

# Intraoperative High-Dose Dexamethasone and Severe AKI after Cardiac Surgery

Kirolos A. Jacob,<sup>\*†</sup> David E. Leaf,<sup>‡</sup> Jan M. Dieleman,<sup>\*</sup> Diederik van Dijk,<sup>\*</sup> Arno P. Nierich,<sup>§</sup> Peter M. Rosseel,<sup>||</sup> Joost M. van der Maaten,<sup>¶</sup> Jan Hofland,<sup>\*\*</sup> Jan C. Diephuis,<sup>††</sup> Fellery de Lange,<sup>‡‡</sup> Christine Boer,<sup>§§</sup> Jolanda Kluin,<sup>†</sup> and Sushrut S. Waikar,<sup>‡</sup> for the Dexamethasone for Cardiac Surgery (DECS) Study Group

Departments of <sup>\*</sup>Anesthesiology and Intensive Care Medicine and <sup>†</sup>Cardiothoracic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>‡</sup>Division of Renal Medicine, the Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts; <sup>§</sup>Department of Anesthesiology, Isala Klinieken, Zwolle, The Netherlands; <sup>||</sup>Department of Anesthesiology Amphia Ziekenhuis, Breda, The Netherlands; <sup>¶</sup>Department of Anesthesiology University Medical Center, Groningen, The Netherlands; <sup>\*\*</sup>Department of Anesthesiology Erasmus Medical Center, Rotterdam, The Netherlands; <sup>††</sup>Department of Anesthesiology Medisch Spectrum Twente, Enschede, The Netherlands; <sup>‡‡</sup>Department of Cardiac Anesthesiology Medical Center Leeuwarden, Leeuwarden, The Netherlands; and <sup>§§</sup>Department of Anesthesiology Vrije Universiteit University Medical Center, Amsterdam, The Netherlands

## ABSTRACT

Administration of prophylactic glucocorticoids has been suggested as a strategy to reduce postoperative AKI and other adverse events after cardiac surgery requiring cardiopulmonary bypass. In this *post hoc* analysis of a large placebo-controlled randomized trial of dexamethasone in 4465 adult patients undergoing cardiac surgery, we examined severe AKI, defined as use of RRT, as a primary outcome. Secondary outcomes were doubling of serum creatinine level or AKI-RRT, as well as AKI-RRT or in-hospital mortality (RRT/death). The primary outcome occurred in ten patients (0.4%) in the dexamethasone group and in 23 patients (1.0%) in the placebo group (relative risk, 0.44; 95% confidence interval, 0.19 to 0.96). In stratified analyses, the strongest signal for potential benefit of dexamethasone was in patients with an eGFR < 15 ml/min per 1.73 m<sup>2</sup>. In conclusion, compared with placebo, intraoperative dexamethasone appeared to reduce the incidence of severe AKI after cardiac surgery in those with advanced CKD.

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Acute kidney injury is one of the most ominous complications after cardiac surgery with cardiopulmonary bypass (CPB). Approximately 1% of patients undergoing cardiac surgery require RRT for severe postoperative AKI, and experience strikingly high in-hospital mortality rates exceeding 40%.<sup>1–3</sup> Less severe AKI is far more common and identifies patients still at increased risk of short- and long-term mortality, prolonged length of hospital stay, and higher hospital costs.<sup>4,5</sup> The pathogenesis of AKI after cardiac surgery is complex and includes patient-related factors such as age

and comorbidities (e.g., CKD and diabetes mellitus) as well as surgical factors such as type of procedure and duration of CPB.<sup>6–8</sup> Cardiac surgery results in a postoperative systemic inflammatory response syndrome due to a variety of factors including surgical trauma, exposure of blood to the artificial surface of the bypass circuit, tissue hypoperfusion, hemolysis, hemodilution, blood transfusion, and hypothermia.<sup>9–12</sup> Inflammation is believed to play a key role in the pathophysiology of AKI after cardiac surgery with CPB. A number of proinflammatory pathways are activated during CPB and can lead to leukocyte extravasation, lipid

peroxidation, renal medullary congestion, and tubular cell injury.<sup>1,9</sup>

Multiple strategies have been proposed to attenuate the inflammatory response after cardiac surgery with CPB, including the use of glucocorticoids. To date, the effect of glucocorticoids on AKI after cardiac surgery has been evaluated as a primary outcome in 14 randomized controlled trials, the largest of which included 216 patients.<sup>3</sup> A meta-analysis of these studies (which included a total of 888 patients) concluded that glucocorticoids have no protective effect on AKI after cardiac surgery.<sup>3</sup> However, these studies were underpowered, particularly to detect severe AKI.

We therefore conducted a *post hoc* analysis of severe AKI in the Dexamethasone for Cardiac Surgery (DECS) trial, a large,

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**Correspondence:** Dr. Kirolos A. Jacob, University Medical Center Utrecht, Department of Anesthesiology, Intensive Care and Emergency Medicine, Mail Stop F.06.149, PO Box 85500, 3508 GA Utrecht, The Netherlands. Email: k.a.jacob@umcutrecht.nl

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randomized, placebo-controlled study investigating the effects of a single intraoperative dose of dexamethasone (1 mg/kg) on major postoperative complications among 4494 adult patients undergoing cardiac surgery with CPB.<sup>13</sup> Postoperative ARF was reported in the primary analysis and was defined according to RIFLE "F"<sup>14</sup> as an increase in serum creatinine  $\geq 3\times$  preoperative levels or an increase to  $\geq 4.0$  mg/dl associated with an increase of  $\geq 0.5$  g/dl.<sup>13</sup> Using this definition, the incidence of ARF among patients randomized to dexamethasone versus placebo was 1.3% and 1.8%, respectively (relative risk [RR], 0.70; 95% confidence interval [95% CI], 0.44 to 1.14;  $P=0.18$ ).<sup>13</sup> However, the study definition did not include the use of RRT as a criterion, which may have missed clinically important cases of AKI, for example where RRT was started before a substantial increase in serum creatinine occurred. Therefore, we conducted this *post hoc* analysis to evaluate the effects of dexamethasone on severe AKI, defined by use of RRT (hereafter termed AKI-RRT).

The current analysis includes 4465 patients (99.4%) of the original DECS trial (2229 [49.9%] randomized to dexamethasone and 2236 [50.1%] randomized to placebo). We excluded 29 patients for reasons detailed in Supplemental Figure 1. Baseline demographic, clinical, and surgical characteristics, including the EuroSCORE<sup>27</sup> and preoperative renal function, were similar between the two groups (Table 1).

AKI-RRT occurred in ten patients (0.4%) in the dexamethasone group and 23 patients (1.0%) in the placebo group (RR, 0.44; 95% CI, 0.19 to 0.96;  $P=0.02$ , Table 2). This finding persisted after adjustment for preoperative serum creatinine concentration (odds ratio, 0.44; 95% CI, 0.21 to 0.94;  $P=0.03$ ). Other renal end points are shown in Table 2. All patients who developed AKI-RRT had preexisting CKD stage 3 (eGFR  $< 60$  ml/min per  $1.73$  m<sup>2</sup>) or greater (Supplemental Table 1).<sup>26</sup> In stratified analyses according to baseline eGFR, the potential protective effect of dexamethasone versus placebo was most pronounced in those with the most severely reduced baseline eGFR: among 102

**Table 1.** Demographic, Clinical, and Surgical Characteristics of the Dexamethasone and Placebo Groups<sup>a</sup>

Characteristic	Dexamethasone (n=2229)	Placebo (n=2236)
Demographics		
Age, mean (SD), y	66.3 (11.0)	66.1 (10.7)
Male sex	1622 (72.6)	1626 (72.4)
Weight, mean (SD), kg	82.4 (14.3)	82.0 (14.4)
Height, mean (SD), cm	174 (9.1)	173 (9.2)
Coexisting medical conditions		
Hypertension	1178 (54.7)	1178 (54.7)
Diabetes mellitus, insulin dependent	106 (4.8)	124 (5.5)
Non-insulin dependent	309 (13.9)	311 (13.9)
Pulmonary disease	243 (10.9)	265 (11.8)
Previous cerebrovascular event Stroke	86 (3.9)	78 (3.5)
Transient ischemic attack	107 (4.8)	103 (4.6)
Peripheral vascular disease	191 (8.6)	191 (8.5)
Preoperative creatinine, mean (SD), mg/dl	1.04 (0.35)	1.06 (0.54)
eGFR, mean (SD), ml/min per $1.73$ m <sup>2b</sup>	62.1 (23.2)	61.1 (23.8)
Chronic kidney disease <sup>c</sup>	1090 (48.8)	1128 (50.2)
Stage 3	900 (40.3)	916 (40.8)
Stage 4	147 (6.6)	153 (6.8)
Stage 5	43 (1.9)	59 (2.6)
Cardiac status		
Recent myocardial infarction (<90 days)	195 (8.7)	176 (7.8)
Left ventricular function <sup>d</sup>		
Moderate	502 (22.6)	534 (23.9)
Poor	103 (4.6)	117 (5.2)
EuroSCORE, median (IQR) <sup>e</sup>	5 (3–7)	5 (3–7)
Preoperative medication		
$\beta$ -Blocker	1484 (68.4)	1478 (68.2)
Statin	836 (58.0)	769 (53.7)
Glucocorticoids <sup>f</sup>	129 (7.1)	97 (5.4)
Type of surgery		
Isolated CABG	882 (39.9)	891 (40.2)
CABG plus valve	360 (16.3)	372 (16.8)
Single valve	574 (25.9)	560 (25.3)
Surgery on multiple valves	86 (3.9)	94 (4.2)
Other procedures	310 (14.0)	298 (13.5)
Repeat surgery		
Duration of procedure, mean (SD), min	244 (102)	242 (93)
Duration of CPB, mean (SD), min	125 (68)	124 (64)
Duration of aortic cross-clamping, mean (SD), min	87 (47)	85 (44)
Deep hypothermic circulatory arrest	15 (0.7)	22 (1.0)
Use of cell-saving device	1151 (51.8)	1103 (49.4)
Use of antifibrinolytic drug		
Tranexamic acid	1833 (82.4)	1834 (81.8)
Other antifibrinolytic drug	10 (0.4)	18 (0.8)

CABG, coronary artery bypass graft; IQR, interquartile range. SI conversion: To convert creatinine to  $\mu\text{mol/L}$ , multiply by 88.4.

<sup>a</sup>Data are shown as No. (%) unless otherwise indicated.

<sup>b</sup>eGFR was calculated using the CKD-EPI formula.<sup>26</sup>

<sup>c</sup>Chronic kidney disease was defined as an eGFR of  $< 60$  ml/min per  $1.73$  m<sup>2</sup> assessed using the CKD-EPI equation.<sup>26</sup>

<sup>d</sup>Definition of left ventricular function classes: moderate, ejection fraction of 30%–50%; and poor, ejection fraction of  $< 30\%$ .<sup>27</sup>

<sup>e</sup>Higher EuroSCOREs present increased risk of perioperative mortality.<sup>27</sup>

<sup>f</sup>Patients on glucocorticoids preoperatively were allowed to continue this medication.

**Table 2.** Acute kidney injury end points in the dexamethasone and placebo groups<sup>a</sup>

Outcome	Dexamethasone (n=2229)	Placebo (n=2236)	RR (95% CI)	P Value
Primary Outcome				
AKI-RRT	10 (0.4)	23 (1.0)	0.44 (0.19 to 0.96)	0.02
Secondary Outcomes				
Doubling of serum creatinine and/or AKI-RRT	72 (3.2)	96 (4.3)	0.75 (0.55 to 1.03)	0.07
RRT/death	29 (1.3)	42 (1.9)	0.69 (0.42 to 1.13)	0.15
RIFLE "R": up to 100% increase in SCr	142 (6.4)	188 (8.4)	0.76 (0.61 to 0.94)	0.01
RIFLE "I": up to 200% increase in SCr	66 (3.0)	89 (4.0)	0.74 (0.54 to 1.03)	0.07
RIFLE "F": up to 300% increase, or 0.5 mg/dL increase to at least 4.0 mg/dL	28 (1.3)	42 (1.9)	0.67 (0.41 to 1.10)	0.09

"R", risk; SCr, serum creatinine; "I", injury; "F", failure.

<sup>a</sup>Data are shown as No. (%).

**Table 3.** Stratified analyses of AKI-RRT in the dexamethasone and placebo groups according to baseline kidney function<sup>a</sup>

Baseline kidney function	Number	Number of AKI-RRT events	Dexamethasone	Placebo	RR (95% CI)	P Value
eGFR>90	602	0	—	—	—	—
eGFR 60–90	1645	0	—	—	—	—
eGFR≤60	2218	33	10 of 1090 (0.9)	23 of 1128 (2.0)	0.45 (0.20 to 0.98)	0.04
eGFR 30–59	1816	5	3 of 900 (0.3)	2 of 916 (0.2)	1.53 (0.21 to 13.0)	0.64
eGFR 15–29	300	11	4 of 147 (2.7)	7 of 153 (4.6)	0.60 (0.15 to 2.21)	0.54
eGFR<15	102	17	3 of 43 (7.0)	14 of 59 (23.7)	0.29 (0.07 to 0.99)	0.03

<sup>a</sup>Data are shown as No. (%).

patients with baseline eGFR<15 ml/min per 1.73 m<sup>2</sup>, AKI-RRT occurred in three patients (7.0%) in the dexamethasone group and in 14 patients (23.7%) in the placebo group (RR, 0.45; 95% CI, 0.20 to 0.99; *P*=0.031, Table 3).

In summary, in this *post hoc* analysis of the DECS trial, we found that administration of intraoperative dexamethasone appeared to reduce the incidence of AKI-RRT, a clinically relevant end point that occurred only in patients with baseline CKD stage 3 or greater. These results suggest a potential beneficial effect of glucocorticoids on adverse renal outcomes in patients with advanced CKD after cardiac surgery that requires confirmation.

There is a strong pathophysiologic rationale for testing glucocorticoids as a potential prevention strategy for AKI-RRT in cardiac surgery. Cardiac surgery induces a rapid and potent increase in circulating levels of proinflammatory cytokines such as IL-6 and TNF- $\alpha$ ).<sup>9,15,16</sup> These proinflammatory cytokines promote adherence of inflammatory cells to activated endothelium in the peritubular capillaries of the outer medulla, ultimately resulting in medullary congestion and hypoxic injury to the

proximal.<sup>17,18</sup> Glucocorticoids are likely to interfere with this process through direct transcriptional regulation of target genes, including upregulation of anti-inflammatory cytokines such as lipocortin 1 and downregulation of proinflammatory cytokines through inhibition of NF- $\kappa$ B.<sup>17,18</sup> Additionally, glucocorticoids may have important downstream effects that are independent of gene transcription (e.g., stimulation of phosphatidylinositol 3-kinase).<sup>19</sup>

Glucocorticoids may also exert renoprotective effects after cardiac surgery by attenuating hemolysis/iron-mediated toxicity. During CPB, blood is exposed to nonphysiologic surfaces and shear forces, leading to cell lysis and release of free hemoglobin into the circulation.<sup>11,12,20</sup> Free hemoglobin is removed from the circulation through binding to CD163,<sup>21</sup> a scavenger receptor on the cell surface of monocytes and macrophages that is upregulated by glucocorticoids in multiple cell lines.<sup>22–24</sup> Hence, enhanced removal of free hemoglobin through upregulated CD163 represents a biologically plausible pathway through which glucocorticoids may decrease the incidence of CPB-associated AKI.

To our knowledge, this AKI *post hoc* analysis is the largest randomized, double-blind, placebo-controlled trial showing a potential benefit of any therapeutic agent for the prevention of severe AKI after cardiac surgery with CPB. The large number of patients in this study allowed us to use a rigorous definition of AKI—use of RRT—as the primary outcome.

However, our findings must be interpreted cautiously and require confirmation. AKI-RRT was not a prespecified outcome at the time the original study was designed. Also, the total number of RRT events was low and the need for RRT was subjectively decided upon by clinicians. Therefore, the current findings, although intriguing, must be viewed only as hypothesis-generating, particularly in light of the main DECS trial negative findings for the primary composite outcome (death, myocardial infarction, stroke, renal failure, or respiratory failure within 30 days) and for renal failure (RIFLE-F) as a single end point. Baseline differences in the cohort that received RRT in rates of stage 5 CKD were imbalanced, even though insignificantly, and these differences in baseline kidney

function could have influenced the results. However, in stratified analyses as well as in adjusted analyses for baseline serum creatinine levels, the finding of a potential beneficial effect of dexamethasone remained significant and strongest in the subgroup of patients with the most advanced stages of CKD. Whether this represents a chance finding because of *post hoc* comparisons in subgroup analyses, or an important signal of a potential benefit in patients at the highest risk of AKI-RRT, deserves further investigation. Our findings do suggest that any beneficial effect of dexamethasone on postoperative renal outcomes may be limited to those at highest risk of RRT. In this regard, it is important to note that the majority of AKI-RRT events occurred in those with advanced CKD (85% had stage 4 or greater; 52% had stage 5 CKD), a finding that has practical implications for trial design in AKI prevention.

In conclusion, in this *post hoc* analysis of the DECS trial, we found that intraoperative high-dose dexamethasone may reduce the incidence of AKI-RRT among patients with advanced CKD. Additional studies are needed to confirm this finding and to explore underlying mechanisms. Future studies of glucocorticoids for AKI prevention after cardiac surgery should focus on the small but extremely high-risk population of patients with advanced CKD.

## CONCISE METHODS

### Study Design and Patients

The DECS study was a multicenter, double-blind, randomized controlled trial comparing intraoperative dexamethasone (1 mg/kg intravenously) with placebo in patients undergoing cardiac surgery with CPB.<sup>13</sup> Detailed study procedures are described elsewhere.<sup>13</sup> In brief, patients aged  $\geq 18$  years who were scheduled for any type of elective or urgent cardiac surgical procedure requiring CPB were considered eligible. Exclusion criteria included an emergent or planned off-pump procedure and a life expectancy of less than 6 months. All patients in the DECS trial were included in the current AKI substudy with the exception of those with missing renal function data and those on preoperative RRT. All patients provided written informed consent and all protocols were approved by the

research ethics committee of the University Medical Center Utrecht.

### Data Collection, Outcomes, and Analysis

At least one preoperative serum creatinine measurement was obtained and recorded during the 30 days before surgery. If more than one value was available, the serum creatinine measurement closest to the time of surgery was used as the baseline preoperative value. Postoperative serum creatinine values were routinely obtained on a daily basis throughout the hospital stay.

The primary outcome for the current *post hoc* analysis was postoperative AKI defined by use of RRT (AKI-RRT) during hospitalization. We also evaluated alternate definitions of AKI—postoperative doubling of serum creatinine (during hospitalization) and/or RRT, an AKI definition that has been used in several large AKI observational studies,<sup>2,25</sup> RRT and/or in-hospital mortality (RRT/death), and AKI defined by the RIFLE criteria (Risk, Injury, Failure, Loss and ESRD).<sup>14</sup>

### Statistical Analyses

All data were analyzed according to the intention-to-treat principle. Normally distributed continuous variables are presented as means with standard deviations ( $\pm$ SD) and were compared using an independent *t* test. Continuous variables that were not normally distributed are presented as medians with 25th to 75th interquartile range and were compared using the Mann–Whitney *U* test. Dichotomous variables are presented as absolute numbers with percentages and were compared using the Fisher's exact test. We also calculated RR and 95% CI for dichotomous outcomes. We performed stratified analyses according to baseline eGFR subgroups as well as logistic regression analyses adjusting for baseline serum creatinine concentration. A two-sided *P* value  $< 0.05$  was considered significant. Statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL).

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This trial is registered with ClinicalTrials.gov, NCT00293592. No conflict of interest declared.

Sushrut S. Waikar has served as a consultant to Abbvie, CVS Caremark, Harvard Clinical Research Institute, and Takeda. S.S. Waikar has provided expert testimony or consultation for litigation related to nephrogenic systemic fibrosis (GE Healthcare) and mercury exposure; and has received grants from the National Institute of Diabetes and Digestive Kidney Diseases, Genzyme, Merck, Otsuka, Pfizer, and Satellite Healthcare.

## DISCLOSURES

None.

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