities
Methods	Parallel, assessor-blinded study Control group: Intravenous immunoglobulin (2 g/kg) over 24 h with aspirin (30 mg/kg/day). The dosage of aspirin can be reduced to 5 mg/kg/day after resolution of fever Treatment group: Intravenous immunoglobulin (2 g/kg) over 24 h plus intravenous prednisolone (2 mg/kg/day) with aspirin (30 mg/kg/day). The dosage of aspirin can be reduced to 5 mg/kg/day after resolution of fever Prednisolone will be given intravenously for 3 days at least and then can be given orally after resolution of fever. When concentration of C-reactive protein becomes 1.0 mg/dL or less, the dose of prednisolone will be tapered over 9 days
Participants	Target sample size 240 Inclusion criteria: 1. Severe KD patients of risk score 4 points or more 2. Written informed consent is obtained from patients or their parents 3. Streptococcus, Epstein-Barr virus, adenovirus, or yersinia infection, or measles, or Stevens-Johnson syndrome is ruled out Exclusion criteria: 1. Patients with past histories of KD 2. Patients diagnosed as KD on the ninth day of illness or later 3. KD patients with coronary artery lesions before treatment 4. KD patients with defervescence before treatment

JPRN-UMIN000009524 *(Continued)*	5. Patients given steroids within 28 days before treatment 6. Patients given IVIG within 180 days before treatment 7. Patients with severe underlining diseases 8. Patients with a concurrent infection
Interventions	Control group: Intravenous immunoglobulin (2 g/kg) over 24 h with aspirin (30 mg/kg/day). The dosage of aspirin can be reduced to 5 mg/kg/day after resolution of fever Treatment group: Intravenous immunoglobulin (2 g/kg) over 24 h plus intravenous prednisolone (2 mg/kg/day) with aspirin (30 mg/kg/day). The dosage of aspirin can be reduced to 5 mg/kg/day after resolution of fever Prednisolone will be given intravenously for 3 days at least and then can be given orally after resolution of fever. When concentration of C-reactive protein becomes 1.0 mg/dL or less, the dose of prednisolone will be tapered over 9 days
Outcomes	Primary outcome: Incidence of coronary artery lesions within 4 weeks after primary treatment Secondary outcome: Incidence of coronary artery lesions at 4 weeks after primary treatment, z-score of coronary artery diameters, incidence of resistance to primary treatment or relapse, duration of fever after primary treatment, serum concentrations of C-reactive protein at 1 week and 2 weeks after primary treatment, and incidence of adverse events
Starting date	17 December 2012
Contact information	Taichi Kato Nagoya University Graduate School of Medicine Department of Pediatrics 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan +81-52-744-2298 ktaichi@med.nagoya-u.ac.jp
Notes	

IVIG: Intravenous immunoglobulin

DATA AND ANALYSES

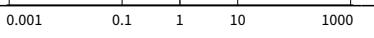
Comparison 1. Corticosteroids vs no corticosteroid use

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of coronary artery abnormalities	7	907	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.18, 0.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Incidence of serious adverse effects attributable to steroid use	6	737	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality (all-cause)	7	915	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Duration of clinical symptoms: fever, rash	2	210	Mean Difference (IV, Random, 95% CI)	-1.65 [-3.31, 0.00]
5 Time for laboratory parameters to normalise: CRP, ESR	1	178	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-4.38, -1.22]
6 Length of hospital stay	1	39	Mean Difference (IV, Fixed, 95% CI)	-1.41 [-2.36, -0.46]

Analysis 1.1. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 1 Incidence of coronary artery abnormalities.

Study or subgroup	Corticosteroid n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ikeda 2006	2/90	10/88		13.79%	0.18[0.04,0.83]
Inoue 2006	2/90	10/88		13.79%	0.18[0.04,0.83]
Kobayashi 2012	4/121	28/121		37.76%	0.11[0.04,0.34]
Newburger 2007	15/95	18/95		21.14%	0.8[0.38,1.7]
Ogata 2012	2/22	10/26		11.62%	0.16[0.03,0.84]
Okada 2003	0/14	0/18			Not estimable
Sundel 2003	0/18	1/21		1.89%	0.37[0.01,9.64]
Total (95% CI)	**450**	**457**		**100%**	**0.29[0.18,0.46]**
Total events: 25 (Corticosteroid), 77 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.22, df=5(P=0.05); I^2=55.42%					
Test for overall effect: Z=5.15(P<0.0001)					



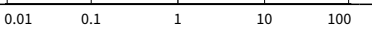
favours corticosteroid — favours control

Analysis 1.2. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 2 Incidence of serious adverse effects attributable to steroid use.

Study or subgroup	Corticosteroid n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Inoue 2006	0/90	0/88			Not estimable
Kobayashi 2012	0/121	0/121			Not estimable
Newburger 2007	0/101	0/97			Not estimable
Ogata 2012	0/22	0/26			Not estimable
Okada 2003	0/14	0/18			Not estimable
Sundel 2003	0/18	0/21			Not estimable
Total (95% CI)	**366**	**371**			**Not estimable**

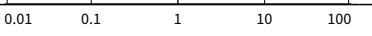
favours corticosteroid — favours control

Study or subgroup	Corticosteroid n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 0 (Corticosteroid), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



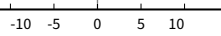
Analysis 1.3. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 3 Mortality (all-cause).

Study or subgroup	Corticosteroid n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ikeda 2006	0/90	0/88			Not estimable
Inoue 2006	0/90	0/88			Not estimable
Kobayashi 2012	0/121	0/121			Not estimable
Newburger 2007	0/101	0/97			Not estimable
Ogata 2012	0/22	0/26			Not estimable
Okada 2003	0/14	0/18			Not estimable
Sundel 2003	0/18	0/21			Not estimable
Total (95% CI)	**456**	**459**			**Not estimable**
Total events: 0 (Corticosteroid), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



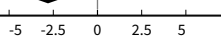
Analysis 1.4. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 4 Duration of clinical symptoms: fever, rash.

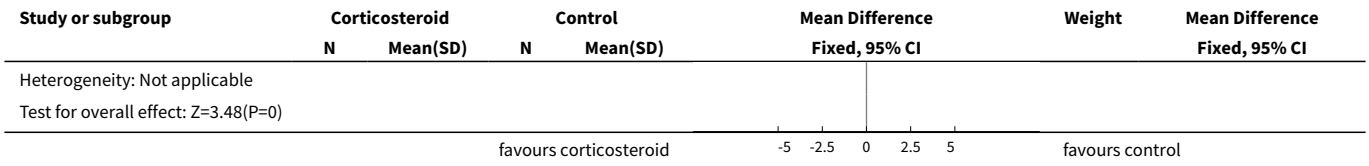
Study or subgroup	Corticosteroid N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Inoue 2006	90	0.6 (0.5)	88	1.5 (1)		55.6%	-0.9[-1.13,-0.67]
Okada 2003	14	0.3 (0.5)	18	2.9 (2.4)		44.4%	-2.6[-3.74,-1.46]
Total ***	**104**		**106**			**100%**	**-1.65[-3.31,0]**
Heterogeneity: Tau^2=1.27; Chi^2=8.21, df=1(P=0); I^2=87.82%							
Test for overall effect: Z=1.96(P=0.05)							



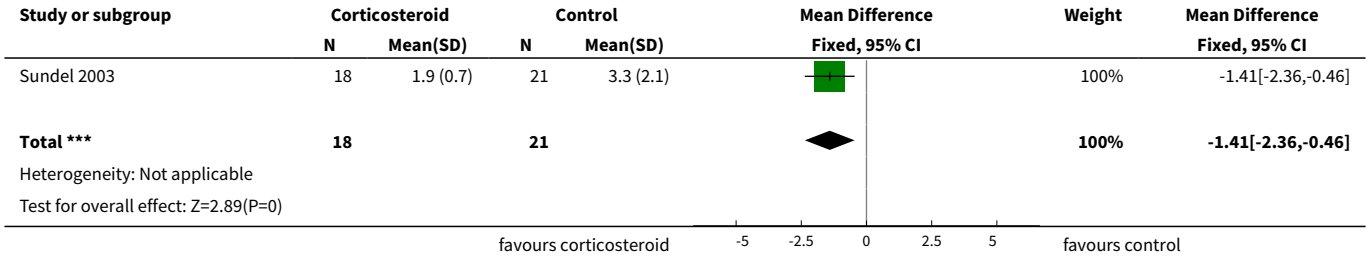
Analysis 1.5. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 5 Time for laboratory parameters to normalise: CRP, ESR.

Study or subgroup	Corticosteroid N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Inoue 2006	90	8.4 (3.7)	88	11.2 (6.6)		100%	-2.8[-4.38,-1.22]
Total ***	**90**		**88**			**100%**	**-2.8[-4.38,-1.22]**





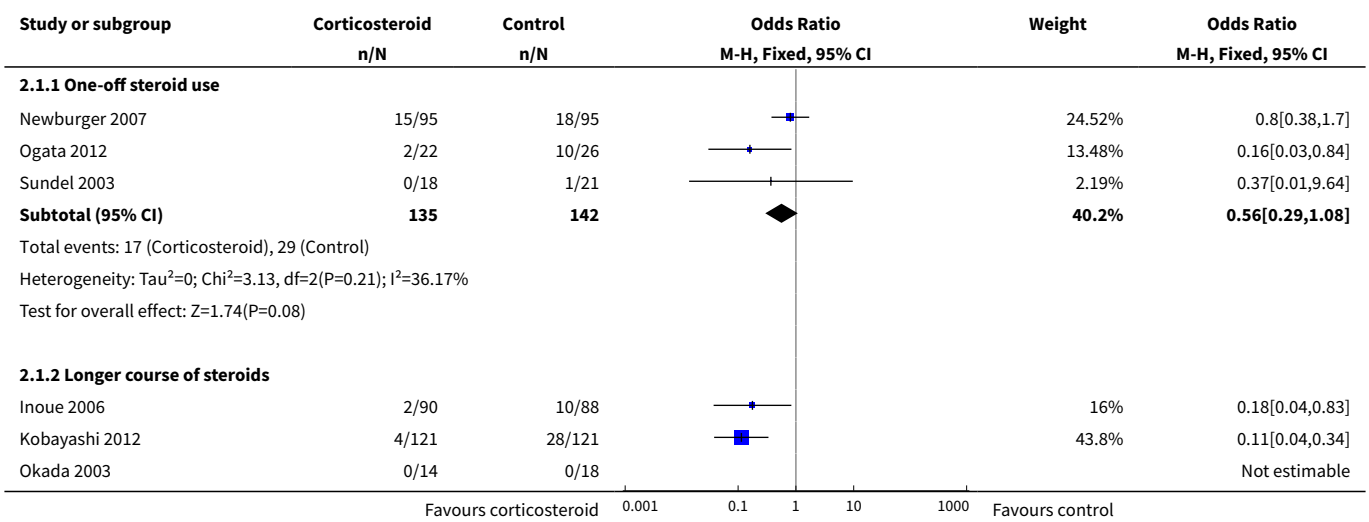
Analysis 1.6. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 6 Length of hospital stay.

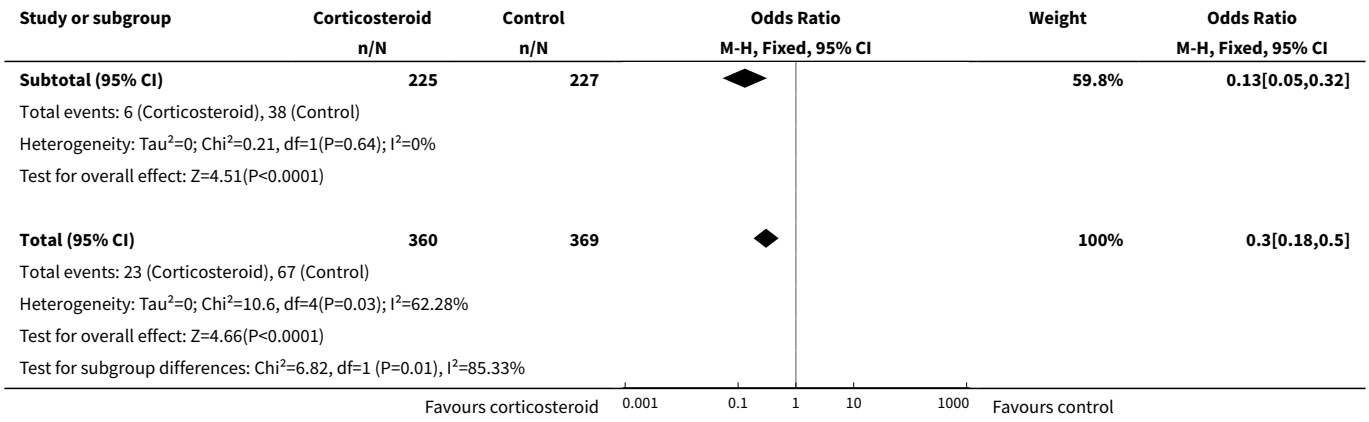


Comparison 2. Subgroup: One-off steroid use vs longer course of steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Coronary artery abnormalities	6	729	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.18, 0.50]
1.1 One-off steroid use	3	277	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.08]
1.2 Longer course of steroids	3	452	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.05, 0.32]

Analysis 2.1. Comparison 2 Subgroup: One-off steroid use vs longer course of steroids, Outcome 1 Coronary artery abnormalities.

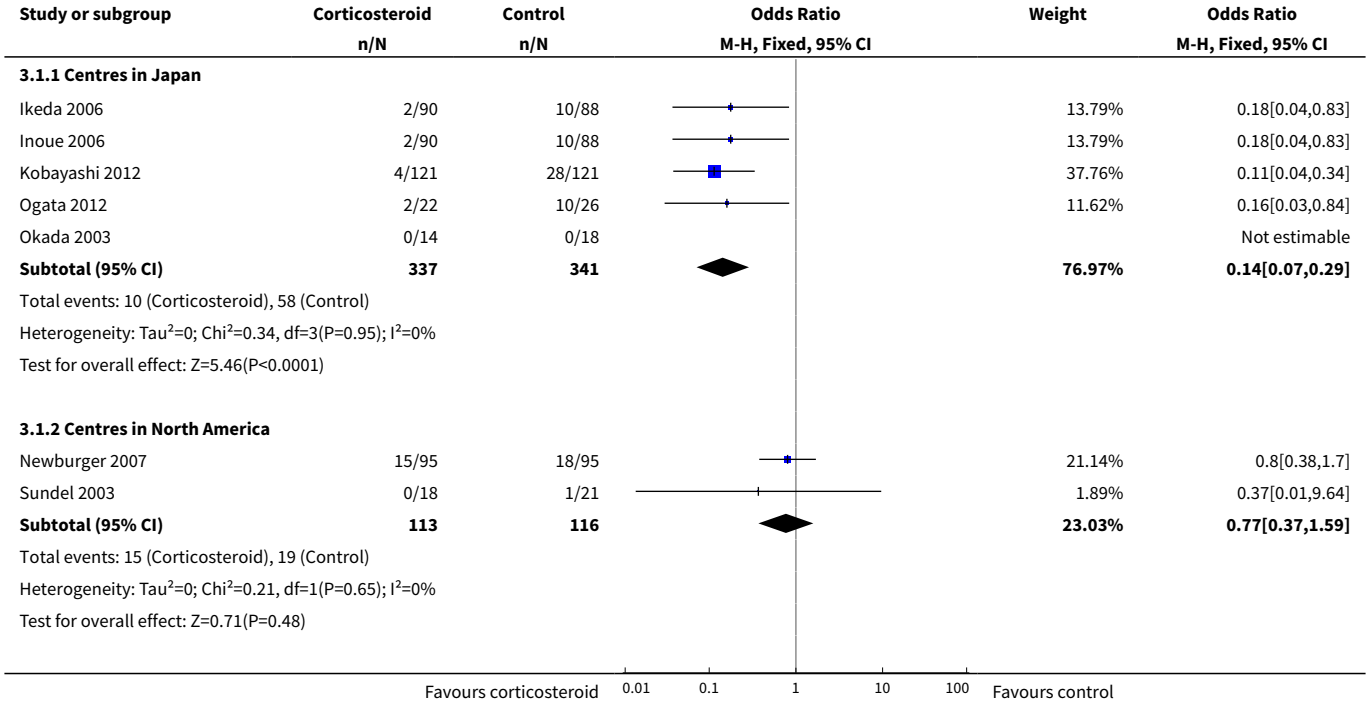


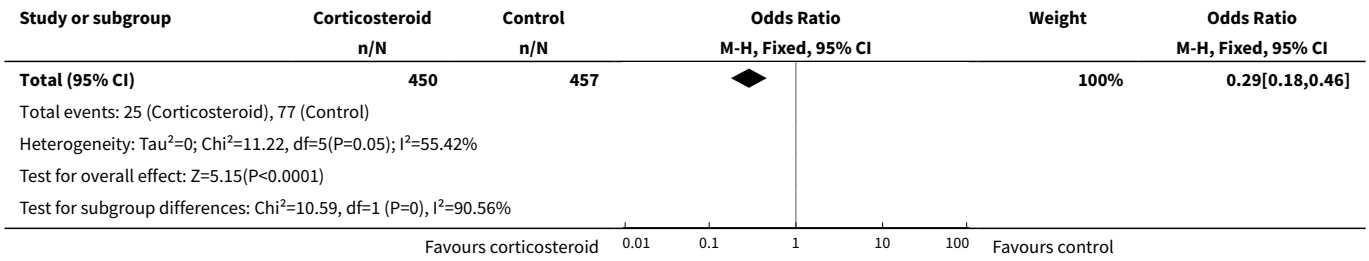


Comparison 3. Subgroup: Geography

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Coronary artery abnormalities	7	907	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.18, 0.46]
1.1 Centres in Japan	5	678	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.07, 0.29]
1.2 Centres in North America	2	229	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.37, 1.59]

Analysis 3.1. Comparison 3 Subgroup: Geography, Outcome 1 Coronary artery abnormalities.

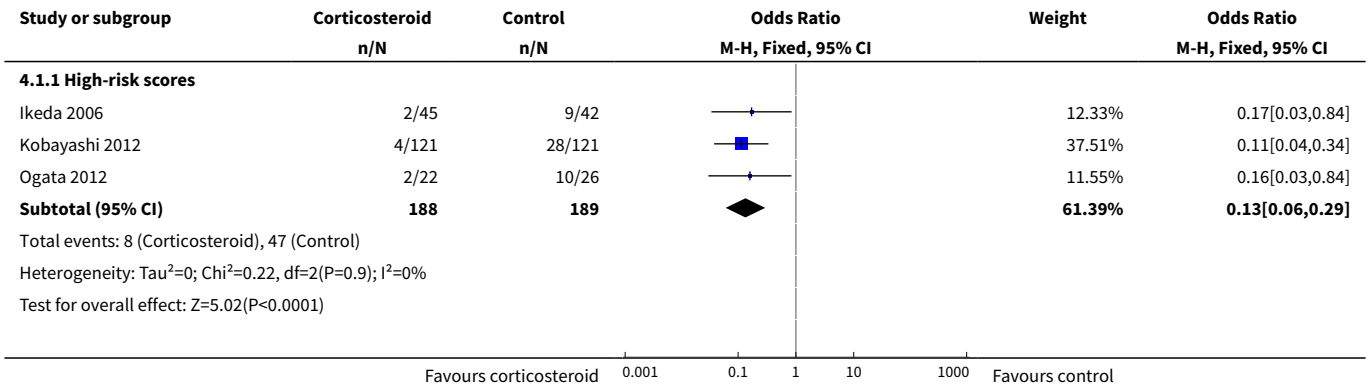


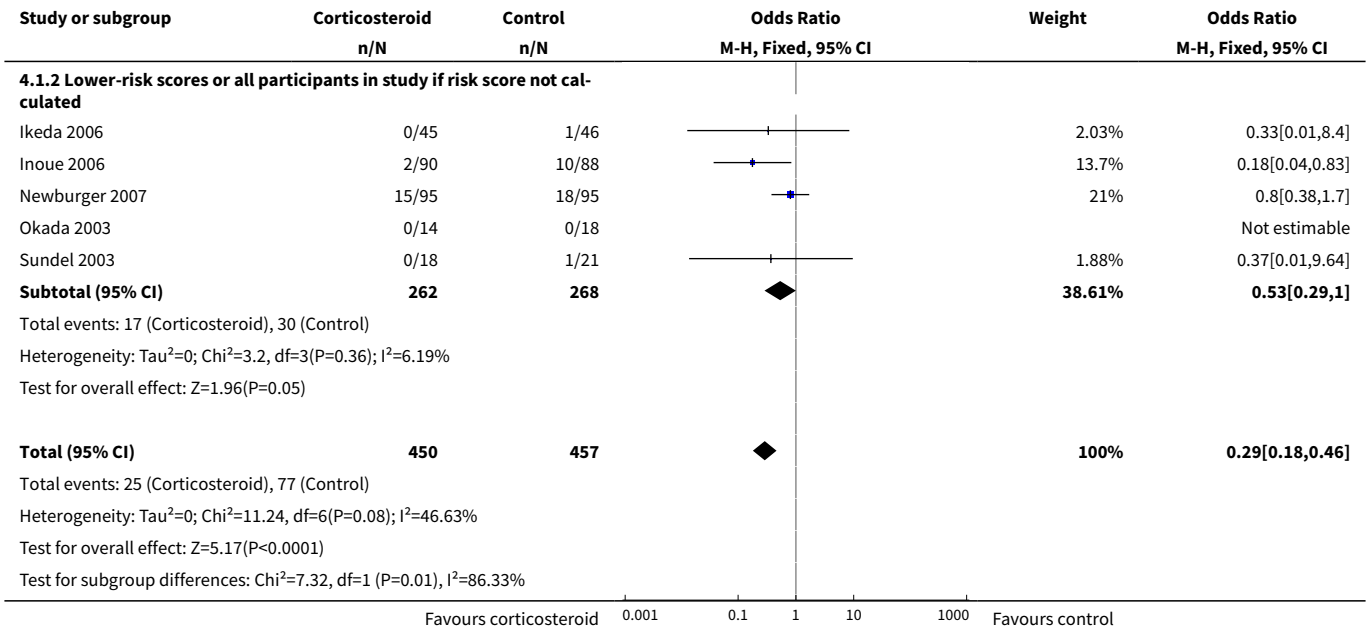


Comparison 4. Subgroup: High-risk scores vs lower-risk scores or all participants if risk score not calculated in study

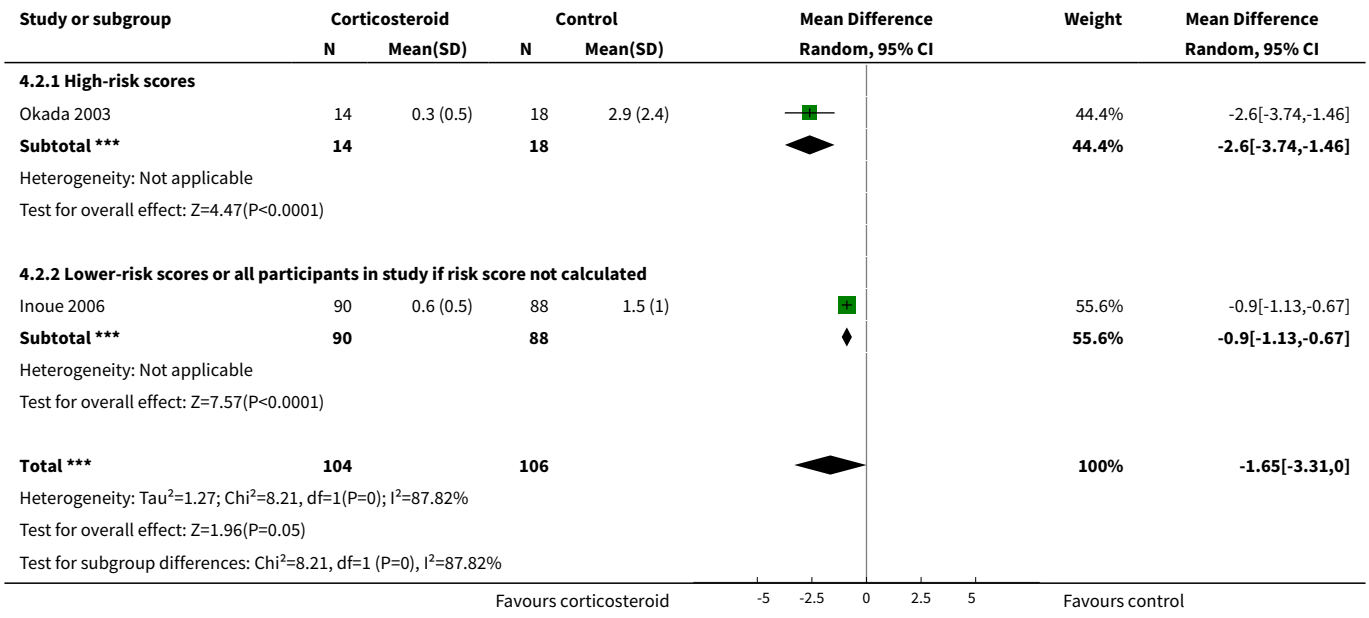
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Coronary artery abnormalities	7	907	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.18, 0.46]
1.1 High-risk scores	3	377	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.06, 0.29]
1.2 Lower-risk scores or all participants in study if risk score not calculated	5	530	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.29, 1.00]
2 Duration of clinical symptoms	2	210	Mean Difference (IV, Random, 95% CI)	-1.65 [-3.31, 0.00]
2.1 High-risk scores	1	32	Mean Difference (IV, Random, 95% CI)	-2.6 [-3.74, -1.46]
2.2 Lower-risk scores or all participants in study if risk score not calculated	1	178	Mean Difference (IV, Random, 95% CI)	-0.9 [-1.13, -0.67]

Analysis 4.1. Comparison 4 Subgroup: High-risk scores vs lower-risk scores or all participants if risk score not calculated in study, Outcome 1 Coronary artery abnormalities.





Analysis 4.2. Comparison 4 Subgroup: High-risk scores vs lower-risk scores or all participants if risk score not calculated in study, Outcome 2 Duration of clinical symptoms.



ADDITIONAL TABLES

Table 1. High-risk subjects' criteria

Study	High risk criteria

Table 1. High-risk subjects' criteria *(Continued)*

Ikeda 2006	Developed own risk score based upon IVIG unresponsiveness in a multiple logistic regression analysis. 42/178 randomly identified KD patients were deemed high risk.
Kobayashi 2012	Kobayashi risk score of 5 or greater (≤ 4 days fever pre-diagnosis, ≤ 12 years old, CRP ≥ 10 mg/dL, ≤ 300 platelets, ALT ≥ 100, sodium ≤ 133, neutrophils ≥ 80%)
Ogata 2012	Egami score of 3 or greater (≤ 6 months old, ≤ 4 days fever pre diagnosis, ≤ 300 platelets, CRP ≥ 7 mg/dL, ALT ≥ 80)

ALT: alanine transaminase
CRP: C-reactive protein
IVIG: intravenous immunoglobulin
KD: Kawasaki disease

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MESH DESCRIPTOR Mucocutaneous Lymph Node Syndrome EXPLODE ALL TREES	74
#2	kawasaki*:TI,AB,KY	182
#3	(mucocutaneous near5 syndrome):TI,AB,KY	121
#4	#1 OR #2 OR #3	193
#5	MESH DESCRIPTOR Glucocorticoids EXPLODE ALL TREES	13302
#6	steroid*:TI,AB,KY	19295
#7	(corticosteroid* or corticoid* or glucocorticoid*):TI,AB,KY	15794
#8	dexamethasone :TI,AB,KY	5923
#9	methylprednis*:TI,AB,KY	3345
#10	prednisone:TI,AB,KY	6256
#11	prednisolone:TI,AB,KY	4294
#12	hydroxycorticosteroid*:TI,AB,KY	113
#13	corticosterone:TI,AB,KY	84
#14	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	44334
#15	#4 AND #14	48

Appendix 2. Trials' registries searches

WHO

69 records for 65 trials found Kawasaki clinical trials in children

Clinicaltrials.gov

86 studies found for Kawasaki/Child

ISRCTN

4 results found for Kawasaki

Appendix 3. Glossary of terms

Term	Definition
Aetiology	Cause of a condition
Defervesence	The abatement of a fever
Deleterious	Negative effect
Desquamation	Loss of the outermost layer of a surface
Erythematous	Reddening - a term generally reserved for the skin
Exanthem	A virus known to be associated with a rash
Mucocutanoeous	Type of bodily surface, such as that inside the mouth
Oropharyngeal	Area of the body encompassing the mouth and throat
Polymorphous rash	Rash of varying appearance
Sequelae	Consequence
Stenosis	Restriction in the diameter of a vessel
Thrombosis	The formation of a blood clot within a blood vessel

CONTRIBUTIONS OF AUTHORS

AJW was involved in the conception, creation and reviewing of the protocol. AJW is the guarantor of the review. AJW and MJS were involved in the drafting of the protocol and identification of studies. GMC and AJW performed the analysis. RMRT was involved in the final reviewing and re-drafting of the review for submission.

DECLARATIONS OF INTEREST

AJW: none known
GMC: none known
MJS: none known
RMRT: none known

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Internal sources

- No sources of support supplied

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In conducting this study it was decided that we would refer to coronary 'aneurysms' in the context of coronary 'abnormalities'. This is due to a wide variation in the literature, including trials included in this review, as to what the definition of an aneurysm is.

Odds ratio was used instead of risk ratio to report dichotomous data, in line with standard statistical analysis.

We renamed the outcome 'incidence of any adverse effects...' to 'incidence of serious adverse events' to reflect more accurately the side effects we intended to study.

NOTES

This review replaces the withdrawn protocol 'Steroid hormone treatment for Kawasaki disease in children' (Jones 2014).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adrenal Cortex Hormones [*therapeutic use]; Coronary Artery Disease [*prevention & control]; Immunoglobulins, Intravenous [therapeutic use]; Methylprednisolone [therapeutic use]; Mucocutaneous Lymph Node Syndrome [complications] [*drug therapy]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Infant; Male