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RISK FACTORS FOR SURGICAL SITE INFECTION AFTER CARDIAC SURGERY IN THE PAEDIATRIC AGE GROUP

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Abstract:

Postoperative surgical site infections are a major cause of postoperative morbidity and mortality in cardiac surgery. While surgical site infection in adult cardiac surgery has been well characterized and studied, in paediatric cardiac surgery, the classification, prevention, and management is less well studied and significant practice variation exists.

We performed a post hoc exploratory analysis of 980 children from birth to 36 months of age at the time of cardiac surgery who were randomized to postoperative TGC or STD in the intensive care unit. Significant interactions were observed between the treatment group and both neonates (age ≤30 days; P=0.03) and intraoperative glucocorticoid exposure (P=0.03) on the risk of infection. The rate and incidence of infections in subjects ≤60 days old were significantly increased in the TGC compared with the STD group (rate: 13.5 versus 3.7 infections per 1000 cardiac intensive care unit days, P=0.01; incidence: 13% versus 4%, P=0.02), whereas infections among those >60 days of age were significantly reduced in the TGC compared with the STD group (rate: 5.0 versus 14.1 infections per 1000 cardiac intensive care unit days, P=0.02; incidence: 2% versus 5%, P=0.03);The interaction of treatment group by age subgroup was highly significant (P=0.001). Multivariable logistic regression controlling for the main effects revealed that previous cardiac surgery, chromosomal anomaly, and delayed sternal closure were independently associated with increased risk of infection.

This exploratory analysis demonstrated that TGC may lower the risk of infection in children >60 days of age at the time of cardiac surgery compared with children receiving STD. Meta-analyses of past and ongoing clinical trials are necessary to confirm these findings before clinical practice is altered.

Keywords: Antibiotic prophylaxis, cardiac surgery, complications, morbidity, Readmissions.

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BACKGROUND:

Delayed sternal closure (DSC) is frequently required in the care of paediatric patients who have undergone cardiac surgery to minimize postoperative respiratory and hemodynamic instability. Although necessary for the treatment of unstable patients, DSC may expose patients to an increased risk of hospital-acquired infections, including bloodstream4 and surgical site infections (SSIs). SSI remains a rare complication for patients undergoing congenital heart surgery (CHS), but when present it is associated with significant morbidity, mortality, and health care costs. Recent studies demonstrate that the incidence of SSI and associated mortality rate in CHS patients undergoing DSC [1].

Accordingly, paediatric patients with critical illness experience high rates of hyperglycaemia while hospitalized in the intensive care unit. Almost 90% of children undergoing cardiac surgery develop hyperglycaemia in the postoperative period. Previous observational studies provide conflicting evidence about the association between hyperglycaemia and morbidity and mortality in these patients. Data from adult cardiac surgical populations8 suggested the need for an experimental trial to determine whether postoperative tight glycaemic control (TGC) with insulin therapy provided benefit over standard blood glucose management [2].

We previously reported the results of the Safe Paediatric Euglycemia after Cardiac Surgery (SPECS) trial in which we compared TGC with standard care (STD) in patients from birth to 36 months of age undergoing cardiac surgery with cardiopulmonary bypass and showed that TGC did not reduce the incidence of postoperative health care–associated infections or mortality [1]. Vulnerable patient populations likely to be at high risk of SSI, such as that requiring extracorporeal membrane oxygenation (ECMO) support, have been excluded from previous studies. Furthermore the potential causative factors for SSI in this patient population have been as yet incompletely explored or characterized. A clear understanding of outcomes and risk factors is essential because they may affect clinical decision making for cardiac surgeons and intensivists caring for these patients [3].

Although we found no differences between the TGC and STD groups in the SPECS trial, it remains possible that heterogeneity of treatment effect exists across the study population; both the effectiveness and safety of the treatment can vary between patients with different risks for the primary outcome and treatment harm. Therefore, we aimed to investigate whether there were differential effects of TGC on outcomes in certain identifiable subgroups within the SPECS trial cohort. We focused this analysis on subgroups believed a priori to be at higher risk for infections and other morbidities. The results of this exploratory analysis are meant to inform subsequent research on TGC in critically ill children so that conflicting evidence and remaining knowledge gaps can be specifically addressed in future experimental trials and meta-analyses [4].

METHODS:

The present study is a post hoc analysis of the SPECS study database. The SPECS trial methods, statistical analysis plan, and results have previously been published. The primary outcome for the trial was the incidence of 30-day health care–associated infections, which included pneumonia, bloodstream, urinary tract, and surgical site infections, as defined by Centres for Disease Control and Prevention; per 1000 CICU days. Secondary outcomes included mortality, cardiac index, duration of vasoactive support and mechanical ventilation, and CICU length of stay. Cardiac index was determined on postoperative day 2 in patients who were mechanically ventilated and sedated and had a superior vena cava or pulmonary artery catheter in situ.

We calculated cardiac index by the Fick principle using oxygen consumption (o2) measured by indirect calorimetric, haemoglobin concentration,

and the difference between arterial and mixed venous oxygen saturation, as previously validated. In the overall cohort, no treatment effect was identified in any of the primary or secondary outcomes.

To compare infection rates of SPECS subjects with historical trends, we compiled infection data for children <3 years of age who were admitted to the Children Hospital ICU after cardiopulmonary bypass surgery but who did not participate in SPECS. All patients meeting these criteria were included. Infections in non-study patients were defined according to the same "Centres for Disease Control and Prevention" criteria used in SPECS and were adjudicated by the same individuals.

STATISTICAL ANALYSIS

We previously reported pre-specified, high-risk subgroup analyses for patients with a Risk Adjustment in Congenital Heart Surgery (RACHS-1) category16 of ≥3 (or not assignable) or a length of stay in the CICU of ≥3 days; the latter analysis was based on a post-randomization factor. We subsequently performed several stratified post hoc analyses to determine whether TGC had a differential effect on infection incidence in 7 other specific subgroups of the patient cohort. On the basis of chance alone, we would expect that 0.35 of 7 tests for interaction would be statistically significant at the P<0.05 level. The variables used for stratification were those that identified certain subgroups at greater risk of infection and other postoperative morbidities. Seven risk factors present before protocol initiation were considered:

(1) Age at surgery (≤30 versus >30 days),

(2) Previous cardiac surgery,

(3) Chromosomal anomaly,

(4) Intraoperative glucocorticoid therapy,

(5) Non-biological surgical implant used for repair,

(6) Delayed sternal closure, and (7) first postoperative blood glucose (>110 versus ≤110 mg/dL). Some of these variables, for example, surgical complexity and delayed sternal closure, have been associated with increased risk of health care–associated infection in prior analyses, whereas others (e.g., chromosomal anomalies and age) have been known to be associated with mortality and morbidity generally but not specifically with infection.

Within a subgroup, the effect of TGC on infection was assessed with the use of odds ratios and exact 95% confidence intervals derived from conditional logistic regression. Potential differential effects of TGC on infection across subgroups were analysed with the use of exact logistic regression that included the interaction between treatment group and risk factor after both were included as main effects. Given the observed heterogeneity of treatment effect by age at surgery, we explored logistic regression models that included the effects of treatment group, age subgroup, and their interaction using different age cut offs. We then used maximum likelihood and a likelihood ratio test–based confidence interval to select an optimal age cut off. Using this optimal age cut off, we then assessed the potential differential effects of TGC on other outcomes across age subgroups using exact logistic regression for binary outcomes, exact Poisson regression for count outcomes or rates, Cox proportional hazards regression for time-to-event outcomes, and linear regression for continuous outcomes. To explore other potential predictors of infection, multivariable stepwise logistic regression was used. Infections rates in non-study patients ≤60 days old were compared with rates in non-study patients >60 days old with the use of exact Poisson regression. The reporting of results below follows the guidelines for reporting subgroup analyses.

RESULTS:

All 980 subjects from the original SPECS trial were included in the analyses. It was observed that the proportion of subjects with any 30-day health care–associated infection and the odds ratio for infection by treatment arm (TGC versus STD) within each of the subgroups and the results of the associated tests for interaction. Exact logistic regression analyses demonstrated significant interactions between treatment group and both neonate (age ≤30 days, P=0.03) and intraoperative glucocorticoid use (P=0.03) on the risk of infection. Although the point estimates suggested a possible harmful effect of TGC in neonates (age ≤30 days at surgery) and a possible benefit of TGC in patients who did not receive intraoperative glucocorticoids, neither effect was statistically significant at the 0.05 level (P=0.07 and P=0.09, respectively).

Table 1

Effect of Tight Glycemic Control on Healthcare-Associated Infections in Subgroups

Subgroup	Patients, No.		Patients with Infection[a], No. (%)		Odds Ratio (Exact 95% CI)	Exact *P* Value for Interaction
	TGC	STD	TGC	STD		
Overall	490	490	24 (5)	24 (5)	1.00 (0.54-1.87)	-
RACHS-1 category[c]						0.09
≥3 or Not assignable	263	250	21 (8)	15 (6)	1.36 (0.65-2.91)	
1-2	227	240	3 (1)	9 (4)	0.34 (0.06-1.40)	
Age at surgery						0.03
≤30 days	99	99	12 (12)	4 (4)	2.95 (0.85-13.05)	
>30 days	391	400	12 (3)	20 (5)	0.60 (0.26-1.31)	
Previous cardiac surgery						0.37
Yes	119	118	7 (6)	10 (8)	0.68 (0.21-2.05)	
No	371	372	17 (5)	14 (4)	1.23 (0.56-2.74)	
Chromosomal anomaly						0.33
Yes	94	98	5 (5)	9 (9)	0.56 (0.14-1.94)	
No	396	392	19 (5)	15 (4)	1.27 (0.60-2.72)	
Intraoperative glucocorticoid therapy						0.03
Yes	255	247	19 (7)	11 (4)	1.73 (0.76-4.11)	
No	235	243	5 (2)	13 (5)	0.39 (0.11-1.18)	
Implant left during surgery						1.0
Yes	317	320	18 (6)	19 (6)	0.95 (0.46-1.96)	
No	173	170	6 (3)	5 (3)	1.19 (0.30-5.01)	
Delayed sternal closure						0.53
Yes	63	58	10 (16)	7 (12)	1.37 (0.43-4.59)	
No	427	432	14 (3)	17 (4)	0.83 (0.37-1.81)	
First post-operative blood glucose						1.0
>110 mg/dL	352	356	19 (5)	19 (5)	1.01 (0.50-2.06)	
≤110 mg/dL	138	134	5 (4)	5 (4)	0.97 (0.22-4.32)	

Given the observed heterogeneity of treatment effect by age at surgery, we next sought to determine empirically an optimal age cutoff. We explored this by running logistic regression models that included the main effects of treatment group and age subgroup and the interaction term as covariates, in which age subgroup was defined using different cutoffs from 30 days to 12 months. Plotting the log likelihood from these models versus age cutoff demonstrated that an age cutoff of 59 days (95% confidence interval, via the likelihood ratio test) best discriminated age subgroups with differential risk of infection based on treatment arm. The difference in model characteristics was negligible when comparing models using an age cutoff of ≤59 days versus ≤60 days, so for subsequent analyses and ease of reporting, we defined the age subgroups as those ≤60 days or >60 days at the time of surgery [5].

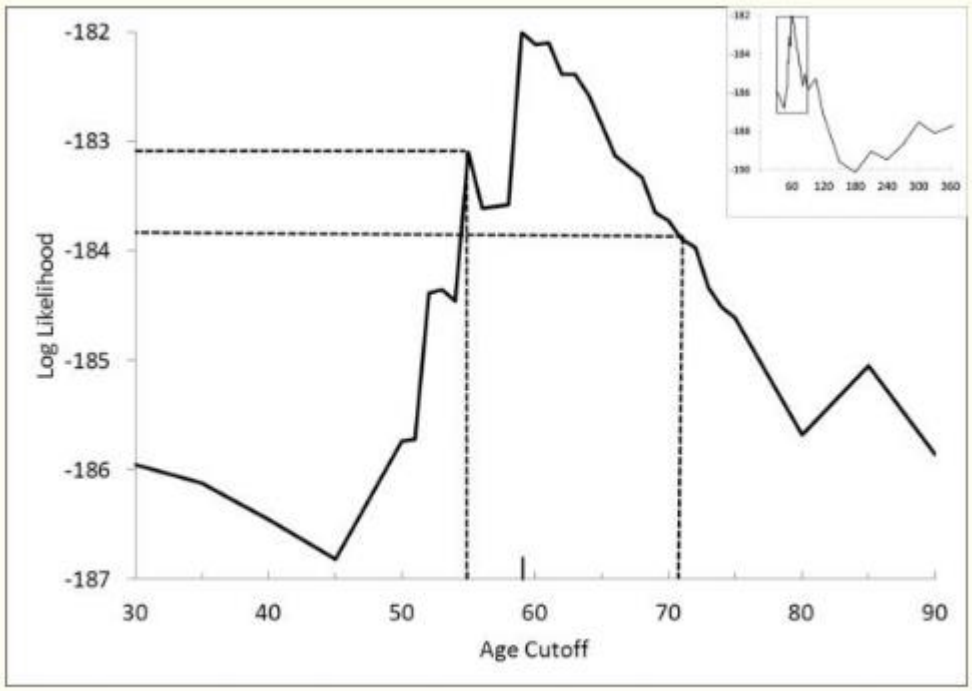


Figure 1

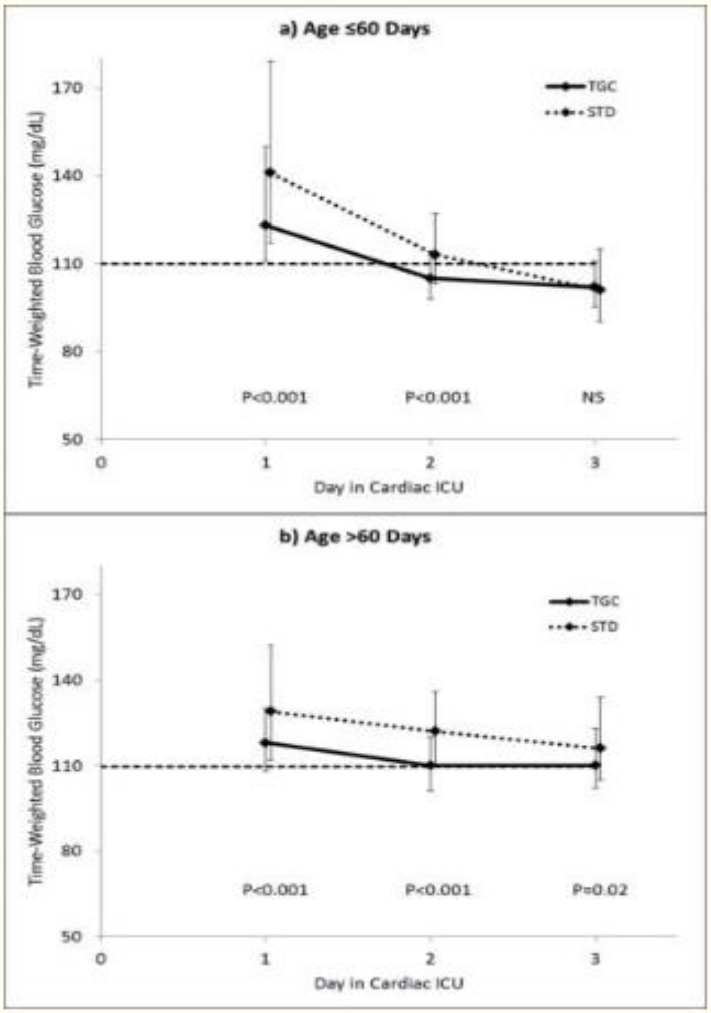
The rate and incidence of health care–associated infections in subjects ≤60 days of age were significantly increased among those in the TGC group compared with the STD group (rate: 13.5 versus 3.7 infections per 1000 CICU days, P=0.01; incidence: 13% versus 4%, P=0.02), whereas the rate and incidence of infections among those >60 days of age were significantly reduced in the TGC group compared with the STD group (rate: 5.0 versus 14.1 infections per 1000 CICU days, P=0.02; incidence: 2% versus 5%, P=0.03). The treatment group–by–age subgroup interactions were highly significant (P=0.001 for each). These analyses did not appreciably change with adjustment for site. There was a differential treatment group–by–age subgroup effect across the 4 Centres for Disease Control and Prevention–defined infection types [6] [7].

Table 2

Healthcare-Associated Infections, According to Treatment Group and Age Subgroup

Infections Outcome	Age ≤60 Days		Relative Risk or Odds Ratio (Exact 95% CI)	Age >60 Days		Relative Risk or Odds Ratio (Exact 95%)	Exact *P* Value for Interaction[a]
	TGC (n=128)	STD (n=113)		TGC (n=362)	STD (n=377)		
Infections[b], no. of patients (%)							
Any infections							
Yes	16 (13)	4 (4)	3.87 (1.20-16.43)	8 (2)	20 (5)	0.40 (0.15-0.97)	0.001
No	112 (88)	109 (96)		354 (98)	357 (95)		
No. of infections							
0	112 (88)	109 (96)		354 (98)	357 (95)		0.001
1	16 (13)	4 (4)		8 (2)	18 (5)		
2	0	0		0	2 (<1)		
30-day rate of healthcare-associated infections, no. of infections/1,000 days in CICU	13.5	3.7	3.68 (1.19-15.11)	5.0	14.1	0.39 (0.15-0.92)	0.001
Type of infection, no.							
Pneumonia	1	0		2	3		
Bloodstream	3	0		0	4		
Urinary tract	1	0		1	6		
Surgical site	11	4		5	9		

TGC denotes Tight Glycemic Control, STD Standard Care, CI confidence interval, and CICU cardiac intensive care unit.



Blood glucose management differed slightly across the 2 age subgroups, with the percentage of subjects receiving insulin being slightly higher in the younger subgroup (age ≤60 days: TGC, 95% versus STD, 6%; age >60 days: TGC, 89% versus STD, <1%; P for interaction=0.048) but was otherwise not distinguishable. Rates of any hypoglycemia (blood glucose <60 mg/dL) were similarly (P for interaction=0.84) elevated in the TGC arm compared with the STD arm in both the younger cohort (TGC, 35% versus STD, 18%) and the older cohort (TGC, 13% versus STD, 7%). The overall time-weighted glucose average was significantly different (P<0.001) between treatment groups in both age subgroups (age ≤60 days: TGC [median], 107 mg/dL [interquartile range, 100–115 mg/dL] versus STD, 112 [interquartile range, 104–125 mg/dL]; age >60 days: TGC, 114 mg/dL [interquartile range, 106–122 mg/dL] versus STD, 124 mg/dL [interquartile range, 111–140 mg/dL]). Examination of daily time-weighted glucose average revealed that time-weighted glucose average in the TGC group was significantly lower on days 1 and 2 compared with the STD group for patients ≤60 days, whereas in the older cohort, the time-weighted glucose average difference between treatment arms extended to 3 days, increasing the duration of exposure to treatment differences from TGC within the subgroup of patients >60 days of age [8] [9]

There was an increased incidence of transfusion amongst those ≤60 days randomized to TGC (TGC 76% vs. STD 63%; P=0.04), while there was no difference between treatment groups in the >60 days subgroup. The frequency of blood glucose sampling in the overall TGC cohort was greater than in the STD cohort (TGC mean 17 times per CICU day vs. STD 4 times per CICU day). The interaction between treatment group and age subgroup for this analysis was not significant at the 0.05 level (P=0.058).

To explore the potential effects of other factors present prior to protocol initiation on infection, we performed multivariable stepwise logistic

regression adjusting for treatment group, age subgroup, and their interaction. Other factors significantly associated with infection included previous cardiac surgery [OR (95% CI) 3.08 (1.41-6.72); P=0.003], chromosomal anomaly [3.05 (1.39-6.51); P=0.005], and delayed sternal closure [4.32 (1.83-10.19); P<0.001]. Although intraoperative glucocorticoid use differed by age (71% subjects ≤60 days received glucocorticoids vs. 45% subjects >60 days; P<0.001), further adjustment for intraoperative glucocorticoid use did not appreciably affect these results. Similarly, further adjustment for site did not appreciably affect the results [10]

DISCUSSION:

In this exploratory analysis of our study cohort from a large, randomized, controlled trial of TGC, we found differential response to the intervention among patients ≤60 days versus those >60 days of age at the time of surgery. Our analysis suggests that younger patients had an increased rate of health care–associated infections with TGC compared with STD, whereas the older patients had a lower rate with TGC compared with STD. There is a history of younger children having increased mortality with insulin therapy in the Neonatal Insulin Replacement Therapy in Europe (NIRTURE) trial. The NIRTURE study was ongoing at the time of the design of our trial and was subsequently halted early as a result of potential for harm in the treatment group. Other TGC trials in children have not reported analyses of the interaction of treatment group with age subgroups [11] [12].

The striking interaction between treatment group and age subgroup on infection rates led us to investigate other clinical outcomes to further explore the benefits of TGC in the older patients. We observed that patients >60 days treated with TGC had significantly higher cardiac index on post-operative day 2 compared to those in the STD arm, though the interaction between treatment group and age subgroup on this outcome was not statistically significant. This analysis was limited to those in the Boston Children's Hospital CICU with a central venous catheter in the superior vena caval circulation, and who remained intubated on the second post-operative day, as the measurement of oxygen consumption was conducted via the ventilator exhalation valve. Though it is a smaller subset of the overall cohort (N=191), this group of patients, due to higher illness severity, may be most likely to derive benefit from TGC if benefit exists. Both in vitro studies and prior clinical reports demonstrate the potential benefits to the myocardium of controlling blood glucose with insulin infusion, specifically in mitigating the effects of ischemia-reperfusion injury. Improved myocardial recovery should lead to other important outcome differences, but we observed similar durations of mechanical ventilation, vasoactive support, and CICU and hospital length of stay between treatment arms in the >60 days subgroup. However, these outcomes were calculated for the entire >60 days subgroup, so it may be that only those patients with greater post-operative organ dysfunction (e.g., those mechanically ventilated greater than 48 hours) reap the benefits of TGC. Further analysis of past and ongoing pediatric TGC clinical trials, focusing on patients with the greatest illness severity, may elucidate the possible benefits of TGC to cardiopulmonary recovery [13] [14].

Younger patients in the TGC arm also had a higher transfusion rate compared to the STD arm, and there was a trend toward a significant interaction between treatment group and age subgroup on transfusion (P=0.058). The increased transfusion rate in the TGC subjects in the ≤60 days cohort is likely a reflection of the increased frequency of blood glucose sampling in the overall TGC cohort compared with STD. Given the smaller body mass and circulating blood volume in the ≤60 day's cohort, a similar volume of blood drawn would represent a greater relative amount of blood loss, possibly leading to an increased transfusion rate. This would explain why the same difference in number of blood draws was not associated with increased transfusion rate in the older cohort. We attempted to mitigate this effect in the trial design by using a blood conservation device as well as a bedside glucose meter that required small amounts of blood. There are important limitations to the findings reported in this manuscript. Most importantly, these are exploratory findings based on our initial observation that statistically significant interactions existed between treatment group and age subgroup on rate and incidence of infection [15] [16].

Although there is biologic plausibility for differential immune function at 60 days of age, the age cut off we report here has not been suggested before in the critical care or TGC clinical literature. Some strengths of our analysis, however, are that this secondary analysis showed a statistically significant treatment group with age subgroup interaction on our primary outcome variable, the 95% confidence interval for the optimal age cut-off was fairly tight (55-71 days), and the characteristics of our STD cohort are consistent with a historical CICU population. We have conducted our analysis and reported the findings in accordance with guidelines recommended by other authors for subgroup analyses of randomized clinical trials. To remain consistent with these

recommendations, the findings herein should be interpreted conservatively. The results are appropriately considered hypothesis-generating, rather than confirmatory. It will be crucial to evaluate whether patients greater than 60 days of age demonstrate benefit from TGC in analyses of recent and ongoing clinical trials in the context of a planned meta-analysis. However, based on the overall null finding in the trial, and the results of this analysis, we would not recommend post-operative TGC for patients ≤60 days of age who undergo cardiac surgery [17] [18].

To the best of our knowledge, there are no other data suggesting a 60-day age cut off for differential response to TGC. It is conceivable that TGC confers benefits that have more relevance to the older child whose maternally-acquired, antibody-mediated immunity has waned, as opposed to the infant who also may be more susceptible to protocol-associated hypoglycemia and anemia. These theories will remain speculative, however, until further data can confirm the presence of a differential effect >60 versus ≤60 days of age in other TGC trial populations [19] [20] .

CONCLUSION:

We have conducted our analysis and reported the findings in accordance with guidelines recommended by other authors for subgroup analyses of randomized, clinical trials. To remain consistent with these recommendations, the findings presented here should be interpreted conservatively. The results are appropriately considered hypothesis generating rather than confirmatory. It will be crucial to evaluate whether patients >60 days of age demonstrate benefit from TGC in analyses of recent and ongoing clinical trials in the context of a planned meta-analysis. However, on the basis of the overall null finding in the trial and the results of this analysis, we would not recommend postoperative TGC for patients ≤60 days of age who undergo cardiac surgery.

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