Dexamethasone for Preventing Major Adverse Kidney Events following Cardiac Surgery – Post-Hoc Analysis to Identify Subgroups

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Acute kidney injury (AKI) is a serious and frequent complication of cardiac surgery, occurring in up to one-third of patients (1). Despite years of investigation, therapies to prevent cardiac surgery-associated AKI (CSA-AKI) are lacking.

Glucocorticoids have been suggested as a potential therapy to prevent CSA-AKI, since inflammation induced by cardiac surgery could contribute to AKI in this setting. The Dexamethasone for Cardiac Surgery (DECS) study tested this hypothesis in a multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT00293592) in 4494 adults undergoing cardiac surgery with cardiopulmonary bypass (CPB) (2). Patients received a single intravenous dose of dexamethasone (1mg/kg) or placebo prior to initiation of CPB (additional details are reported elsewhere) (2).

Although the DECS trial did not find an effect of dexamethasone on the incidence of AKI, the definition used for AKI – a tripling of serum creatinine (SCr) postoperatively – did not include the requirement for renal replacement therapy (RRT). Thus, extracorporeal clearance of creatinine in patients who required RRT could have resulted in a discrepancy between actual AKI events and its protocol definition. We therefore previously conducted a post hoc analysis in which we defined AKI as the requirement for RRT. We found the incidence of AKI requiring RRT was lower in dexamethasone- vs. placebo-treated patients (relative risk [RR], 0.44; 95% confidence interval [CI], 0.19 to 0.96). In stratified analyses, the benefit of dexamethasone appeared greatest in patients with lower baseline eGFR (3).

Since it is unknown whether factors other than kidney function might modify the effect of dexamethasone on CSA-AKI, we investigated the treatment effect of dexamethasone on AKI across various subgroups of patient- and surgical characteristics. We reasoned that detection of heterogeneity across subgroups in the efficacy of dexamethasone could allow for more precise targeting of high-risk patients in future trials of glucocorticoid prophylaxis.

In the current analyses, we included 4465 (99.4%) of the 4494 patients enrolled in the original DECS trial (29 were excluded for reasons published previously) (3). We defined the baseline SCr as the value prior to and closest to cardiac surgery (in all cases at least one value was available within 30 days preceding surgery). The primary endpoint for the current
analyses was Major Adverse Kidney Events within 30 days (MAKE30) of surgery, defined as an increase in SCr ≥50%, RRT, or death at any time within the first 30 days after surgery. Secondary endpoints were AKI stages 1, 2, and 3, respectively, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (4). We performed subgroup analyses according to pre-determined baseline patient- and surgical variables (Table 1B), and we assessed for effect modification by subgroup using logistic regression. P values <0.05 were considered significant.

The incidence of MAKE30, along with AKI stages 1, 2, and 3, was lower in dexamethasone- compared to placebo-treated patients (Table 1A). Table 1B shows the incidence of MAKE30 according to the following subgroups: age, EuroSCORE (European System for Cardiac Operative Risk Evaluation) (5), gender, BMI, hypertension, diabetes mellitus, pulmonary disease, peripheral vascular disease, chronic kidney disease, left ventricular function, type of surgery, duration of CPB, and use of a cell-saving device. The magnitude of the effect of dexamethasone on MAKE30 differed according to both age (P=0.009) and EuroSCORE (P=0.029). Specifically, we found a monotonic effect between both younger age and lower EuroSCORE and increasing benefit from dexamethasone. Since age is one of the components of the EuroSCORE, we also performed multivariable analyses in which we adjusted for age. The interaction between EuroSCORE and treatment group on MAKE30 remained significant even after adjusting for age (odds ratio 0.41, 95% CI 0.23-0.70, P-value for interaction 0.016). Other subgroups did not demonstrate interaction with dexamethasone on the risk of MAKE30 (Table 1B).

Intraoperative high-dose dexamethasone decreased the incidence of MAKE30 and all stages of AKI. Moreover, we report interactions between both age and EuroSCORE on the beneficial effect of dexamethasone, such that the benefit was greatest in younger patients and in those with lower EuroSCOREs, whereas older patients and those with higher EuroSCOREs did not appear to benefit.

The age-related findings we report are consistent with observations in the original DECS trial, which found age-dependent beneficial effects of dexamethasone (particularly in
patients < 65 years old) on several major adverse events following cardiac surgery (2). These findings may be explained by the suggested higher risk of developing postoperative SIRS in younger patients (6), resulting in greater benefit from glucocorticoids. These findings are also consistent with earlier hypotheses suggesting that chronic low-grade inflammation could result in an age-related decline in the capacity of immune cells to elicit a proper immune response (6). Our finding that a lower EuroSCORE, independent of age, also associated with greater efficacy of dexamethasone in preventing CSA-AKI suggests that an increased burden of comorbidities may diminish the efficacy of glucocorticoids.

Our previously demonstrated interaction according to baseline eGFR, in which greater efficacy of steroids was observed in patients with lower baseline eGFR (3), was not be seen in the current study. The reasons for these discrepant findings are unclear, but they raise interesting questions about the complex interactions between steroids and AKI according to both AKI severity and baseline renal function.

Moreover, our results differ from those observed in the substudy of the SIRS (Steroids in Cardiac Surgery) trial, in which there was no effect of perioperative methylprednisolone administration on the incidence of AKI (7). This could be due to important differences in the selection of trial participants. The SIRS trial only included patients with a EuroSCORE ≥6 in their cohort (8). In contrast, in our cohort patients tended to have a lower EuroSCORE and thus fewer comorbidities. Consistent with the SIRS substudy findings, we found that the subgroup of patients in our cohort with EuroSCORE >6 had no benefit from glucocorticoid administration with respect to the incidence of MAKE30 (Table 1B: RR=0.92, 95%CI, 0.72-1.19) (7). These findings support the hypothesis that EuroSCORE might be an effect modifier of the association between glucocorticoid administration and MAKE30. Secondly, differences in the pharmacokinetic/pharmacodynamic profiles of dexamethasone and methylprednisolone could have contributed to the discrepant findings, with dexamethasone being more potent and having a longer half-life than methylprednisolone.
This well-powered study generated several novel findings with respect to potential protective effects of glucocorticoids on AKI across clinical subgroups. However, we also acknowledge several limitations. The results should be interpreted cautiously, as the analyses were not prespecified in the original DECS trial. Further, we did not adjust for multiple comparisons given the hypothesis generating nature of the study and the limited number of subgroups analyzed. Nonetheless, this approach increases the chance of a type 1 error.

The role of perioperative corticosteroids in decreasing the incidence of adverse postoperative outcomes following cardiac surgery has now been assessed by two large RCTs: DECS and SIRS. These trials both failed to demonstrate significant protective effects of steroids on the primary composite endpoints that were assessed (2)(8). Overall negative findings in large heterogenous populations, however, do not preclude a beneficial effect in subpopulations. Our current study underscores this by demonstrating several interactions between treatment assignment and various subgroups. Future trials of steroids in cardiac surgery should consider focusing on those most likely to benefit – namely, younger patients and those with few comorbidities. Finally, the primary outcomes in both the DECS and SIRS trials were composites strongly determined by thrombotic events and not necessarily inflammation. Thus, beneficial effects of steroids on major adverse events that are mediated by inflammation could have been missed. The DECS-II trial (ClinicalTrials.gov NCT03002259), currently underway, will assess the effect of steroids on more clinically relevant patient-centered outcomes, such as hospital length of stay, and will provide additional data to help inform clinicians on whether to use steroids in this setting.
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TABLE LEGEND

Table 1. AKI endpoints in the dexamethasone and placebo groups with stratified analyses for major adverse kidney events at 30 days across patient and surgical subgroups

TABLE 1A
*We used a modified definition for KDIGO-AKI stage 1, excluding the increase in SCr ≥0.3 mg/dL in the first 48 hours (4).

TABLE 1B
1P values refer to the significance of interaction terms testing for effect modification by subgroup.
2Higher EuroSCOREs indicate increased burden of comorbidities, and thus increased risk of perioperative mortality.
3Chronic kidney disease was defined as an eGFR <60 ml/min per 1.73m² assessed using the CKD-EPI equation.

Abbreviations:
AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass time; DEX, dexamethasone; LVEF, left ventricular function; MAKE30, Major Adverse Kidney Events at 30 days; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy; SCr, serum creatinine.
### Table 1A

| Outcome | DEX-group | Placebo-group | RR (95% CI) | P-Value |
|---------|-----------|---------------|-------------|---------|
| **Primary Endpoint** | | | | |
| MAKE 30: ↑SCr ≥50%, RRT or death in the first 30 days | 161 (7.2) | 206 (9.2) | 0.78 (0.64-0.96) | | |
| **Secondary Endpoints** | | | | |
| KDIGO-AKI stage 1: ↑SCr ≥50% in the first 7 days | 141 (6.3) | 189 (8.5) | 0.75 (0.61-0.92) | | |
| KDIGO-AKI stage 2: ↑SCr ≥100% in the first 7 days | 65 (2.9) | 90 (4.0) | 0.72 (0.53-0.99) | | |
| KDIGO-AKI stage 3: ↑SCr ≥200% or RRT in the first 7 days | 22 (1.0) | 39 (1.7) | 0.57 (0.34-0.95) | | |

### Table 1B

| Subgroup | No. Pts | Event-rate n (%) | DEX-group n/n (%) | Placebo-group n/n (%) | RR (95% CI) | P-Value |
|----------|---------|------------------|-------------------|-----------------------|-------------|---------|
| **MAKE30: ↑SCr ≥50%, RRT or death in the first 30 days** | | | | | | 0.009 |
| Age | | | | | | |
| <65 years | 1869 | 92 (4.9) | 28/909 (3.1) | 64/960 (6.7) | 0.46 (0.30-0.71) | | |
| 65-70 years | 770 | 55 (7.1) | 20/374 (5.3) | 35/396 (8.8) | 0.61 (0.36-1.03) | | |
| >70 years | 1824 | 220 (12.1) | 113/944 (12.0) | 107/880 (12.2) | 0.98 (0.77-1.26) | | |
| EuroSCORE² | | | | | | 0.029 |
| <4 | 1564 | 55 (3.5) | 15/779 (1.9) | 40/785 (5.1) | 0.38 (0.21-0.68) | | |
| 4-6 | 1606 | 105 (6.5) | 47/807 (5.8) | 58/799 (7.3) | 0.80 (0.55-1.16) | | |
| >6 | 1237 | 200 (16.2) | 96/618 (15.5) | 104/619 (16.8) | 0.92 (0.72-1.19) | | |
| Sex | | | | | | 0.59 |
| Male | 3234 | 238 (7.4) | 102/1615 (6.3) | 136/1619 (8.4) | 0.75 (0.59-0.96) | | |
| Female | 1229 | 129 (10.5) | 59/612 (9.6) | 70/617 (11.3) | 0.85 (0.61-1.18) | | |
| BMI | | | | | | |
| <25 | 1415 | 104 (7.3) | 48/702 (6.8) | 56/713 (7.9) | 0.87 (0.66-1.16) | | |
| 25-29 | 2013 | 155 (7.7) | 66/1001 (6.6) | 89/1012 (8.8) | 0.75 (0.55-1.02) | | |
| ≥30 | 1017 | 200 (19.5) | 96/618 (15.5) | 104/619 (16.8) | 0.92 (0.72-1.19) | | |
| Hypertension | | | | | | 0.96 |
| No | 1941 | 140 (7.2) | 65/973 (6.7) | 75/968 (7.7) | 0.86 (0.63-1.19) | | |
| Yes | 2348 | 210 (8.9) | 91/1173 (7.8) | 119/1175 (10.1) | 0.77 (0.59-0.99) | | |
| Diabetes Mellitus | | | | | | |
| No | 3606 | 261 (7.2) | 115/1809 (6.4) | 146/1797 (8.1) | 0.78 (0.62-0.99) | | |
| Yes | 847 | 105 (12.4) | 45/414 (10.9) | 60/433 (13.9) | 0.78 (0.55-1.13) | | |
| Pulmonary disease | | | | | | 0.96 |
| No | 3951 | 301 (7.6) | 126/1981 (6.4) | 175/1970 (8.9) | 0.72 (0.57-0.99) | | |
| Yes | 508 | 65 (12.8) | 34/243 (14.0) | 31/265 (11.7) | 1.20 (0.76-1.88) | | |
| Peripheral vascular disease | | | | | | 0.96 |
| No | 4079 | 312 (7.6) | 136/2034 (6.7) | 176/2045 (8.6) | 0.78 (0.63-0.96) | | |
| Yes | 381 | 54 (14.2) | 24/191 (12.6) | 30/190 (15.8) | 0.80 (0.48-1.31) | | |
| Chronic Kidney Disease³ | | | | | | 0.33 |
| No | 2255 | 33 (1.5) | 12/1140 (1.1) | 21/1115 (1.9) | 0.56 (0.28-1.13) | | |
| Yes | 2208 | 334 (15.1) | 149/1087 (13.7) | 185/1121 (16.5) | 0.83 (0.68-1.01) | | |
| LVEF | | | | | | 0.90 |
| >50% | 3194 | 218 (6.8) | 97/1612 (6.0) | 121/1582 (7.6) | 0.79 (0.61-1.02) | | |
| 30-50% | 1034 | 110 (10.6) | 46/502 (9.2) | 64/532 (12.0) | 0.76 (0.53-1.09) | | |
| <30% | 218 | 36 (16.5) | 16/102 (15.7) | 20/116 (17.2) | 0.91 (0.50-1.66) | | |
| Type of surgery | | | | | | 0.11 |
| CABG | 1767 | 97 (5.5) | 38/879 (4.3) | 59/888 (6.6) | 0.65 (0.44-0.97) | | |
| Valve | 1310 | 90 (6.9) | 49/659 (7.4) | 41/652 (6.3) | 1.18 (0.79-1.77) | | |
| CABG + Valve | 729 | 109 (15.0) | 48/359 (13.4) | 61/370 (16.5) | 0.81 (0.57-1.15) | | |
| Duration of CPB | | | | | | 0.97 |
| <120 min | 2626 | 137 (5.2) | 60/1318 (4.6) | 77/1308 (5.9) | 0.77 (0.56-1.07) | | |
| ≥120 min | 1808 | 230 (12.7) | 101/897 (11.3) | 129/911 (14.2) | 0.80 (0.62-1.01) | | |
| Use of cell-saving device | | | | | | 0.79 |
| No | 2197 | 128 (5.8) | 55/1070 (5.1) | 73/1127 (6.5) | 0.79 (0.56-1.11) | | |
| Yes | 2244 | 237 (10.6) | 105/1147 (9.2) | 132/1097 (12.0) | 0.76 (0.60-0.97) | | |

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**Legend for Table 1B**

- **Favors DEX**
- **Favors Placebo**
- **0.00 0.50 1.00 1.50 2.00**
- **Favors DEX**
- **Favors Placebo**