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Methylprednisolone for heart surgery in infants - A randomized, controlled trial

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ORIGINAL ARTICLE

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

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ABSTRACT

BACKGROUND

Although perioperative prophylactic glucocorticoids have been used for decades, whether they improve outcomes in infants after heart surgery with cardiopulmonary bypass is unknown.

METHODS

We conducted a multicenter, prospective, randomized, placebo-controlled, registry-based trial involving infants (<1 year of age) undergoing heart surgery with cardiopulmonary bypass at 24 sites participating in the Society of Thoracic Surgeons Congenital Heart Surgery Database. Registry data were used in the evaluation of outcomes. The infants were randomly assigned to receive prophylactic methylprednisolone (30 mg per kilogram of body weight) or placebo, which was administered into the cardiopulmonary-bypass pump-priming fluid. The primary end point was a ranked composite of death, heart transplantation, or any of 13 major complications. Patients without any of these events were assigned a ranked outcome based on postoperative length of stay. In the primary analysis, the ranked outcomes were compared between the trial groups with the use of odds ratios adjusted for prespecified risk factors. Secondary analyses included an unadjusted odds ratio, a win ratio, and safety outcomes.

RESULTS

A total of 1263 infants underwent randomization, of whom 1200 received either methylprednisolone (599 infants) or placebo (601 infants). The likelihood of a worse outcome did not differ significantly between the methylprednisolone group and the placebo group (adjusted odds ratio, 0.86; 95% confidence interval [CI], 0.71 to 1.05; P=0.14). Secondary analyses (unadjusted for risk factors) showed an odds ratio for a worse outcome of 0.82 (95% CI, 0.67 to 1.00) and a win ratio of 1.15 (95% CI, 1.00 to 1.32) in the methylprednisolone group as compared with the placebo group, findings suggestive of a benefit with methylprednisolone; however, patients in the methylprednisolone group were more likely than those in the placebo group to receive postoperative insulin for hyperglycemia (19.0% vs. 6.7%, P<0.001).

CONCLUSIONS

Among infants undergoing surgery with cardiopulmonary bypass, prophylactic use of methylprednisolone did not significantly reduce the likelihood of a worse outcome in an adjusted analysis and was associated with postoperative development of hyperglycemia warranting insulin in a higher percentage of infants than placebo. (Funded by the National Center for Advancing Translational Sciences and others; STRESS ClinicalTrials.gov number, NCT03229538.)

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Approximately 30,000 operations for congenital heart disease are performed in the United States every year, the majority of which involve infants younger than 1 year of age.[1,2] Congenital heart disease surgery in infants is a high-risk procedure, with death and complications often directly related to severe systemic inflammatory response syndrome after cardiopulmonary bypass.[3-7]

For decades, perioperative glucocorticoids have been administered to attenuate cardiopulmonary bypass–mediated systemic inflammation, but such use remains controversial. Two large, randomized, controlled trials involving adults showed that the use of perioperative glucocorticoids had no benefit and led to an increased risk of myocardial injury[8] and hyperglycemia.[9] However, outcomes may be different in infants owing to a more pronounced systemic inflammatory response to cardiopulmonary bypass,[4,10] with an increased risk of complications and death.[1,11,12] The results of a 2014 meta-analysis of randomized, controlled trials of glucocorticoids during cardiopulmonary bypass in children suggested that mortality was lower with the use of perioperative glucocorticoids than with other clinical interventions, placebo, or no treatment ($P=0.07$).[13] However, two recent meta-analyses showed no difference in mortality.[14,15] Together, these three meta-analyses included data from a total of 1320 children from 23 trials (conducted during a span of four decades) that investigated the use of glucocorticoids during cardiopulmonary bypass.

The limited number of children enrolled in previous cardiopulmonary bypass trials evaluating glucocorticoids highlights the challenges of conducting randomized, controlled trials in this population. The cost of enrolling children is the greatest barrier. A trial with a registry-based design is one mechanism for reducing costs to improve feasibility.[16] We sought to leverage the infrastructure of the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD) to conduct a lower cost, pragmatic trial to evaluate the safety and efficacy of perioperative methylprednisolone in infants undergoing surgery for congenital heart disease.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Steroids to Reduce Systemic Inflammation after Infant Heart Surgery (STRESS) trial was a multicenter, prospective, double-blind, randomized, placebo-controlled trial involving infants undergoing surgery for congenital heart disease. The STS-CHSD was used in the trial to facilitate data collection. The rationale and design of the STRESS trial have been published previously.[17] The protocol, available with the full text of this article at NEJM.org, was approved by a central institutional review board at Vanderbilt University and by the institutional review board and ethics committee at each site. Trial administration, data management, and statistical analyses were performed at the Duke Clinical Research Institute. Database coordination and registry data–extraction protocols are described in detail in the Supplementary Appendix, available at NEJM.org. An independent data and safety monitoring board reviewed the trial data and safety events; an executive steering committee designed and guided the conduct of the trial. The authors wrote and approved all drafts of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

PATIENT POPULATION

Patients were recruited from 24 congenital heart disease centers in the United States that passed STS-CHSD data-quality submission checks. Infants undergoing elective cardiac surgery with cardiopulmonary bypass were eligible for inclusion if they were younger than 1 year of age at the time of surgery. Written informed consent was obtained from a parent or legal guardian before enrollment. Patients were excluded if they had an adjusted gestational age (i.e., the gestational age at birth plus the age at the time of surgery) of less than 37 weeks at the time of surgery, had received any glucocorticoids within 2 days before surgery, had any infection contraindicating the use of glucocorticoids, or were receiving preoperative mechanical circulatory support or active resuscitation at the time of randomization or were receiving known cytochrome P450 3A4 inhibitors at the time of surgery. The trial was conducted under an investigational new drug application (number 129,266) submitted to the Division of Cardiovascular and Renal Products of the Food and Drug Administration.

RANDOMIZATION AND MASKING

The local trial team used a central computerized Web-based system to randomly assign patients

in a 1:1 ratio to receive methylprednisolone at a dose of 30 mg per kilogram of body weight or placebo, both of which were administered into the cardiopulmonary-bypass pump-priming fluid. Methylprednisolone was chosen over other glucocorticoids (e.g., dexamethasone) because it is the glucocorticoid most widely used for infant congenital heart disease surgery. Previous trials have shown no evidence to support preferential use of any particular glucocorticoid.[13-15] Patients were assigned to a trial group with the use of permuted block randomization with random block sizes of 2 and 4, stratified according to trial center. Methylprednisolone or placebo was obtained from the center's local investigational pharmacy and was prepared and concealed according to the procedures described in the trial protocol.

OUTCOMES

The primary end point was a hierarchically assessed composite of operative death (defined in accordance with international consensus recommendations[18,19] as death during the initial hospitalization or within 30 days after the surgery if discharged), heart transplantation during hospitalization, or the occurrence of any of 13 individual major complications (Table S1 in the Supplementary Appendix). Outcomes in the composite end point were ranked into 97 levels of clinical prioritization as follows: operative death was ranked as 97 (worst outcome); heart transplantation during hospitalization as 96; permanent dialysis, tracheostomy, or neurologic deficit at discharge as 95; postoperative mechanical circulatory support or unplanned cardiac reoperation (exclusive of reoperation for bleeding) as 94; reoperation for bleeding, unplanned delayed sternal closure, or postoperative unplanned interventional cardiac catheterization as 93; postoperative cardiac arrest, multisystem organ failure, kidney failure with temporary dialysis, or postoperative mechanical ventilator support for more than 7 days as 92; and postoperative length of hospital stay of 91 days or longer as 91. Patients with none of these postoperative complications were assigned ranked outcomes according to postoperative length of hospital stay (1 to 90 days). Definitions used in the database (see the Supplementary Appendix) were reviewed by the investigators with the local-site data-entry coordinators before enrollment of the first patient at the site and during quarterly webinars.

Secondary end points were defined with the use of standard STS-CHSD data element definitions. These end points included in-hospital death and death after discharge (within 30 days after the last dose of methylprednisolone or placebo), death or a major complication (defined as an outcome in one of the six highest-ranked outcomes [91 to 96] before operative death described above), postoperative length of hospital stay, prolonged ventilation, postoperative low cardiac output syndrome or severe dysfunction, severe infections, and surgical complications. The secondary end points are described in detail in the Supplementary Appendix. Adverse events, suspected adverse reactions, and serious adverse events were defined according to the final regulations addressing the safety reporting requirements for investigational new drug applications that were issued by the Food and Drug Administration (http://edocket.access.gpo.gov/2010/pdf/2010-24296.pdf).

STATISTICAL ANALYSIS

We estimated that 1200 patients (600 per trial group) would provide the trial with more than 90% power to detect superiority of methylprednisolone over placebo with respect to the primary end point, assuming that the magnitude of the treatment effect could be described with the use of an ordinal logistic-regression model with a common odds ratio parameter of 0.70. This assumption implies that the odds of having a less favorable outcome is 30% lower among patients randomly assigned to receive methylprednisolone than among those assigned to receive placebo and that this statement is true for any possible definition of a "less favorable outcome" based on a dichotomization of the primary end point. Between-group comparisons were performed in a population of patients who had undergone randomization and surgery and received methylprednisolone or placebo (the modified intention-to-treat population). We chose this population because eligibility was defined with respect to surgery, and the trial end points were all postoperative outcomes.

The distribution of the ranked outcome components of the primary end point was compared between the trial groups with the use of a pro-

portional-odds logistic-regression model for ordered categorical data. A model-based analysis was chosen in order to incorporate covariate adjustment to increase statistical power.[20] Treatment effects were expressed with the use of odds ratios, with an odds ratio lower than 1 favoring methylprednisolone and suggesting that the outcomes are shifted toward more favorable rankings. Estimates are presented with Wald-type approximate 95% confidence intervals. The prespecified covariates were selected for inclusion in the model on the basis of previous analyses by the STS[21] and trial simulations[22] and included the following: age, weight, prematurity status, and the 2020 STS–European Association for Cardio-Thoracic Surgery (STAT) Mortality Category[23]; in addition, adjustment was made for the random effect of enrollment site. Imputation of missing data was performed in three records for prematurity and STAT Mortality Category. The underlying proportionality assumption in the model was assessed graphically by comparing empirical with predicted logits and statistically by conducting a score test. Graphical testing revealed no large visible violations of proportionality. Statistical testing indicated strong evidence of at least a small violation ($P<0.001$). The statistical analysis plan, available with the protocol, anticipated that there would be interpretability issues for the logistic model if its assumptions were violated and therefore specified the use of the win ratio[24] (also known as a generalized odds ratio[25]) as an additional assumption-free measure of treatment effect. The win ratio is calculated by forming all possible pairs consisting of one patient from the methylprednisolone group and one from the placebo group, then dividing the number of pairs in which the patient in the methylprednisolone group has a better outcome than the patient in the placebo group (i.e., a win) by the number of pairs in which the opposite occurs (i.e., a loss). A 95% confidence interval for the win ratio was calculated with the use of the Agresti formula.[25]

Exploratory analyses of heterogeneity of the treatment effect with respect to the primary end point were performed in prespecified subgroups. We used the covariate-adjusted proportional-odds model and modified it by estimating subgroup-by-trial-group interactions. Between-group differences with respect to all secondary end points were analyzed by means of regression modeling with adjustment for the same covariates as in the proportional-odds model used in the primary analysis. For binary outcomes, we used logistic regression. For postoperative length of hospital stay, we used the Fine and Gray model for time-to-event data,[26] with in-hospital death as a competing risk.

The statistical analysis plan did not include a provision to formally adjust for multiple comparisons in the secondary end-point and subgroup analyses. Confidence intervals were not adjusted for multiplicity and should not be used in place of a hypothesis test.

RESULTS

TRIAL POPULATION

A total of 1263 patients underwent randomization. Of these, 1200 patients received methylprednisolone or placebo as assigned and were included in the modified intention-to-treat population (599 patients in the methylprednisolone group and 601 patients in the placebo group) (Fig. S1 and Table S2). The 63 patients who did not receive methylprednisolone or placebo were excluded from the final analysis (Fig. S1). The methylprednisolone group and placebo group were balanced with respect to sex, race, ethnic group, age distribution, case mix, and baseline risk factors (Table 1) and were broadly representative of the population of infants undergoing heart surgery in the United States (Table S3).

PRIMARY END POINT

The hierarchical categories of the primary end-point events that occurred in the methylprednisolone group and placebo group are summarized in Table 2 and Figure 1. The cumulative number of end-point events was lower in the methylprednisolone group than in the placebo group for all successive end-point categories (Tables S4A and S4B). The prespecified primary analysis with adjustment for baseline characteristics showed that the likelihood of a worse outcome did not differ significantly between the methylprednisolone group and the placebo group (adjusted odds ratio, 0.86; 95% confidence interval [CI], 0.71 to 1.05; $P=0.14$). An unadjusted analysis of the primary end point showed an odds ratio for a worse outcome of 0.82 (95% CI,

Table 1. Demographic and Clinical Characteristics of the Infants at Baseline.*

Characteristic	Methylprednisolone (N = 599)	Placebo (N = 601)
Median age at surgery (IQR) — days	126.0 (14.0–191.0)	124.0 (14.0–182.0)
Age category — no./total no. (%)		
≤30 days	177/599 (29.5)	187/601 (31.1)
>30 to ≤60 days	21/599 (3.5)	20/601 (3.3)
>60 to ≤90 days	31/599 (5.2)	32/601 (5.3)
>90 to ≤180 days	189/599 (31.6)	208/601 (34.6)
>180 days	181/599 (30.2)	154/601 (25.6)
Median weight at surgery (IQR) — kg	5.2 (3.7–6.4)	5.0 (3.6–6.3)
Male sex — no./total no. (%)	320/599 (53.4)	334/600 (55.7)
Race or ethnic group — no./total no. (%)†		
White	428/585 (73.2)	425/583 (72.9)
Black	90/585 (15.4)	102/583 (17.5)
Hispanic or Latino	80/580 (13.8)	63/584 (10.8)
Asian	15/585 (2.6)	12/583 (2.1)
American Indian or Alaska Native	5/585 (0.9)	4/583 (0.7)
Native Hawaiian or other Pacific Islander	4/585 (0.7)	0
Multiracial	13/585 (2.2)	15/583 (2.6)
Other	30/585 (5.1)	25/583 (4.3)
Premature birth — no./total no. (%)	100/598 (16.7)	93/599 (15.5)
Any noncardiac congenital anatomical abnormality — no./total no. (%)	26/599 (4.3)	15/600 (2.5)
Any chromosomal abnormality or syndrome — no./total no. (%)	200/599 (33.4)	183/600 (30.5)
Trisomy 21 chromosomal abnormality or Down's syndrome	108/598 (18.1)	94/600 (15.7)
DiGeorge syndrome or 22q11.2 deletion	18/598 (3.0)	29/600 (4.8)
Previous cardiothoracic operation — no./total no. (%)	81/599 (13.5)	110/600 (18.3)
Any preoperative risk factor — no./total no. (%)	223/594 (37.5)	212/594 (35.7)
Shock that was persistent at the time of surgery	2/594 (0.3)	2/594 (0.3)
Kidney dysfunction, kidney failure warranting dialysis, or both	20/594 (3.4)	27/594 (4.5)
Mechanical ventilator support	76/594 (12.8)	98/594 (16.5)
Neurologic deficit	14/594 (2.4)	9/594 (1.5)
Any other preoperative risk factor	169/594 (28.5)	163/594 (27.4)
Hypoplastic left heart syndrome or other single ventricle diagnosis — no./total no. (%)	92/599 (15.4)	99/600 (16.5)
Median duration of cardiopulmonary bypass (IQR) — min	122.0 (88.0–161.0)	121.0 (90.0–160.0)
STAT Mortality Category — no./total no. (%)‡		
1	225/598 (37.6)	194/599 (32.4)
2	179/598 (29.9)	198/599 (33.1)
3	87/598 (14.5)	86/599 (14.4)
4	54/598 (9.0)	62/599 (10.4)
5	53/598 (8.9)	59/599 (9.8)

Table 1. (Continued.)

Characteristic	Methylprednisolone (N=599)	Placebo (N=601)
Common primary procedures — no./total no. (%)		
Truncus arteriosus repair	4/599 (0.7)	8/600 (1.3)
Total anomalous pulmonary venous connection	21/599 (3.5)	14/600 (2.3)
Tetralogy of Fallot repair	70/599 (11.7)	74/600 (12.3)
Pulmonary atresia–VSD repair	7/599 (1.2)	15/600 (2.5)
Norwood procedure	45/599 (7.5)	48/600 (8.0)
Arterial switch operation	21/599 (3.5)	28/600 (4.7)
Coarctation of the aorta and aortic arch hypoplasia repair	47/599 (7.8)	45/600 (7.5)
Systemic to pulmonary artery shunt	11/599 (1.8)	19/600 (3.2)
VSD repair	96/599 (16.0)	80/600 (13.3)
Complete atrioventricular canal defect repair	80/599 (13.4)	62/600 (10.3)
Stage II single-ventricle palliation	44/599 (7.3)	56/600 (9.3)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and VSD ventricular septal defect.
† Race or ethnic group was reported by the patient's family.
‡ The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT) Mortality Category is based on a scale of 1 to 5, with lower values indicating less complex operations.

0.67 to 1.00) and a win ratio of 1.15 (95% CI, 1.00 to 1.32) in the methylprednisolone group as compared with the placebo group, findings suggestive of a benefit with methylprednisolone.

SECONDARY END POINT

The odds of bleeding warranting reoperation were lower in the methylprednisolone group than in the placebo group (adjusted odds ratio, 0.34; 95% CI, 0.14 to 0.81). With regard to other individual end-point events, operative death occurred in a similar percentage of patients in the methylprednisolone group and the placebo group (2.0% vs. 2.8%; adjusted odds ratio, 0.74; 95% CI, 0.34 to 1.57), as did the composite of death or major complication (17.2% vs. 20.3%; adjusted odds ratio 0.83; 95% CI, 0.61 to 1.13), prolonged mechanical ventilation (6.8% vs. 8.5%; adjusted odds ratio, 0.79; 95% CI, 0.50 to 1.25), postoperative low cardiac output syndrome (5.2% vs. 6.2%; adjusted odds ratio, 0.91; 95% CI, 0.52 to 1.57), and any postoperative infectious complication (5.2% vs. 4.0%; adjusted odds ratio, 1.39; 95% CI, 0.80 to 2.42) (Table S5). The median postoperative length of hospital stay was 10 days (interquartile range, 6 to 20) in the methylprednisolone group and 11 days (interquartile range, 6 to 23) in the placebo group (adjusted discharge rate ratio, 1.11; 95% CI, 0.99 to 1.25).

ADVERSE EVENTS AND OTHER OUTCOMES

The mean (±SD) peak blood glucose level within 72 hours after surgery was higher among the patients in the methylprednisolone group than among those in the placebo group (227.2±75.4 mg per deciliter vs. 188.7±60.1 mg per deciliter [12.6±4.2 mmol per liter vs. 10.5±3.3 mmol per liter], P<0.001), and the patients in the methylprednisolone group were more likely to receive postoperative insulin (19% vs. 6.7%, P<0.001). The percentage of patients who received hydrocortisone within 72 hours after surgery was lower in the methylprednisolone group than in the placebo group (20.2% vs. 29.0%, P=0.004). The percentages of patients with postoperative complications did not differ between the methylprednisolone group and the placebo group (Table 3 and Tables S6 and S7). Unexpected suspected serious adverse reactions occurred in two patients in the placebo group (one had a postoperative infection and the other underwent a second cardiopulmonary bypass procedure to repair a residual lesion); both events were determined by the data and safety monitoring board to be unrelated to placebo.

Table 2. Components of the Primary End Point with Global Rank.

End-Point Event	Rank According to Level of Prioritization	Methylprednisolone (N=599)	Placebo (N=601)
		no. of infants (%)	
Operative death	97	12 (2.0)	17 (2.8)
Heart transplantation during hospitalization	96	3 (0.5)	7 (1.2)
Kidney failure with permanent dialysis, neurologic deficit persistent at discharge, or respiratory failure warranting tracheostomy	95	4 (0.7)	8 (1.3)
Postoperative mechanical circulatory support or unplanned cardiac reoperation, exclusive of reoperation for bleeding	94	44 (7.3)	36 (6.0)
Reoperation for bleeding, unplanned delayed sternal closure, or unplanned interventional cardiac catheterization after surgery	93	12 (2.0)	30 (5.0)
Postoperative cardiac arrest, multisystem organ failure, kidney failure with temporary dialysis, or mechanical ventilator support for more than 7 days	92	24 (4.0)	22 (3.7)
Postoperative length of hospital stay			
>90 days	91	4 (0.7)	2 (0.3)
81 to 90 days	81 to 90	0	1 (0.2)
71 to 80 days	71 to 80	0	0
61 to 70 days	61 to 70	2 (0.3)	5 (0.8)
51 to 60 days	51 to 60	5 (0.8)	3 (0.5)
41 to 50 days	41 to 50	6 (1.0)	7 (1.2)
31 to 40 days	31 to 40	14 (2.3)	18 (3.0)
21 to 30 days	21 to 30	44 (7.3)	46 (7.7)
11 to 20 days	11 to 20	115 (19.2)	112 (18.6)
0 to 10 days	0 to 10	310 (51.8)	287 (47.8)

HETEROGENEITY OF TREATMENT EFFECT

An analysis of heterogeneity of treatment effect yielded results consistent with those of the primary end-point analysis (Fig. 2). Point estimates favored methylprednisolone over placebo across the majority of subgroups. Groups with relatively greater evidence of benefit included patients undergoing less complex operations (STAT Mortality Category of 1 to 3 [on a scale of 1 to 5, with lower values indicating less complex operations]) (adjusted odds ratio, 0.75; 95% CI, 0.60 to 0.94), patients with a longer duration of cardiopulmonary bypass (adjusted odds ratio for a duration of 180 minutes, 0.77; 95% CI, 0.60 to 0.99), and patients who were born premature (adjusted odds ratio, 0.80; 95% CI, 0.64 to 0.99). There was no site-dependent treatment effect (Fig. S2).

DISCUSSION

In this registry-based, randomized, controlled trial, perioperative use of methylprednisolone (30 mg per kilogram) did not significantly reduce the likelihood of a worse outcome but was associated with a higher likelihood of the patient receiving insulin for the treatment of hyperglycemia. Our overall findings are consistent with those from contemporary cardiopulmonary bypass trials of glucocorticoids in adults and children. The two largest adult trials, the Dexamethasone for Cardiac Surgery (DECS)[9] and the Steroids in Cardiac Surgery (SIRS)[8] trials, showed no benefit associated with prophylactic use of glucocorticoids. A mortality benefit with glucocorticoids was not observed in a subsequent meta-analysis that combined the data from the

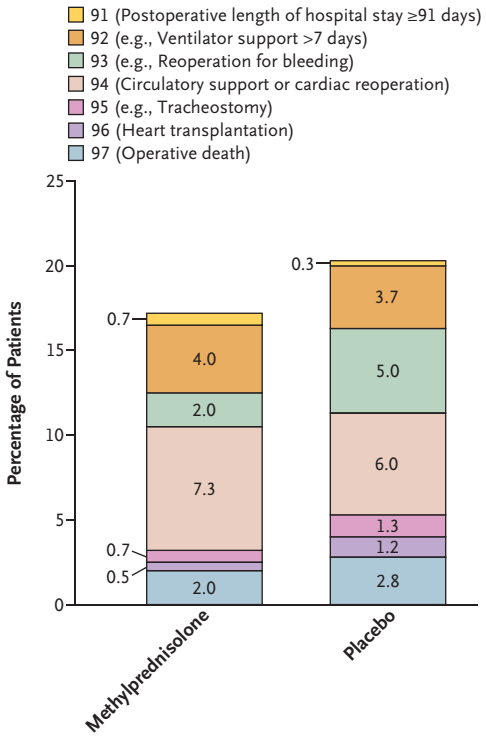

Figure 1. Binary Components of the Primary End Point in the Trial Population.

Components of the primary end point are ranked according to level of clinical prioritization, with operative death (ranked as 97) being the worst outcome.

DECS and SIRS trials, but the meta-analysis showed that the use of glucocorticoids led to reductions in the risks of respiratory failure (odds ratio, 0.83; 95% CI, 0.75 to 0.99) and infection (odds ratio, 0.80; 95% CI, 0.72 to 0.89) and in the lengths of stays in the intensive care unit ($P<0.001$) and hospital ($P=0.006$).[27]

The results of our trial are consistent with the results for the primary outcomes in the two most recent and largest pediatric trials: the Dexamethasone in Pediatric Cardiac Surgery (DECISION) trial[28] and the trial by Graham et al.[29] The DECISION trial involved 394 infants undergoing relatively lower-risk operations (85% of which were Risk Adjustment for Congenital Heart Surgery [RACHS-1] category 1 or 2 [categories range from 1 to 6, with higher values indicating higher-risk operations]) who were randomly assigned to receive dexamethasone or placebo, whereas the trial by Graham et al. involved a higher-risk cohort of 176 neonates who were randomly assigned to receive methylprednisolone or placebo. Both trials failed to show an overall benefit from prophylactic administration. However, Graham et al. found a benefit in patients undergoing palliative rather than reparative operations, and methylprednisolone recipients had lower overall requirements for vasoactive or inotropic agents.

Although we found no significant between-group difference in the covariate-adjusted primary analysis, the current trial showed a possible benefit with methylprednisolone in an unadjusted analysis of the primary end point and in our secondary analysis that used the win ratio. We chose to perform a covariate-adjusted primary analysis because of the heterogeneous nature of our population of patients with congenital heart disease[20] and because covariate adjustment increased the power in our trial simulations.[22] It is possible that methylprednisolone provides a small benefit that is negated by patient or procedural characteristics or by perioperative management strategies that are larger contributors to discrepancies in outcomes.

The only adverse effect judged to be associated with methylprednisolone was an increased incidence of hyperglycemia warranting insulin. Glucocorticoids cause insulin resistance, and hyperglycemia has been shown to be associated with glucocorticoids in previous trials.[8,9,28,29] Hyperglycemia may contribute to postoperative sepsis, acute kidney injury, prolonged mechanical ventilation, neurologic injury, and prolonged length of hospital stay.[30] Results of studies on the effect of glycemic control on morbidity and mortality after infant heart surgery are mixed, with some studies showing an improvement in outcomes and others not.[30-34]

The current trial was conducted as a pragmatic trial and leveraged registry resources to reduce costs, improve trial efficiency, and increase enrollment.[17] Direct trial costs were approximately $3.2 million, a cost estimated to be approximately a third of that for a traditional trial with similar enrollment. Other registry-based pragmatic trials involving adults have shown similar cost savings.[35,36] Resources are limited in pediatric cardiology,[37] and our trial, with an enrollment of 1200 infants, is among the largest trials involving children undergoing surgery for heart disease. Reducing trial costs and improving efficiency is necessary to facilitate

Table 3. Adverse Events.*

Adverse Event	Methylprednisolone (N = 599)	Placebo (N = 601)
	no. of infants (%)	
Patients with any adverse event	306 (51.1)	331 (55.1)
Cardiac disorders	155 (25.9)	176 (29.3)
Arrhythmia	133 (22.2)	135 (22.5)
Cardiac dysfunction	31 (5.2)	37 (6.2)
Cardiac arrest	14 (2.3)	21 (3.5)
Pericardial effusion	8 (1.3)	10 (1.7)
Intracardiac thrombus	2 (0.3)	1 (0.2)
Injury, poisoning, or procedural complication	153 (25.5)	162 (27.0)
Respiratory, thoracic, or mediastinal disorder	135 (22.5)	160 (26.6)
Surgical or medical procedure	74 (12.4)	76 (12.6)
Infection or infestation	43 (7.2)	38 (6.3)
Wound infection	14 (2.3)	21 (3.5)
Sepsis	22 (3.7)	11 (1.8)
Pneumonia	7 (1.2)	11 (1.8)
Mediastinitis	4 (0.7)	3 (0.5)
Vascular disorder	25 (4.2)	47 (7.8)
Venous occlusion	12 (2.0)	19 (3.2)
Hemorrhage	7 (1.2)	21 (3.5)
Deep-vein thrombosis	7 (1.2)	14 (2.3)
Investigation: cardiac catheterization	22 (3.7)	33 (5.5)
Nervous system disorder	17 (2.8	17 (2.8)
General disorder or administration site condition: multiple-organ dysfunction syndrome	3 (0.5)	6 (1.0)
Renal or urinary disorder: acute kidney injury	4 (0.7)	4 (0.7)

* In this type of trial involving patients undergoing surgery, adverse events related to the operation are expected. A full list of adverse events is provided in Tables S6 and S7.

future randomized, controlled trials in this vulnerable patient population.[37]

This trial has several limitations. First, it is possible that registry data are not as accurate as data collected and placed into a traditional trial database. Nathan et al.[38] previously documented an overall accuracy of 98% for nonmissing data in the STS-CHSD. Trial personnel received additional training on data element definitions, and our trial had no missing data regarding complication-related outcomes. We did not perform separate outcome adjudication in order to limit expense, a practice consistent with the overarching objective of our registry-embedded design. Second, enrolled patients were permitted to receive postoperative glucocorticoids. Hydrocortisone is sometimes administered to treat low cardiac output syndrome and was more frequently administered to patients in the placebo group in the trial, a circumstance that may have limited the benefit of the active intervention. Limiting the postoperative administration of glucocorticoids would have compromised trial enrollment and threatened physician equipoise. Moreover, this trial design was consistent with that of a pragmatic trial in that it allowed for evaluation in a real-world setting. Our primary end point was developed on the basis of investigator consensus with support from extensive trial simulations with the use of STS-CHSD data.[17,22] The investigators had agreed that all the components of the outcome were important and

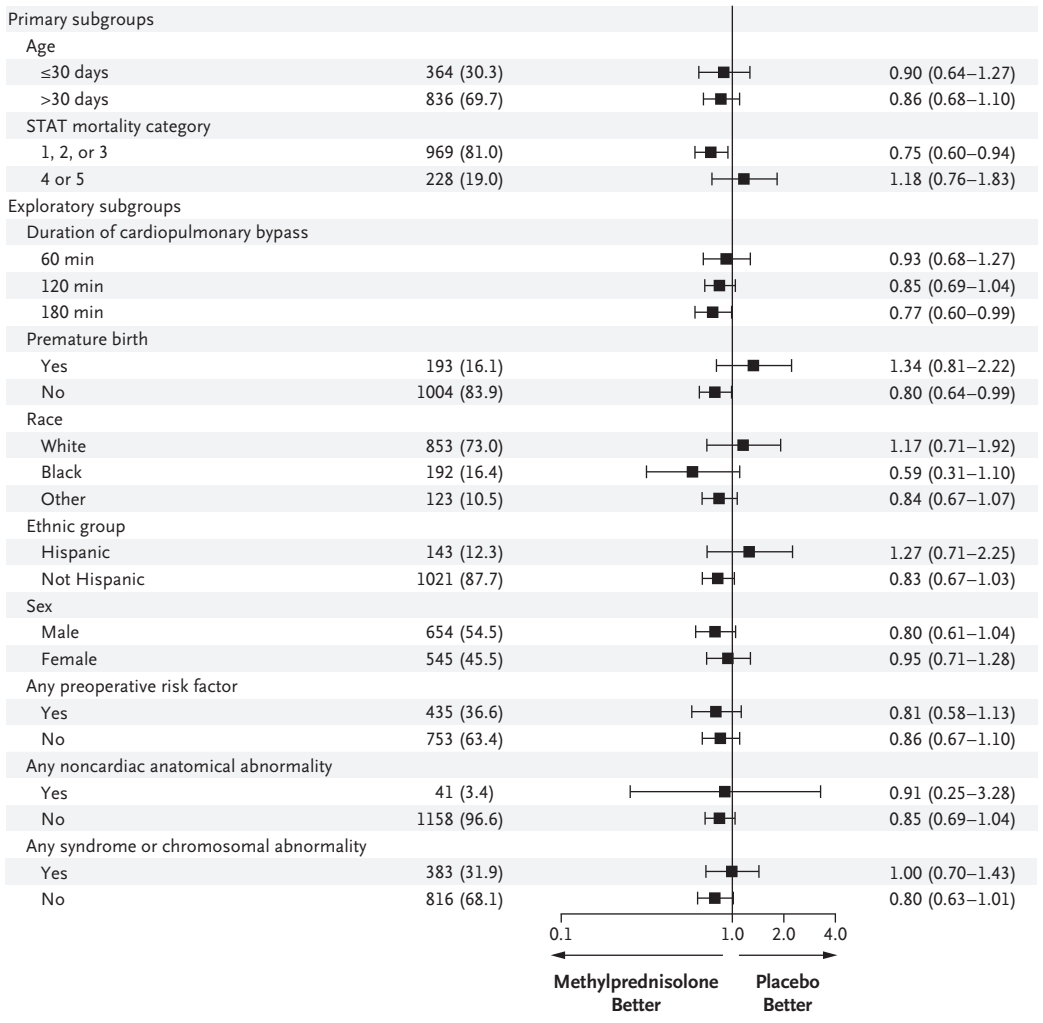

Figure 2. Subgroup Analyses of Estimated Treatment Effects across Categories of Prespecified Baseline Risk Factors.

The adjusted odds ratios are for a worse outcome with respect to the primary composite end point. The odds ratios were adjusted for age, weight, prematurity status, and the 2020 Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT) Mortality Category. Factors associated with relatively greater evidence of a treatment benefit included less complex operations (STAT Mortality Category 1 to 3 [on a scale of 1 to 5, with lower values indicating less complex operations]), longer duration of cardiopulmonary bypass, and no history of prematurity. The duration of cardiopulmonary bypass was analyzed as a continuous variable; the values of 60, 120, and 180 minutes are representative durations, and the adjusted odds ratios reflect the odds of a worse outcome at each of these time points in the continuous distribution. Race and ethnic group were reported by the patient's family.

could be affected by prophylactic glucocorticoids. In the subgroup analysis, there appeared to be a suggestion of directionality of the between-group differences in favor of methylprednisolone over placebo with respect to improved outcomes across the subgroups, although this subgroup analysis was underpowered. In the secondary unadjusted analysis and the analysis that used the win ratio, there appeared to be a benefit associated with methylprednisolone administration. Further study is needed to evaluate the role of postoperative glucocorticoids and whether a more targeted approach might offer benefit in select subpopulations.

In this randomized trial involving infants younger than 1 year of age who were undergoing heart surgery with cardiopulmonary bypass, prophylactic use of methylprednisolone did not reduce the likelihood of a worse outcome — a ranked composite of death, heart transplantation, major complications, and length of hospital stay — in an adjusted analysis and was associated with an increased risk of postoperative hyperglycemia.

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

APPENDIX

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REFERENCES

1. Jacobs JP, Mayer JE Jr, Pasquali SK, et al. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2019 update on outcomes and quality. Ann Thorac Surg 2019;107:691-704.
2. Anderson BR, Fieldston ES, Newburger JW, Bacha EA, Glied SA. Disparities in outcomes and resource use after hospitalization for cardiac surgery by neighborhood income. Pediatrics 2018;141(3):e20172432.
3. Ashraf SS, Tian Y, Zacharrias S, Cowan D, Martin P, Watterson K. Effects of cardiopulmonary bypass on neonatal and paediatric inflammatory profiles. Eur J Cardiothorac Surg 1997;12:862-8.
4. Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996-1002.
5. Asimakopoulos G. Systemic inflammation and cardiac surgery: an update. Perfusion 2001;16:353-60.
6. Moat NE, Shore DF, Evans TW. Organ dysfunction and cardiopulmonary bypass: the role of complement and complement regulatory proteins. Eur J Cardiothorac Surg 1993;7:563-73.
7. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest 1997;112:676-92.
8. Whitlock RP, Devereaux PJ, Teoh KH, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243-53.
9. Dieleman JM, Nierich AP, Rosseel PM, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 2012;308:1761-7.
10. Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995;92:2226-35.
11. Jacobs JP, He X, Mayer JE Jr, et al. Mortality trends in pediatric and congenital heart surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg 2016;102:1345-52.
12. Jacobs ML, O'Brien SM, Jacobs JP, et al. An empirically based tool for analyzing morbidity associated with operations for congenital heart disease. J Thorac Cardiovasc Surg 2013;145(4):1046.e1-1057.e1.
13. Scrascia G, Rotunno C, Guida P, et al. Perioperative steroids administration in pediatric cardiac surgery: a meta-analysis of randomized controlled trials. Pediatr Crit Care Med 2014;15:435-42.
14. Li Y, Luo Q, Wu X, Jia Y, Yan F. Perioperative corticosteroid therapy in children undergoing cardiac surgery: a systematic

review and meta-analysis. Front Pediatr 2020;8:350.
15. Bronicki RA, Flores S, Loomba RS, et al. Impact of corticosteroids on cardiopulmonary bypass induced inflammation in children: a meta-analysis. Ann Thorac Surg 2021;112:1363-70.
16. Lauer MS, D'Agostino RB Sr. The randomized registry trial — the next disruptive technology in clinical research? N Engl J Med 2013;369:1579-81.
17. Hill KD, Baldwin HS, Bichel DP, et al. Rationale and design of the STeroids to REduce Systemic inflammation after infant heart Surgery (STRESS) trial. Am Heart J 2020;220:192-202.
18. Jacobs JP, Mavroudis C, Jacobs ML, et al. What is operative mortality? Defining death in a surgical registry database: a report of the STS Congenital Database Taskforce and the Joint EACTS-STS Congenital Database Committee. Ann Thorac Surg 2006;81:1937-41.
19. Overman DM, Jacobs JP, Prager RL, et al. Report from the Society of Thoracic Surgeons National Database Workforce: clarifying the definition of operative mortality. World J Pediatr Congenit Heart Surg 2013;4:10-2.
20. Kahan BC, Jairath V, Doré CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. Trials 2014;15:139.
21. O'Brien SM, Jacobs JP, Pasquali SK, et al. The Society of Thoracic Surgeons Congenital Heart Surgery Database mortality risk model: part 1 — statistical methodology. Ann Thorac Surg 2015;100:1054-62.
22. Hill KD, Baldwin HS, Bichel DP, et al. Overcoming underpowering: trial simulations and a global rank end point to optimize clinical trials in children with heart disease. Am Heart J 2020;226:188-97.
23. Jacobs ML, Jacobs JP, Thibault D, et al. Updating an empirically based tool for analyzing congenital heart surgery mortality. World J Pediatr Congenit Heart Surg 2021;12:246-81.
24. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33:176-82.
25. Agresti A. Generalized odds ratios for ordinal data. Biometrics 1980;36:59-67.
26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
27. Whitlock RP, Dieleman JM, Belley-Cote E, et al. The effect of steroids in patients undergoing cardiopulmonary bypass: an individual patient meta-analysis of two randomized trials. J Cardiothorac Vasc Anesth 2020;34:99-105.
28. Lomivorotov V, Kornilov I, Boboshko V, et al. Effect of intraoperative dexamethasone on major complications and mortality among infants undergoing cardiac surgery: the DECISION randomized clinical trial. JAMA 2020;323:2485-92.
29. Graham EM, Martin RH, Buckley JR, et al. Corticosteroid therapy in neonates undergoing cardiopulmonary bypass: randomized controlled trial. J Am Coll Cardiol 2019;74:659-68.
30. Polito A, Thiagarajan RR, Laussen PC, et al. Association between intraoperative and early postoperative glucose levels and adverse outcomes after complex congenital heart surgery. Circulation 2008;118:2235-42.
31. Ballweg JA, Wernovsky G, Ittenbach RF, et al. Hyperglycemia after infant cardiac surgery does not adversely impact neurodevelopmental outcome. Ann Thorac Surg 2007;84:2052-8.
32. DeCampli WM, Olsen MC, Munro HM, Felix DE. Perioperative hyperglycemia: effect on outcome after infant congenital heart surgery. Ann Thorac Surg 2010;89:181-5.
33. Agus MSD, Steil GM, Wypij D, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. N Engl J Med 2012;367:1208-19.
34. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.
35. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587-97.
36. Rao SV, Hess CN, Barham B, et al. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial. JACC Cardiovasc Interv 2014;7:857-67.
37. Torok RD, Li JS, Kannankeril PJ, et al. Recommendations to enhance pediatric cardiovascular drug development: report of a multi-stakeholder think tank. J Am Heart Assoc 2018;7(4):e007283.
38. Nathan M, Jacobs ML, Gaynor JW, et al. Completeness and accuracy of local clinical registry data for children undergoing heart surgery. Ann Thorac Surg 2017;103:629-36.