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# Original Article

## Long-term outcomes and cost effectiveness of high-dose dexamethasone for cardiac surgery: a randomised trial

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### Summary

Prophylactic intra-operative administration of dexamethasone may improve short-term clinical outcomes in cardiac surgical patients. The purpose of this study was to evaluate long-term clinical outcomes and cost effectiveness of dexamethasone versus placebo. Patients included in the multicentre, randomised, double-blind, placebo-controlled DExamethasone for Cardiac Surgery (DECS) trial were followed up for 12 months after their cardiac surgical procedure. In the DECS trial, patients received a single intra-operative dose of dexamethasone 1 $mg.kg^{-1}$ (n = 2239) or placebo (n = 2255). The effects on the incidence of major postoperative events were evaluated. Also, overall costs for the 12-month postoperative period, and cost effectiveness, were compared between groups. Of 4494 randomised patients, 4457 patients (99%) were followed up until 12 months after surgery. There was no difference in the incidence of major postoperative events, the relative risk (95%CI) being 0.86 (0.72-1.03); p = 0.1. Treatment with dexamethasone reduced costs per patient by £921 [€1084] (95%CI £−1672 to −137; p = 0.02), mainly through reduction of postoperative respiratory failure and duration of postoperative hospital stay. The probability of dexamethasone being cost effective compared with placebo was 97% at a threshold value of £17,000 [€20,000] per quality-adjusted life year. We conclude that intra-operative high-dose dexamethasone did not have an effect on major adverse events at 12 months after cardiac surgery, but was associated with a reduction in costs. Routine dexamethasone administration is expected to be cost effective at commonly accepted threshold levels for cost effectiveness.

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## Introduction

Cardiac surgery is among the most common surgical interventions, with over 2 million procedures performed worldwide each year [1]. Despite considerable improvements over the last decades, cardiac surgery still carries a substantial risk of complications with significant associated costs [1–3].

The intense, multi-modal inflammatory response associated with cardiac surgery and cardiopulmonary bypass has the potential to increase the risk of organ dysfunction and postoperative complications [4, 5]. Several strategies can be employed in attempts to reduce inflammatory activation, and thus improve outcomes.

Routine administration of intra-operative high-dose corticosteroids is controversial but widely used. Recently, we published the short-term outcomes of the DECS (DExamethasone for Cardiac Surgery) trial, a randomised trial of high-dose dexamethasone versus placebo in 4494 patients undergoing cardiac surgery with cardiopulmonary bypass [6]. There was no significant benefit of dexamethasone on the primary composite outcome of major adverse events in the first 30 days after surgery. However, analysis of pre-specified secondary outcomes indicated that high-dose dexamethasone was associated with fewer respiratory complications and reduced postoperative length of stay in the hospital. Also, dexamethasone resulted in a reduced incidence of severe acute kidney injury in patients with advanced chronic kidney disease [7].

Here we report the 12-month follow-up of the patients in the DECS trial, including a cost effectiveness analysis. Given the benefits that were demonstrated for several of the pre-specified secondary outcomes, we hypothesised that a high dose of intra-operative dexamethasone would be associated with a cost reduction in cardiac surgery patients.

## Methods

The DECS trial was conducted in accordance with Good Clinical Practice principles and applicable national regulations. The research ethics committee at each participating centre approved the protocol. All patients provided written informed consent before randomisation.

The DECS trial was a double-blind, randomised, multi-centre study in the Netherlands, comparing high-dose dexamethasone with placebo in patients undergoing cardiac surgery. The design and primary study results have been described in detail [6]. Briefly, 4494 patients were randomly allocated to receive a single intravenous dose of either 1 $mg.kg^{-1}$ dexamethasone, or placebo following the induction of anaesthesia for cardiac surgery, using a computer-generated 1:1 randomisation scheme, which was stratified to participating centre and in blocks of 40. Ampoules of dexamethasone and placebo, each assigned a unique study number, were identical and contained an equal volume (5 ml) of a 20 $mg.ml^{-1}$ dexamethasone solution, or saline, respectively. Patients, caregivers, and re- searchers were unaware of study group assignment. Patients aged 18 or over, who were referred for elective cardiac surgery requiring cardiopulmonary bypass, were eligible for inclusion.

We report the long-term (12-month) effects of intra-operative dexamethasone on major adverse events, and on health-related quality of life at 30 days and 12 months postoperatively. We also report the results of a cost effectiveness analysis of the intervention.

The primary outcome for this study was a composite of predefined major adverse events during the first 12 months of follow-up including: mortality; myocardial infarction; stroke; renal failure; and respiratory failure. Peri-operative myocardial infarction was defined as presence of new Q-waves or a new left bundle branch block on the electrocardiogram, combined with elevated CK-MB or troponin of more than five times the upper reference limit. Myocardial infarction occurring after discharge from hospital or > 30 days postoperatively was defined according to the criteria of the Universal Definition of Myocardial Infarction [8]. Stroke was defined as neurological deficit lasting more than 24 h, with increased invalidity (≥ 1 point increase on the Rankin scale [9]) and signs of new ischaemic cerebral infarction on computed tomography or magnetic resonance imaging. Renal failure in patients not previously undergoing dialysis was defined according to the RIFLE criteria, as an increase in serum creatinine of at least 3 times the pre-operative value, or a serum creatinine level > 4 $mg.dl^{-1}$ (> 354 $\mu mol.l^{-1}$)

associated with an acute increase of serum creatinine $\geq 0.5$ mg.dl$^{-1}$ ($\geq 44$ μmol.l$^{-1}$) [10]. Respiratory failure was defined as postoperative mechanical ventilation or re-institution of mechanical ventilation via a tracheal tube or tracheostomy for an uninterrupted period of at least 48 h.

An independent, blinded critical event adjudication committee reviewed all cases of death, possible myocardial infarction, and possible stroke. Cases of possible myocardial infarction or stroke were either confirmed or dismissed according to the study definitions.

Health-related quality of life after 30 days and 12 months was assessed using two generic, self-administered questionnaires. The SF-36 comprises eight domains and a physical and mental component summary score, all scored on a 0–100 scale, where higher scores indicate higher levels of functioning or well-being [11]. The EQ-5D questionnaire covers five domains of quality of life, each with three levels reflecting severity of problems [12]. We applied the Dutch value set to calculate utility values for each of the 243 ($3^5$) health states derived from the this questionnaire [13]. Using the EQ-5D scores, we further and arbitrarily defined patients as having disability [14] when they had an overall EQ-5D score of $< 0.75$ at 12 months.

Healthcare costs were collected during 12 months of postoperative follow-up and analysed from a healthcare perspective. The cost of the study intervention consisted of the fixed costs of the drug and its administration. Data on resource use in hospital immediately after surgery were collected from study case report forms, administrative hospital databases, and surgical discharge letters. Data on number and length of hospital readmissions following initial postoperative hospital discharge were collected through information from patient questionnaires at 30 days and 12 months, and from discharge letters of hospital readmissions.

Data on resource use consisted of hospitalisations, diagnostic and therapeutic procedures related to complications of surgery, and medication use. Hospitalisation included primary postoperative hospitalisation, postoperative transfer to other hospitals, and hospital readmission. Days in hospital were divided into ward days and days in ICU, and valued according to Dutch guidelines for costing research in healthcare [15]. Medication use was documented by patient questionnaires. Medication costs were retrieved from the Dutch formulary and included a pharmacist fee for every 3 months′ prescription [15]. It was assumed that patients used a 'daily defined dose' as reflected in the formulary. Costs of diagnostic and surgical procedures were retrieved from an online database of Diagnosis Related Groups [16], or adapted from published literature. The cost of a repeat sternotomy was estimated in a bottom-up manner (i.e. valuing staff involvement and surgery time based on real use of time and resources). As the study takes a healthcare perspective, we did not monetarily value productivity losses of patients. The most relevant cost estimates are displayed in Table 3. Costs of surgery were omitted from the analysis as these costs are expected to be identical in both study arms. A comprehensive overview of all cost estimates used is provided in Table S1 of the Supporting Information online.

All data were analysed according to the intention-to-treat principle. The incidence of major adverse events within 12 months postoperatively between both groups was compared and presented as relative risk (RR) with a corresponding 95%CI. Dichotomous data were compared using the chi-square statistic. Continuous values were compared using the two-sample t-test. Continuous variables that were not distributed normally were compared using Mann–Whitney tests. Survival and event-free survival were compared using Kaplan–Meier curves analysis. All reported p values are two-sided.

Using age and EuroScore [17], we employed multiple imputation to account for missing data in the healthcare utilisation measures and the EQ-5D [18, 19]. Next, we calculated the total costs for each patient by multiplying healthcare resources used by their unit costs (Table S1 of the Supporting Information online). Quality-adjusted life years (QALY) were calculated for each patient, using an area under the curve approach with linear interpolation of EQ-5D utility values as reported at 30 days and 12 months. Using the mean total costs and effects for both the dexamethasone and placebo groups, we divided the cost difference between groups by the difference in QALY, to obtain the

 

incremental cost effectiveness ratios (ICER) [20, 21]. As the study was not powered for assessment of cost effectiveness, we used bootstrapping (1000 iterations) to estimate possible uncertainty around the costs and effects within the ICER. The bootstrapped pairs of costs and effects were plotted in a cost effectiveness plane. Furthermore, a cost effectiveness acceptability curve for a plausible spectrum of different amounts of money society would be willing to pay for an additional QALY was drawn. In The Netherlands, amounts between £17,000 [€20,000] and £68,000 [€80,000] are regarded acceptable threshold values. As our time frame was limited to 12 months, discounting of costs and effects was not necessary. We employed a sensitivity analysis using complete cases.

## Results

An estimated 25,085 patients were screened, of whom 21,581 were eligible for inclusion. Of the 4827 patients who agreed to take part, 4494 eventually underwent randomisation (Fig. 1). Of these, 2239 (49.8%) were randomised to dexamethasone and 2255 (50.2%) to placebo. Of the 4482 patients for whom 30-day follow-up was completed [6], 31 (0.7%) were unavailable for follow-up at 12 months. Of these 31 patients, six had experienced one or more major adverse events in the first 30 days, and were as such accounted for in the 12-month analysis. Thus, the analysed population consisted of 4457 patients for the comparative analyses. However, for the survival analyses and the cost effectiveness analyses (Table 1), data from all 4487 patients

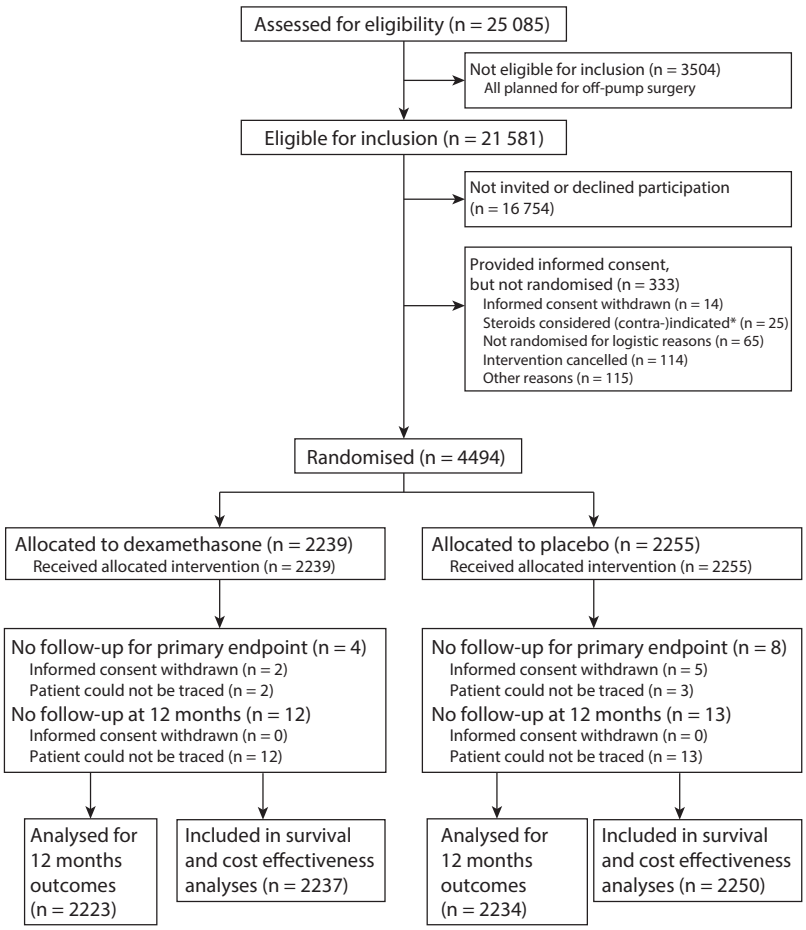


**Figure 1** Overview of patient enrolment, randomisation, and follow-up. *Indication or contra-indication dictated by either the treating medical team or the clinical situation during the start of the procedure in the operating room. Note: Data on the number of patients that were not invited to participate, or that declined participation were not consistently logged in all centres, and are therefore not sufficiently accurate to be reported in detail.

 

**Table 1** Baseline characteristics of the patients. Values are number (proportion), mean (SD) or median (range [IQR]).

| | Dexamethasone group n = 2223 | Placebo group n = 2234 |
|---|---|---|
| Age, yrs | 66.2 (11.0) | 66.1 (10.7) |
| Sex, male | 1614 (72.6%) | 1616 (72.3%) |
| Hypertension | 1176 (54.9%) | 1174 (54.8%) |
| Insulin dependent diabetes mellitus | 106 (4.8%) | 124 (5.6%) |
| Non-insulin dependent diabetes mellitus | 305 (13.7%) | 309 (13.8%) |
| Treatment for pulmonary disease | 241 (10.9%) | 265 (11.9%) |
| Stroke | 85 (3.8%) | 78 (3.5%) |
| Transient ischaemic attack | 107 (4.8%) | 103 (4.6%) |
| Peripheral vascular disease | 188 (8.5%) | 190 (8.5%) |
| Pre-operative creatinine, $\mu mol.L^{-1}$ | 92 (34) | 95 (50) |
| Chronic renal dysfunction | 17 (0.8%) | 29 (1.3%) |
| Recent myocardial infarction <90 days | 194 (8.7%) | 173 (7.8%) |
| Moderate left ventricular function | 498 (22.5%) | 530 (23.8%) |
| Poor left ventricular function | 103 (4.7%) | 117 (5.3%) |
| EuroSCORE | 5 (0–20 [3–7]) | 5 (0–16 [3–7]) |
| Isolated CABG | 883 (39.9%) | 891 (40.2%) |
| CABG plus valve surgery | 372 (16.8%) | 361 (16.3%) |
| Single valve surgery | 574 (25.9%) | 561 (25.3%) |
| Surgery on multiple valves | 86 (3.9%) | 92 (4.2%) |
| Other procedures | 298 (13.5%) | 310 (14.0%) |
| Repeat surgery | 137 (6.2%) | 147 (6.6%) |

Definition of left ventricular function classes [17]: moderate = ejection fraction 30–50%; poor = ejection fraction <30%. CABG, coronary artery bypass grafting.

with an active informed consent were used: patients who were lost to follow-up after 30 days were censored in the survival analyses.

In the dexamethasone group, 208 (9.4%) of 2223 patients had a major adverse event, compared with 242 (10.8%) of 2234 patients in the placebo group, with an RR (95%CI) of 0.86 (0.72–1.03); p = 0.10 (Table 2). The incidence of mortality, myocardial infarction, stroke and renal failure was comparable between the two groups. The incidence of respiratory failure was significantly less in the dexamethasone group, but all the respiratory failure events occurred in the first 30 days [6]. We have already reported the effects of dexamethasone on pre-defined secondary outcomes during the early postoperative period [6]. Repeat sternotomy (for any cause) was not specified as a secondary outcome measure, but was included in the cost effectiveness analysis. This complication occurred in 9.7% of the patients randomly allocated to dexamethasone and in 7.3% of the patients randomly allocated to placebo, with an RR (95%CI) of 1.32 (1.09–1.61); p = 0.005. This difference between the groups was mainly due to an increased incidence of late repeat sternotomy (> 24 h) in the dexamethasone group (6.1% vs. 4.2% in the placebo group; p = 0.005), whereas the incidence of repeat sternotomy within 24 h were comparable between the groups (3.6% vs. 3.1%; p = 0.35).

To better understand the effects of dexamethasone, resternotomy rate, and blood transfusion on respiratory failure, we modelled this outcome in a multivariable

**Table 2** Outcomes: major adverse events after 12 months. Values are number (proportion) or relative risk (95%CI).

| | Dexamethasone group n = 2223 | Placebo group n = 2234 | Relative risk (95%CI) | p value |
|---|---|---|---|---|
| Death | 90 (4.0%) | 83 (3.7%) | 1.09 (0.81–1.46) | 0.56 |
| Myocardial infarction | 46 (2.1%) | 50 (2.2%) | 0.92 (0.62–1.37) | 0.70 |
| Stroke | 41 (1.8%) | 49 (2.2%) | 0.84 (0.56–1.27) | 0.41 |
| Renal failure | 28 (1.3%) | 41 (1.8%) | 0.69 (0.43–1.10) | 0.10 |
| Respiratory failure | 67 (3.0%) | 97 (4.3%) | 0.69 (0.51–0.94) | 0.02 |
| Any major adverse event | 208 (9.4%) | 242 (10.8%) | 0.86 (0.72–1.03) | 0.10 |

model in a post-hoc analysis. This model, which also included centre and interaction terms of blood transfusion with both treatment and resternotomy as variables, showed that respiratory failure was associated with both blood transfusion, with an OR (95%CI) of 4.11 (2.38–7.10) and resternotomy, the odds ratio (95%CI) being 2.11 (1.02–4.38), while the direction of the effect of dexamethasone persisted (OR (95%CI) 0.6 (0.29–1.25)). This showed that, since the association of dexamethasone with either of these two variables is different, there was still a net benefit of both blood transfusion and resternotomy on respiratory failure.

Kaplan-Meier curves for both survival and event-free survival are displayed in Fig. S1 of the Supporting Information online; there were no significant differences.

Mean costs per patient were lower in patients randomly allocated to dexamethasone compared with those randomly allocated placebo (Table 3). Mean (SD) healthcare costs were £10,514 [€12,364] (£11,875) and £11,436 [€13,448] (£14,756), respectively. Hospitalisation comprised the largest part of costs, as patients were on average hospitalised for 15.4 (14.6–16.1) (dexamethasone) and 16.1 (15.2–17.0) (placebo) days during 12-month follow-up.

Quality of life data were available for 3558 (79.4%) patients at 30 days, and for 3449 (77.4%) patients at 12 months. The quality of life scores improved significantly between 30-day and 12-month follow-up. However, there was no difference between the treatment groups in any of the eight domains (data not shown) or component summary scores of the SF-36. Also, average scores on the EQ-5D were similar between the treatment groups, as well as the rates of disability and disability-free survival (Tables S2A and S2B of the Supporting Information online).

Bootstrapping showed costs in the dexamethasone group to be £922 [€1084] lower than in the placebo group (95%CI £−1674 to £−137; p = 0.02), with a QALY difference of −0.0042 (−0.0160 to 0.0067) (Table S3 of the Supporting Information online). The cost effectiveness plane (Fig. 2) resulting from the probabilistic sensitivity analyses shows that healthcare costs in the dexamethasone group were lower than those in the placebo group. Compared with placebo, treatment with dexamethasone was associated with a small loss of QALYs. The cost effectiveness acceptability curve (Fig. 3) demonstrates that at a willingness-to-pay of £17,000 [€20,000], the probability of cost effectiveness was 97%, while it was 84% at a threshold value of £64,000 [€80,000]. Sensitivity analyses (Table S3 of the Supporting Information online) did not alter these conclusions.

## Discussion

This randomised, placebo-controlled trial of high-dose intra-operative dexamethasone in cardiac surgery, showed no statistically significant difference in either survival or the incidence of major adverse events after 12 months. Largely because of a reduction in the incidence of postoperative respiratory failure, and by reducing the length of postoperative hospital stay, treatment with dexamethasone significantly reduced cost by an average of £922 [€1084] per patient. The probability that prophylactic high dose dexamethasone is cost effective compared with placebo is 84–97%.

The DECS study is the largest study on the efficacy of intra-operative, prophylactic high-dose dexamethasone in cardiac surgery. Although no statistically significant effect of dexamethasone on the primary composite endpoint of major adverse events at 30 days could be demonstrated, beneficial effects on short-term secondary endpoints were observed. In the immediate postoperative period, patients treated with dexamethasone had a reduced incidence of respiratory failure requiring prolonged mechanical ventilation [6]. Despite previous concerns about a possible higher risk of infections, the incidence of pneumonia decreased from 10.6% in the placebo group to 6.0% in the dexamethasone group. The risk of wound infection was similar across the two groups, as was the risk of gastro intestinal bleeding. However, there was an unexpected increased incidence of resternotomy. The net result of these effects was a shorter postoperative ICU and hospital stay in patients treated with dexamethasone. Combined with the low costs of this generic drug, this reduction in ICU and hospital utilisation is the principal reason for the substantial cost benefit of dexamethasone found in this study. Considering the large number of cardiac surgical procedures performed in Western countries, prophylactic use of dexamethasone may generate substantial savings in healthcare costs.

 

**Table 3** Cost data: unit costs, number of patients involved, mean resources used and mean costs per patient over 12 months. All costs are in pounds sterling.

| | | Dexamethasone group | | | Placebo group | | |
|---|---|---|---|---|---|---|---|
| | | n = 2237 | | | n = 2250 | | |
| Cost item | Unit cost (£/unit) | n | Number of units [mean (SD)] | Mean (SD) total costs | n | Number of units [mean (SD)] | Mean (SD) total costs |
| Dexamethasone | 6.46 | | 1 | 6.46 | | | 0 |
| Hospitalisation | | | | | | | |
| Hospital days, ICU | 1933.77 | 2227 | 3925 [1.75 (3.69)] | 3393 (7128) | 2238 | 4790 [2.13 (495)] | 4116 (9570) |
| Hospital days, ward | 413.34 | 2215 | 30 453 [13.61 (7.42)] | 5627 (7202) | 2224 | 31 446 [13.98 (21.55)] | 5776 (8907) |
| Blood products and cell saver device | | | | | | | |
| Packed red cells | 181.80 | 711 | 2659 [1.19 (11.78)] | 216 (2142) | 763 | 2209 [0.98 (2.18)] | 179 (397) |
| Fresh frozen plasma | 156.47 | 434 | 1407 [0.63 (1.68)] | 99 (262) | 459 | 1491 [0.66 (1.60)] | 104 (251) |
| Platelets | 438.67 | 359 | 619 [0.28 (1.03)] | 122 (496) | 397 | 694 [0.31 (0.96)] | 135 (419) |
| Use of cell saver | 139.65 | 1151 | 1151 [0.51 (0.50)] | 72 (70) | 1104 | 1104 [0.49 (0.50)] | 68 (70) |
| Complications, excluding hospitalisation | | | | | | | |
| Myocardial infarction | See Table S1 | 46 | 46 [0.02 (0.14)] | 192 (2208) | 50 | 50 [0.02 (0.15)] | 163 (1113) |
| Stroke | 1517.60 | 41 | 41 [0.02 (0.13)] | 28 (204) | 49 | 49 [0.02 (0.15)] | 33 (221) |
| Renal failure | See Table S1 | 28 | 28 [0.01 (0.11)] | 9 (326) | 41 | 41 [0.02 (0.13)] | 90 (1836) |
| Atrial fibrillation | See Table S1 | 739 | 739 [0.33 (0.47)] | 29 (79) | 790 | 790 [0.35 (0.48)] | 31 (82) |
| Resternotomy | 1605.10 | 207 | 207 [0.09 (0.29)] | 175 (533) | 160 | 160 [0.07 (0.26)] | 137 (524) |
| Infections | See Table S1 | 241 | 241 [0.11 (0.35)] | 9 (33) | 377 | 377 [0.17 (0.43)] | 16 (43) |
| Medication during follow-up | | | | | | | |
| Drug use, including dispensing charges | See Table S1 | | | 537 (289) | | | 531 (278) |
| Total costs | | | | 10 527 (11 889) | | | 11 450 (14 774) |

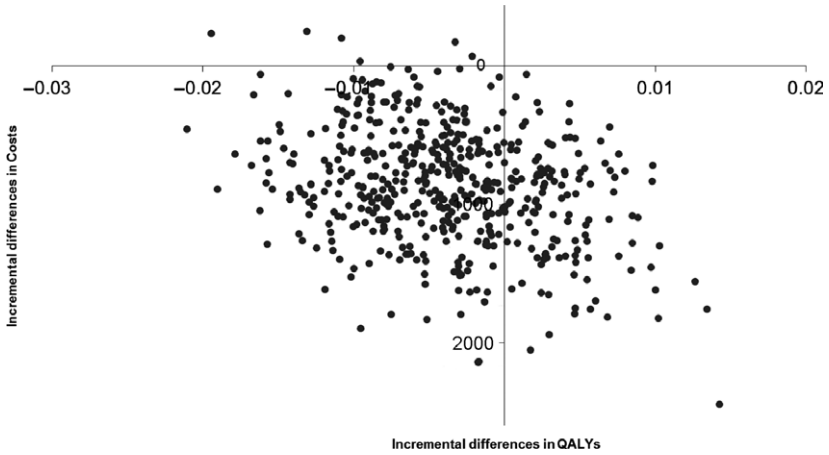


**Figure 2** Cost effectiveness plane. This shows the distribution of 1000 bootstrap replications of differences in costs (y-axis) and effects (x-axis), for dexamethasone compared with placebo. QALY, quality-adjusted life year.

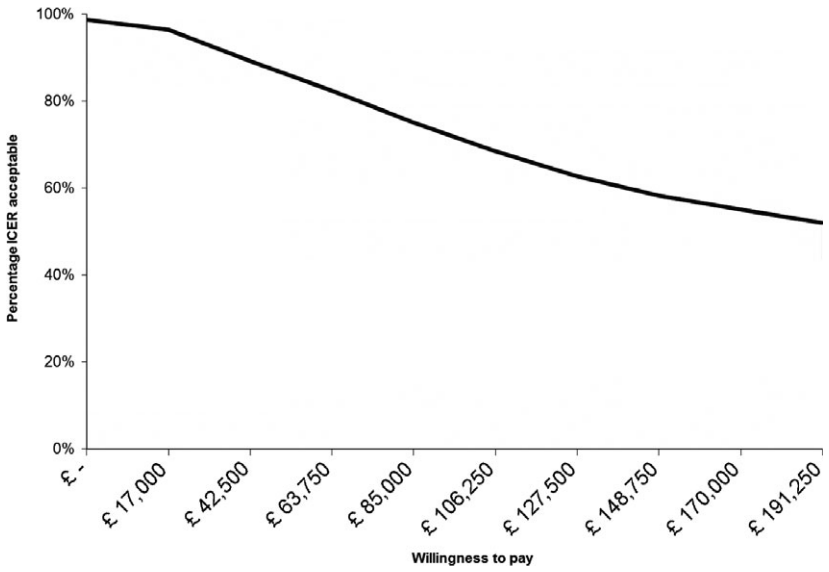


**Figure 3** Cost effectiveness acceptability curve. This shows the probability that dexamethasone is most cost effective (y-axis), depending on the willingness-to-pay per quality-adjusted life year (x-axis). ICER, incremental cost effectivness ratio.

The risk of resternotomy was not specified as a secondary outcome measure, but was included in the cost-effectiveness analysis. This complication appeared to occur more frequently in patients randomly allocated to dexamethasone. We have no plausible explanation for this unexpected but important observation. As far as we know, the effect of steroids on the risk of resternotomy has not been reported before [22, 23].

Another large randomised study (Steroids In caRdiac Surgery [SIRS] trial) that has recently been published [24], examined the effects of intra-operative high-dose methylprednisolone. Similar to the results of the DECS study, the results of the SIRS trial did not show a difference on the co-primary endpoints of both mortality and a composite of major adverse events [24].

There were no significant long-term effects of dexamethasone on major adverse events. The effects on clinical outcomes that were seen were largely comparable to the 30 days outcomes that we have previously

 

reported [6]. Given the nature of the intervention, it was to be expected that the effects of dexamethasone on clinical outcomes in this study, if any, would be present shortly after the surgical procedure rather than in the longer term. Also, most of the cost benefit likely occurred in within the first 30 days postoperatively. However, since full clinical recovery from cardiac surgery in most patients takes much longer than the 30 days of the primary study endpoint of the initial study [6], we believe it is important to have assessed outcomes up to 12 months.

A limitation is that only the effect of a single injection of high-dose dexamethasone was evaluated. Other treatment regimens, which may include lower doses, multiple administrations or different types of corticosteroids, are often used for the same indication [22, 23]. In the design of the DECS study, a single high dose of dexamethasone was chosen because this represented the most commonly used anti-inflammatory treatment during cardiac surgery in The Netherlands and several other countries [22, 23]. Strengths of our study include the well maintained blinding and a very low proportion (0.7%) of patients that could not be followed up to 12 months. Although we cannot be entirely certain that there was selective loss from follow-up, the characteristics of these patients were well balanced between the two treatment groups.

In conclusion, high-dose dexamethasone during cardiac surgery did not have an effect on major postoperative adverse events at 12 months. The use of dexamethasone was associated with a reduction in the average cost per patient, mainly through a reduction in the risk of respiratory failure and reduced hospital stay. Routine dexamethasone administration is expected to be cost effective at common threshold levels for cost effectiveness.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1** Kaplan-Maier curves for survival and event-free survival

**Table S1** Overview of all cost-estimates and their sources

**Table S2** A) Quality of life. B) Disability and survival

**Table S3** Results of the cost effectiveness analysis

 