ANESTHESIOLOGY

Dexamethasone for Cardiac Surgery: A Practice Preference–Randomized Consent Comparative Effectiveness Trial

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ANESTHESIOLOGY 2024; 141:859–69

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Many patients develop a high inflammatory response to cardiac surgery cardiopulmonary bypass.
- Previous studies have provided mixed results about whether administering high-dose corticosteroid (dexamethasone) can reduce morbidities and mortality in cardiac surgical patients.

What This Article Tells Us That Is New

- This study was a pragmatic, assessor-blinded, parallel-arm, multicenter trial that was successfully implemented to study the association between administration of dexamethasone and development of adverse outcomes after cardiac surgery with cardiopulmonary bypass. This pragmatic study design was implemented effectively, demonstrating an alternative approach to randomized controlled clinical trials, with less expense and in a shorter time period.
- This study did not identify a significant association between administration of dexamethasone and increased number of home days during the first 30 days after cardiac surgery (primary study outcome).

ABSTRACT

Background: High-dose corticosteroids have been used to attenuate the inflammatory response to cardiac surgery and cardiopulmonary bypass, but patient outcome benefits remain unclear. The primary aim was to determine whether using dexamethasone was superior to not using dexamethasone to increase the number of home days in the first 30 days after cardiac surgery. The secondary aim was to evaluate efficiency, value, and impact of the novel trial design.

Methods: This pragmatic, international trial incorporating a prerandomized consent design favoring local practice enrolled patients undergoing cardiac surgery across seven hospitals in Australia and The Netherlands. Patients were randomly assigned to dexamethasone 1 mg/kg or not (control). The primary outcome was the number of days alive and at home up to 30 days after surgery ("home days"). Secondary outcomes included prolonged mechanical ventilation (more than 48 h), sepsis, renal failure, myocardial infarction, stroke, and death.

Results: Of 2,562 patients assessed for eligibility, 1,951 were randomized (median age, 63 yr; 80% male). The median number of home days was 23.0 (interquartile range, 20.1 to 24.1) in the no dexamethasone group and 23.1 (interquartile range, 20.1 to 24.6) in the dexamethasone group (median difference, 0.1; 95% CI, –0.3 to 0.5; $P = 0.66$). The rates of prolonged mechanical ventilation (risk ratio, 0.72; 95% CI, 0.48 to 1.08), sepsis (risk ratio, 1.02; 95% CI, 0.57 to 1.82), renal failure (risk ratio, 0.94; 95% CI, 0.80 to 1.12), myocardial infarction (risk ratio, 1.20; 95% CI, 0.30 to 4.82), stroke (risk ratio, 1.06; 95% CI, 0.54 to 2.08), and death (risk ratio, 0.72; 95% CI, 0.22 to 2.35) were comparable between groups (all $P > 0.10$). Dexamethasone reduced intensive care unit stay (median, 29 h; interquartile range, 22 to 50 h *vs.* median, 43 h; interquartile range, 24 to 72 h; $P = 0.004$). The authors' novel trial design was highly efficient (89.3% enrollment).

Conclusions: Among patients undergoing cardiac surgery, high-dose dexamethasone decreased intensive care unit stay but did not increase the number of home days after surgery.

(ANESTHESIOLOGY 2024; 141:859–69)

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Submitted for publication December 7, 2023. Accepted for publication June 10, 2024. Published online first on June 21, 2024.

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<zdoi;10.1097/ALN.0000000000005127>

Cardiac surgery and cardiopulmonary bypass result in an intense inflammatory response associated with many postoperative complications.[1–3] Prophylactic high-dose corticosteroids are sometimes used to attenuate these effects, but there remains variation in practice,[4–7] and numerous small studies[5] and two large randomized trials[6,7] reported mixed findings.

The point estimates of the two largest trials[6,7] suggested a possible reduction in serious complications and mortality, and these benefits were most apparent in patients aged less than 75 yr.[8] Furthermore, the primary endpoints of these trials were focused on thrombotic events (myocardial infarction, stroke) and not specific to other more common and serious inflammatory-mediated complications such as respiratory failure, sepsis, and kidney injury. An individual patient meta-analysis including both major trials[6,7] found evidence that steroids reduced the risk of respiratory failure, infections, and intensive care unit (ICU) and hospital stay, but was associated with increased risk of myocardial injury.[9] An international survey of cardiac surgical practice across 56 countries found that steroids were routinely administered in 37 of 202 centers (18%); the steroid drugs of choice were either dexamethasone (42%) or methylprednisolone (58%).[10]

It is highly plausible that prophylactic steroids can suppress deregulated inflammation and thus improve outcome in cardiac surgery, but likely only when used in a more targeted patient population at increased risk of excess inflammatory activation. Preplanned subgroup analyses of the original Intraoperative High-dose Dexamethasone for Cardiac Surgery trial suggested a strong potential benefit in those less than 75 yr.[6] We therefore used a novel trial design[8,11,12] to determine whether high-dose dexamethasone reduced the risk of serious complications and increased home days after surgery in patients younger than 75 yr undergoing cardiac surgery.

Our primary hypothesis was that prophylactic dexamethasone administration in patients undergoing cardiac surgery increases days alive and spent at home up to 30 days after surgery compared with no dexamethasone administration. Our secondary hypothesis was that a randomized consent design incorporating existing practice preference enhances the efficiency, value, and impact of clinical trials.

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Materials and Methods

Trial Design

The rationale and design of our trial has been published,[8] registered at ClinicalTrials.gov (identifier, NCT03002259; principal investigator, Dr. Myles; first posted December 23, 2016), and the protocol and statistical analysis plan were uploaded through the Open Science Framework in August 2023 (identifier, https://doi.org/10.17605/OSF.IO/UVDE5) before commencing the final analyses. Briefly, this was a pragmatic, assessor-blinded, parallel-arm, multicenter trial using a practice-preference randomized consent design in which we randomly assigned eligible patients who were undergoing cardiac surgery to receive a single dose of dexamethasone or not. The pragmatic study design aimed to enroll a high proportion of eligible patients in real-world settings in order to maximize generalizability, and this was confirmed by the PRagmatic Explanatory Continuum Indicator Summary tool (Supplemental Digital Content 1, https://links.lww.com/ALN/D613). Monash University (Melbourne, Australia) funded the trial. There was no commercial involvement in the trial. The study was approved by the Alfred Health Human Research Ethics Committee (lead site), the Medical Ethical Committee of the University Medical Center Utrecht (Dutch lead site), and the institutional review board at each site. The members of the steering committee designed the trial, gathered and analyzed the data, prepared the manuscript, and, together with their coauthors, made the decision to submit the manuscript for publication.

This practice-preference randomized consent design has two distinct features: (1) unequal treatment assignment favoring existing practice, and (2) randomization before seeking informed consent, such that potential participants are aware of their assigned treatment group when deciding to enroll in the trial. Written informed consent was provided by all patients, but the timing and details of this varied across countries and according to local institutional review board requirements. In brief, in Australia, patients were provided with information outlining the routine collection of perioperative data as part of ongoing quality assurance in cardiac surgery.[13] This was followed by randomization to treatment group (see "Randomization, Blinding, and Procedures"), and only those randomly assigned to dexamethasone (not standard care in Australia) were provided with additional information about the trial, and informed consent was then sought for this nonstandard care—that is, a prerandomized consent design.[14] That is, Australian patients assigned to not receive dexamethasone were not required or asked for consent because this was deemed usual care. In contrast, in The Netherlands, dexamethasone is a standard of care, and the Medical Ethical Committee of the University Medical Center Utrecht required patients to first provide preliminary consent before randomization and then full informed consent if randomly assigned to nontreatment

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with dexamethasone, which led to additional research staff costs. Furthermore, the standard care arm (dexamethasone) was much costlier than anticipated because the dexamethasone was deemed to be study medication requiring trial pharmacy preparation and labeling and externally sourced monitoring. Further details are provided elsewhere[8] and in the study protocol (Supplemental Digital Content 1, https://links.lww.com/ALN/D613).

Trial Participants

All adult patients (aged 18 yr or older) aged less than 75 yr scheduled for elective or nonemergent cardiac surgery including cardiopulmonary bypass were eligible for inclusion. Patients ineligible to receive dexamethasone were those with type I diabetes, recent infection, or currently receiving steroid therapy (Supplemental Digital Content 2, https://links.lww.com/ALN/D614).

Randomization, Blinding, and Procedures

Randomization was stratified by site and country in permuted blocks, and patients were randomly assigned to treatment group from a computer-generated list favoring local practice (2:1), in which dexamethasone is not used routinely in Australia but is near-routine in The Netherlands (fig. 1; figure 1 in Supplemental Digital Content 4, https://links.lww.com/ALN/D616).

The attending anesthesiologist was aware of treatment group assignment. Surgical staff were strictly blinded to treatment assignment as it could potentially influence decisions regarding hospital discharge. Outcome events and patient follow-up were collected by research staff blinded to group assignment. Thus patients, clinicians providing postoperative care, and researchers collecting outcome data, were unaware of treatment group assignment.

All patients received routine surgical and other perioperative care. This included choice of anesthetic medications, antibiotic prophylaxis, surgical procedures, hemostasis, and blood transfusion. Local guidelines were used to manage hyperglycemia.

Intervention and Assessments

Dexamethasone, 1 mg per kg (up to a maximum of 100 mg), was administered to patients assigned to the treatment group as an IV bolus after induction of anesthesia but before surgical incision.

Patient demographic and perioperative characteristics were recorded (table 1). A 12-lead electrocardiogram was done preoperatively and on days 1 to 3 after surgery. Blood for troponin (or if unavailable, creatine kinase–mb fraction [CK-MB]) measurement was collected preoperatively and for 3 days after surgery in most patients. Patients were followed during their hospital admission and up to 30 days after surgery. A medical chart review was done at 30 days after surgery to detect any additional complications, determine discharge date and destination, and record hospital readmissions and survival status.

Outcome Measures

The primary outcome was days at home up to 30 days after surgery ("home days").[15–17] The clinical prespecified secondary endpoints—prolonged mechanical ventilation (greater than 48 h), sepsis, renal failure, myocardial infarction, stroke, and death up to 30 days after surgery—were extracted from the relevant national registries that had comparable definitions (Australian & New Zealand Society of Cardiac & Thoracic Surgeons [Edgecliff, Australia; https://anzscts.org/database/] or Netherlands Association for Cardio-Thoracic Surgery [Utrecht, The Netherlands; https://www.nvtnet.nl] definitions). Other secondary outcomes were peak C-reactive protein (CRP) and cardiac biomarkers, vasopressor requirements, ICU, and hospital stay. Safety outcomes included peak blood glucose, insulin requirements, infections, myocardial injury, and reoperation (Supplemental Digital Content 2, https://links.lww.com/ALN/D614, and Supplemental Digital Content 3, https://links.lww.com/ALN/D615).[8]

Efficiency, Value, and Impact. Our novel trial design was premised on an acceptance that dexamethasone is a widely used adjunct for patients undergoing cardiac surgery[10] and a reassuring safety profile. This justifies a simplified consent process.[11,14] We also weighted the randomization to favor local practice and so greatly reduced the burden of consent for both patients and research staff, and so maximizing the likely recruitment fraction.[8,11,12,14] We thus included secondary aims to demonstrate the efficiency, value, and impact of the novel trial design that takes advantage of practice variation (Supplemental Digital Content 2, https://links.lww.com/ALN/D614).

[1] Assessment of efficiency of the trial design involved two aspects, the statistical efficiency and the recruitment efficiency. Statistical efficiency was obtained by using the continuous outcome measure, days at home up to 30 days after surgery, as the primary outcome because numerical data provide greater statistical power when compared with binary outcomes. The pragmatic practice-preference randomized consent design was further evaluated by documenting patient recruitment (percentage who consent) and enrollment (participants/month) rates, and research cost per patient.

[2] Value will be demonstrated by physician (all treating anesthesiologists and surgeons) survey, rating importance of endpoint measures on 11-point Likert scales.

[3] Impact will be measured at 12 months after publication of the trial, and an updated individual participant data meta-analysis, and according to the results determine whether Australian or Dutch cardiac surgical centers have adopted or ceased use of dexamethasone (note: we have baseline data on file).

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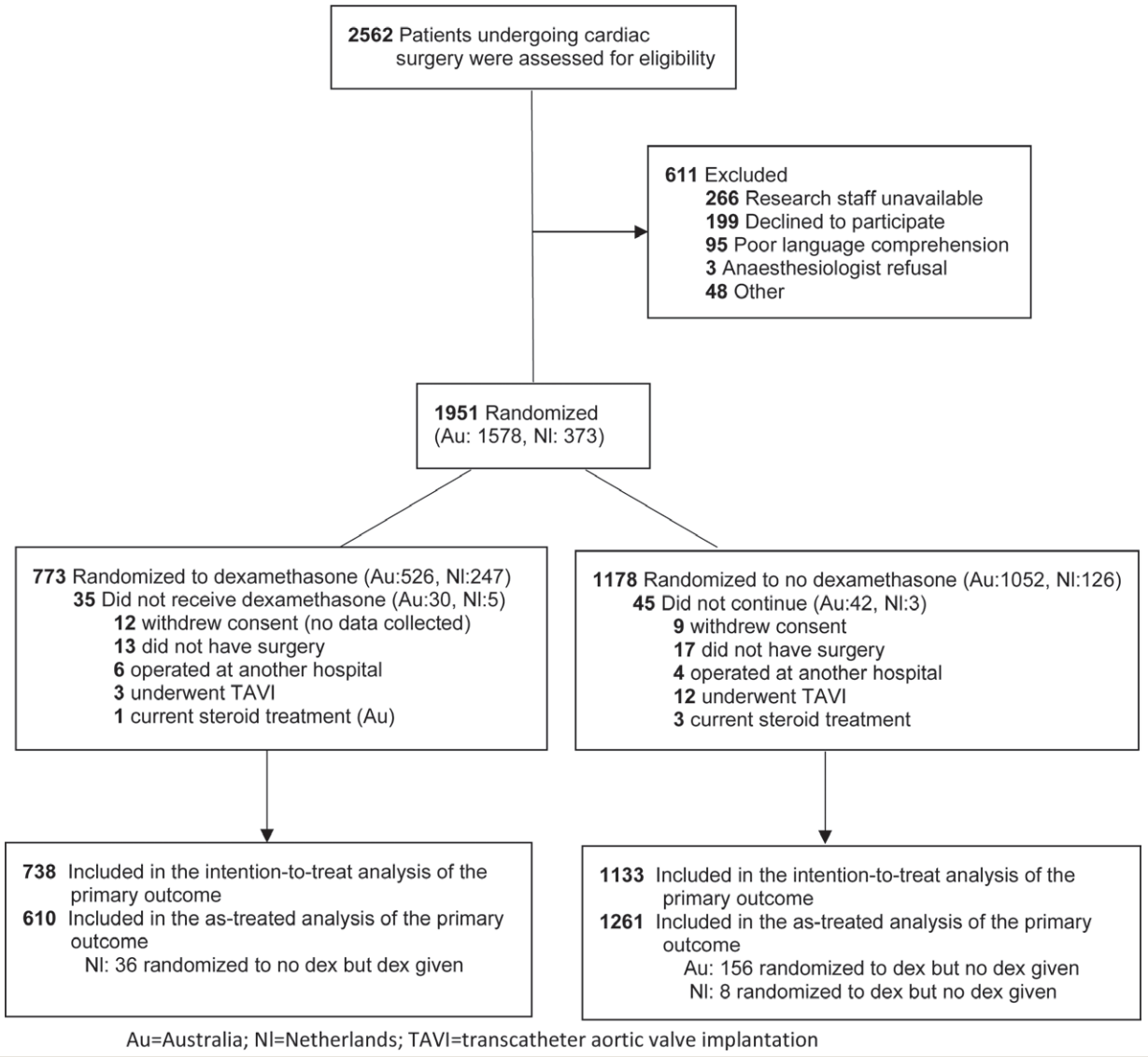

Fig. 1. Patient flow in a trial of dexamethasone for cardiac surgery. Au, Australia; dexamethasone; Nl, Netherlands; TAVI, transcatheter aortic valve implantation.

Sample Size Calculation

We expected that steroids could reduce postoperative complications by up to 40%,[6,18] and this would lead to a reduction in hospital stay and perhaps readmissions.[6,9,19] Modeling was done with a transformed lognormal distribution using a median of 6 days in hospital and variability (log scale; SD, 9.0) to result in a median days at home of 22 days. To account for a 5% loss to follow-up and 15% nonconsent rate, using quantile (median) regression with terms for intervention arm and country, repeated to produce 5,000 simulated trial datasets, indicated that a total sample size of 2,500 patients had 90% power to detect a median increase of 1 day at home in the dexamethasone arm.[8] A 1-day difference has health resource and cost importance for cardiac surgery, and given the low cost and excellent safety profile of dexamethasone, we believed such a difference would be clinically important. We thus planned to enroll 2,800 patients to account for a nonconsent rate of up to 20%.

Statistical Analyses

In addition to publishing details of our trial protocol,[8] we devised a statistical analysis plan before accessing the trial database (Supplemental Digital Content 2, https://links.lww.com/ALN/D614). All patients randomized to study drug administration and meeting eligibility criteria were considered as comprising the intention-to-treat population for all primary, secondary, and safety analyses. Analysis of home days was

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Table 1. Baseline Characteristics

Factor	No Dexamethasone (n = 1,133)	Dexamethasone (n = 738)	Missing
Age, median (interquartile range), yr	63.0 (56.0–69.0)	64.0 (56.0–69.0)	0/1
Sex, No. (%)			5/1
Male	888 (78.7)	595 (80.7)	
Female	240 (21.3)	142 (19.3)	
Marital status, No. (%)			81/159
Married	607 (57.7)	362 (62.5)	
Divorced	93 (8.8)	41 (7.1)	
Widowed	33 (3.1)	13 (2.2)	
De facto	85 (8.1)	52 (9.0)	
Single/other	234 (22.2)	111 (19.2)	
No. adults living with person, median (interquartile range)	2.0 (2.0–2.0)	2.0 (2.0–2.0)	81/160
ASA Physical Status, No. (%)			1/0
II	3 (0.3)	2 (0.3)	
III	564 (49.8)	387 (52.4)	
IV	565 (49.9)	349 (47.3)	
Weight, median (interquartile range), kg	86.3 (76.0–97.5)	86.5 (75.8–98.7)	0/0
Body mass index, median (interquartile range), kg/m^2	28.8 (25.7–32.6)	28.2 (25.1–31.8)	1/0
Preoperative pathology tests			
Hemoglobin, mean ± SD, g/l	141 ± 16.5	142.2 ± 17.6	1/0
Creatinine, median (interquartile range), μmol/l	82 (72–95)	82 (72–97)	1/0
Troponin, median (interquartile range), ng/ml	0.03 (0.00–0.35)	0.01 (0.00–0.17)	713/417
CK-MB, median (interquartile range), U/l	3.0 (1.5–150)	14.0 (1.5–96)	1,114/711
Preoperative HbA1C done	757 (67.1)	486 (66.1)	4/3
HbA1C, median (interquartile range), mmol/mol	41 (37–53)	40 (37–51)	79/48
Pre-existing conditions, No. (%)			
Previous MI	396 (35.4)	238 (32.6)	13/8
MI within 90 days	308 (77.8)	159 (66.8)	0/0
Diabetes	357 (31.5)	199 (27.0)	0/0
Insulin-dependent	105 (29.4)	58 (29.1)	
Non–insulin-dependent	252 (70.6)	141 (70.9)	
Pulmonary disease	146 (12.9)	91 (12.3)	0/0
Steroids (inhaled or systemic)	29 (2.6)	19 (2.6)	0/0
Other medical condition	23 (2.0)	25 (3.4)	0/0
Previous cardiac surgery	53 (4.7)	29 (3.9)	2/1
Medications			
Statin	844 (74.5)	535 (72.5)	0/0
ACE inhibitor/ARB	633 (55.9)	410 (55.6)	0/0
β-Blocker	693 (61.2)	441 (59.8)	0/0
Calcium antagonist	249 (22.0)	147 (19.9)	0/0
EuroSCORE-2, median (interquartile range), %	1.0 (0.7–1.7)	1.1 (0.8–1.8)	3/2

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASA, American Society of Anesthesiologists; CK-MB, creatinine kinase-mb fraction; EuroSCORE, European system for cardiac operative risk evaluation; HbA1C, hemoglobin A1c; MI, myocardial infarction.

performed using quantile regression adjusting for country and site, with results expressed as the difference in medians with 95% CIs. Binary outcomes were analyzed using log-binomial regression adjusting for country to estimate risk ratios and 95% CIs. Other secondary endpoints were compared with linear or Cox proportional hazards regression models, as appropriate.

If the proportion of patients missing the primary days at home up to 30 days after surgery outcome exceeded 5%, an analysis using multiple imputation of the missing outcomes using chained equations under a "missing at random" assumption was to be employed. Relevant baseline and postbaseline variables (including country) were used in the imputation models that were predictive of days at home up to 30 days after surgery, or of days at home up to 30 days after surgery being missing, which were constructed separately for each treatment arm. Patients who withdrew consent for any data to be used were not included in these imputations. The multiple imputation analyses were to be regarded as supplementary. An interim analysis was planned after enrollment of 1,400 patients, with results to be made available to the data and safety monitoring committee.

Prespecified subgroups were patient age and sex, surgical risk strata, surgical subtypes, left ventricular systolic function, and country. All reported *P* values are two-sided and not adjusted for multiple comparisons.

Results

Between September 6, 2019, and October 31, 2022, a total of 1,951 patients across five sites in Australia and two sites in

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The Netherlands were randomly assigned to receive dexamethasone (773 patients) or not (1,178 patients; fig. 1). A total of 35 of 773 patients (4.5%) assigned to the dexamethasone group did not receive dexamethasone, and 45 of 1,178 patients (3.8%) assigned to the no dexamethasone group either received dexamethasone or did not continue in the study. All eligible patients had complete follow-up for the primary outcome and at least 98% for secondary outcomes, with the exception of peak CRP levels not always being measured. Preoperative and postoperative CK-MB or troponin measurements were done in 592 of 738 patients (80.2%) in the dexamethasone group and 844 of 1,133 patients (74.5%) in the no dexamethasone group. There were 1,483 men (80%), overall median age was 63 yr, and 30-day mortality was 0.8%. Demographic, medical, and perioperative characteristics were comparable between groups (tables 1 and 2) and within countries (tables 1 and 2 in Supplemental Digital Content 4, https://links.lww.com/ALN/D616).

The COVID-19 pandemic had a substantial detrimental impact on enrollments because elective surgery programs in both countries were heavily curtailed through 2020 and 2021, and study funding was eventually exhausted. As a result, 75% (1,871 of 2,500 participants) of the maximum planned number of patients were recruited and completed 30 days of follow-up. In addition, completion of all data entry and transfer to the coordinating center were delayed such that the planned interim analysis was cancelled because it was close to the eventual closing date of the trial.

Primary Outcome

The median number of home days was 23.0 (interquartile range, 20.1 to 24.1) in the no dexamethasone group and 23.1 (interquartile range, 20.1 to 24.6) in the dexamethasone group (median difference, 0.1; 95% CI, –0.3 to 0.5; $P = 0.66$; table 3). With the exception of female sex, there were no significant interactions for the primary outcome between treatment group and patient or perioperative characteristics (fig. 2). A subgroup analysis found that women in the dexamethasone group had more days at home compared with the no dexamethasone group (P for interaction = 0.04; median difference, 1.0; 95% CI, 0.0 to 2.0 home days; $P = 0.048$). There was no country-dependent treatment effect.

Secondary and Safety Outcomes

The rates of prolonged mechanical ventilation, sepsis, renal failure, myocardial infarction, and stroke were comparable between groups (table 3). Death within 30 days of surgery occurred in 4 of 736 patients (0.54%) in the dexamethasone group and 10 of 1,130 patients (0.88%) in the no dexamethasone group (risk ratio, 0.72; 95% CI, 0.22 to 2.35; $P = 0.59$).

The duration of ICU stay was lower in the dexamethasone group (median, 1.2; interquartile range, 0.9 to 2.1 days) when compared with the no dexamethasone group (median, 1.8; interquartile range, 1.0 to 3.0 days; discharge rate ratio, 1.13; 95% CI, 1.03 to 1.25; $P = 0.004$); the durations of hospital stay were similar (discharge rate ratio, 1.05; 95% CI, 0.95 to 1.16; $P = 0.13$; table 3). Patients in the dexamethasone group had a lower peak CRP after surgery when compared with the no dexamethasone group (median difference, 25; 95% CI, 11 to 39 mg/l; $P < 0.001$; table 3). The quick sequential organ failure assessment scores on postoperative day 1 (odds ratio, 0.99; 95% CI, 0.83 to 1.19; $P = 0.92$) and day 2 (odds ratio, 0.85; 95% CI, 0.70 to 1.01; $P = 0.07$) and need for vasopressor support in the ICU (risk ratio, 0.98; 95% CI, 0.92 to 1.05; $P = 0.60$) were similar between groups.

Patients in the dexamethasone group had higher peak blood glucose after surgery (median difference, 1.0; 95% CI, 0.7 to 1.29 mmol/l; $P < 0.001$), and were more likely to receive insulin perioperatively (risk ratio, 1.26; 95% CI, 1.13 to 1.42; $P < 0.001$), when compared with the no dexamethasone group (table 4). Peak troponin and/or CK-MB as indicators of myocardial injury (table 3 in Supplemental Digital Content 4, https://links.lww.com/ALN/D616), and reoperation, hospital readmission, and infections were comparable across groups (table 4).

A list of all postrandomization adverse events is provided in tables 4 and 5 in Supplemental Digital Content 4 (https://links.lww.com/ALN/D616).

Sensitivity Analyses

The effects of dexamethasone on home days and other outcomes were comparable in Australia and The Netherlands; adjustment for baseline factors did not meaningfully change the results (tables 5 to 8 in Supplemental Digital Content 4, https://links.lww.com/ALN/D616). Results of the as-treated population were essentially comparable to the modified intention-to-treat analyses (tables 9 to 15 and figure 1 in Supplemental Digital Content 4, https://links.lww.com/ALN/D616).

Efficiency, Value, and Impact

A total of 1,951 of 2,562 potentially eligible patients were enrolled and randomized in the trial (77.2% recruitment), and 1,871 of 2,093 fully eligible and consenting patients enrolled (89.3%); the average monthly enrollment was 53 patients across the seven centers. The estimated research coordinator cost (AUD60 per hour) per participant enrolled was AUD185 in Australia (approximately USD119) and €200 in The Netherlands (approximately USD212). When asked to rate the importance of the primary outcome, days at home up to 30 days after surgery, on a Likert scale from 0 to 10, a random selection of attending physicians treating trial participants (n = 51) provided a median rating of 8 (interquartile range, 7 to 9). The importance ratings were similar between cardiac anesthesiologists (median, 8; interquartile range, 7 to 9.5) and surgeons (median, 8; interquartile range, 7 to 9; $P = 0.67$), with slightly higher scores in Australia (median, 9; interquartile range, 9 to 10) compared with The

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Table 2. Surgical Characteristics

Factor	No Dexamethasone (n = 1,133)	Dexamethasone (n = 738)	Missing
Left ventricular grade, No. (%)			2/4
Good (ejection fraction > 50%)	890 (78.7)	574 (78.2)	
Moderate (ejection fraction 31–50%)	198 (17.5)	132 (18.0)	
Poor (ejection fraction 21–30%)	30 (2.7)	18 (2.5)	
Very poor (ejection fraction ≤ 20%)	13 (1.1)	10 (1.4)	
CABG surgery, No. (%)	759 (67.0)	480 (65.0)	0/0
Valve repair/replacement, No. (%)	342 (30.2)	226 (30.6)	0/0
Other, No. (%)	176 (15.5)	146 (19.8)	0/0
Total bypass time, median (interquartile range), min	94.5 (74.0–120.0)	96.1 (77.0–125.0)	8/8
Deep hypothermic cardiac arrest, No. (%)	22 (2.0)	14 (1.9)	10/7
Duration of surgery, median (interquartile range), h	3.8 (3.2–4.6)	3.8 (3.3–4.6)	0/0

CABG, coronary artery bypass graft.

Table 3. Outcomes

Variable	No Dexamethasone (n = 1,133)	Dexamethasone (n = 738)	Risk Ratio, Hazard Ratio, or Median Δ (95% CI)	*P* Value	Missing
Primary outcome					
Days alive and at home (30 d), median (interquartile range)	23.0 (20.1 to 24.1)	23.1 (20.1 to 24.6)	0.10 (–0.33 to 0.52)*	0.66	0/0
Secondary outcomes					
Complications within 30 d, No. (%)					
Mechanical ventilation > 48 h, No. (%)	80 (7.1)	31 (4.2)	0.72 (0.48 to 1.08)†	0.12	0/1
Sepsis	32 (2.8)	18 (2.4)	1.02 (0.57 to 1.82)†	0.94	2/2
Renal failure	305 (27.1)	152 (20.7)	0.94 (0.80 to 1.12)†	0.51	6/2
Myocardial infarction	4 (0.4)	5 (0.7)	1.20 (0.30 to 4.82)†	0.80	0/2
Stroke	23 (2.0)	14 (1.9)	1.06 (0.54 to 2.08)†	0.87	2/1
Vasopressor support in the ICU, No. (%)	740 (65.5)	506 (68.8)	0.98 (0.92 to 1.05)†	0.60	4/2
qSOFA score day 1			0.99 (0.83 to 1.19)‡	0.92	0/0
0	128 (11.3)	106 (14.4)			
1	435 (38.4)	288 (39.0)			
2	525 (46.3)	317 (43.0)			
3	45 (4.0)	27 (3.7)			
qSOFA score day 2			0.85 (0.70 to 1.01)‡	0.07	0/0
0	180 (15.9)	190 (25.7)			
1	272 (24.0)	188 (25.5)			
2	570 (50.3)	314 (42.5)			
3	111 (9.8)	46 (6.2)			
Peak CRP, median (interquartile range), mg/l	147 (77 to 223)	73 (37 to 152)	–25.0 (–39 to –11)*	< 0.001	724/381
ICU stay, median (interquartile range), h	43 (24 to 72)	29 (22 to 50)	1.13 (1.03 to 1.25)§	0.004	2/0
Hospital stay, median (interquartile range), d	6.4 (5.3 to 8.3)	6.3 (5.3 to 8.3)	1.05 (0.95 to 1.16)§	0.13	0/0

All outcome measures were adjusted for country.

*Difference in medians. †Risk ratio. ‡Odds ratio. §Discharge rate ratio.

CRP, C-reactive protein; ICU, intensive care unit; qSOFA, quick sequential organ failure assessment.

Netherlands (median, 8; interquartile range, 6.5 to 9; $P = 0.046$). The impact of the trial results on clinical practice will be reported 12 months after publication.

Discussion

In this pragmatic, international trial incorporating a prerandomized consent design favoring local practice, dexamethasone did not increase the number of home days (days at home up to 30 days after surgery) when compared with no dexamethasone in cardiac surgery. Dexamethasone was associated with a reduced ICU stay, but this was a secondary outcome, and there was no reduction in hospital stay, and the risk of myocardial injury or infarction did not increase, when compared with no dexamethasone. Dexamethasone was associated with a small increase in peak serum glucose and need for insulin perioperatively when compared with no dexamethasone.

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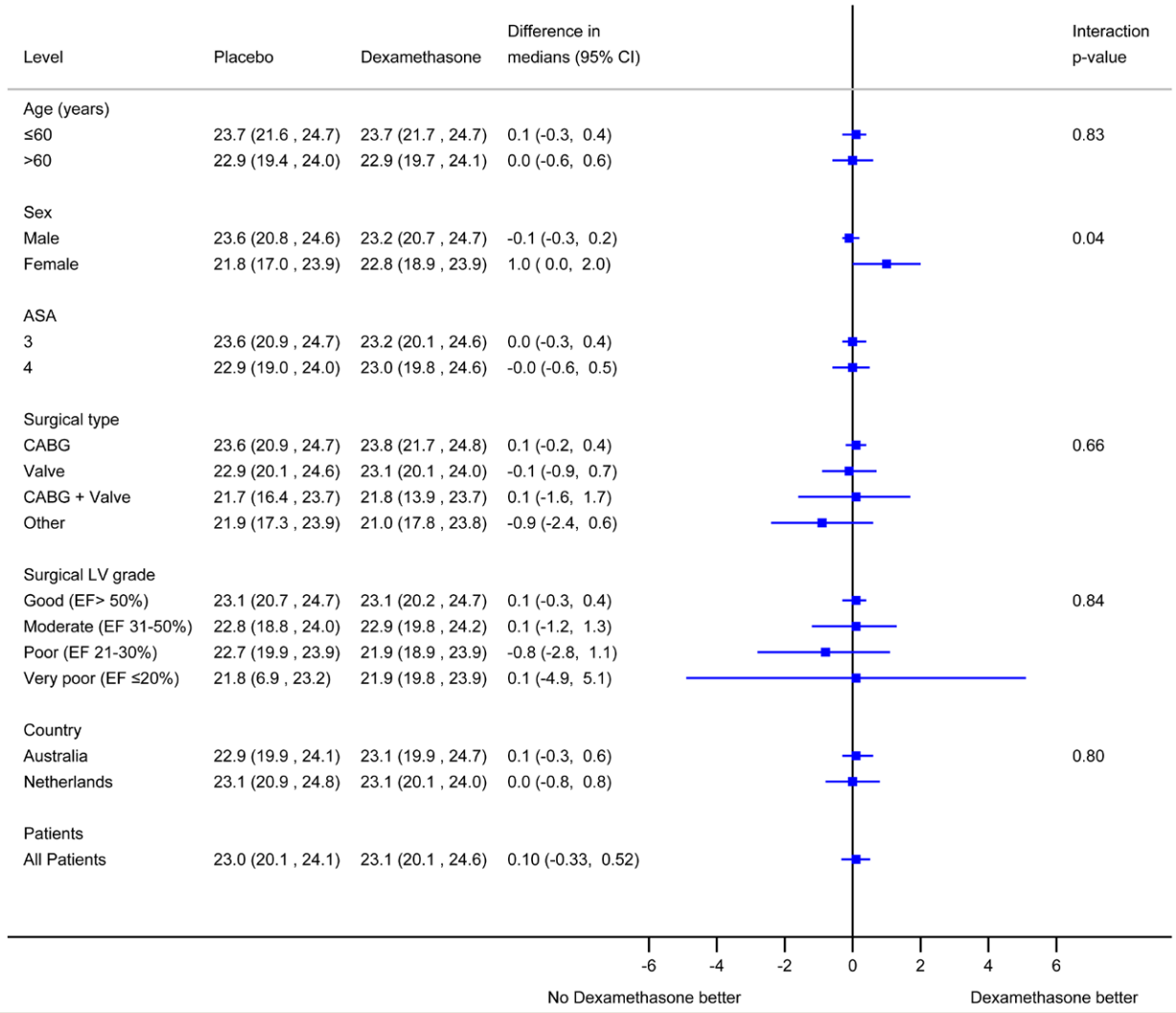

Fig. 2. Mean (95% CI) number of days alive and at home up to 30 days after surgery in prespecified subgroups. ASA, American Society of Anesthesiologists; CABG, coronary artery bypass graft; EF, ejection fraction; LV, left ventricular.

We did identify a subgroup effect, in that dexamethasone was associated with an increase in home days in women but not men. Although this was a prespecified analysis, it should be considered low credibility[20,21] because there was no apparent sex interaction effect reported in the previous large trials of corticosteroids in cardiac surgery.[6,7] There are sex disparities in research and outcomes after cardiac surgery, which may in part relate to underdiagnoses, delayed referral, and completeness of coronary revascularization.[22] Potential sex differences in surgical inflammation and in the response to corticosteroids, and surgical inflammation, need further study.

A previous large trial of methylprednisolone for cardiac surgery found that this corticosteroid was associated with a higher incidence of myocardial injury (as measured by elevation of CK-MB enzyme) but not myocardial infarction.[7] An individual patient meta-analysis of the two largest trials to date[6,7] confirmed an adverse effect on myocardial injury,[9] but found no evidence of a higher risk of myocardial infarction or death; there was also a possible reduction in respiratory failure (odds ratio, 0.83; 95% CI, 0.75 to 0.99), and ICU ($P < 0.001$) and hospital ($P < 0.006$) stay.[9] With the exception of a reduced ICU stay, we could not identify any such benefits in the current study.

Dexamethasone is an anti-inflammatory drug that has been shown to reduce inflammatory markers after cardiac surgery,[23–25] for which CRP is a readily available biomarker.[23,25] We found that dexamethasone was associated with a reduction in peak postoperative CRP in this study, and this might explain why there was a reduction in ICU stay, but this did not otherwise translate into any meaningful improvement in patient outcomes. This was despite younger age subgroup findings from previous large trials of corticosteroids suggesting this possibility.[6,7] Apart from the

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Table 4. Safety Outcomes: Postoperative

Variable	No Dexamethasone (n = 1,133)	Dexamethasone (n = 738)	Risk Ratio, Hazard Ratio, or Median Δ (95% CI)	*P* Value	Missing
Day 1					
Peak glucose, median (interquartile range), mmol/l	10.2 (8.9 to 12.3)	11.0 (9.6 to 12.9)	1.00 (0.71 to 1.29)*	< 0.001	13/3
Insulin treatment, No. (%)	400 (35.5)	323 (43.9)	1.26 (1.13 to 1.42)†	< 0.001	5/3
Peak troponin, median (interquartile range), ng/l	1,657 (807 to 3,505)	1,536 (695 to 3,591)	–55 (–297 to 187)*	0.66	333/238
Up to day 30					
Peak hs-troponin, median (interquartile range), ng/ml	1.66 (0.80 to 3.53)	1.46 (0.67 to 3.54)	–0.07 (–0.03 to 0.16)*	0.55	297/208‡
Peak CK-MB, median (interquartile range), U/l	29.4 (17.0 to 50.3)	29.5 (16.9 to 49.4)	0.10 (–6.15 to 6.35)*	0.97	990/488‡
Reoperation, No. (%)	44 (3.9)	43 (5.8)	1.15 (0.75 to 1.78)†	0.52	0/0
Hospital readmission, No. (%)	112 (9.9)	77 (10.4)	1.13 (0.85 to 1.49)†	0.41	3/1
Surgical site infection, No. (%)	126 (11.1)	71 (9.6)	1.05 (0.80 to 1.39)†	0.71	2/2
Pneumonia, No. (%)	88 (7.8)	49 (6.7)	0.85 (0.60 to 1.21)†	0.37	3/2
Urinary tract infection, No. (%)	28 (2.5)	23 (3.1)	1.47 (0.85 to 2.56)†	0.17	2/2
Sepsis, No. (%)	32 (2.8)	18 (2.4)	1.02 (0.57 to 1.82)†	0.94	2/2
Thromboembolism, No. (%)	7 (0.6)	4 (0.5)	0.89 (0.25 to 3.16)†	0.85	1/1

All outcome measures were adjusted for country.

*Difference in medians. †Risk ratio. ‡Either CK-MB or troponin measurements were done in 592 of 738 patients (80.2%) in the dexamethasone group and 844 of 1,133 patients (74.5%) in the no dexamethasone group.

CK-MB, creatinine kinase-mb fraction; hs, high sensitive.

differential effects between women and men, there were no other significant subgroup interactions for the primary endpoint.

Our trial incorporated a pragmatic randomized consent design (Supplemental Digital Content 3, https://links.lww.com/ALN/D615) and leveraged registry resources that, despite the COVID-19 pandemic, reduced the cost and greatly facilitated the participation rate and timely completion of the trial. Research costs were greater in The Netherlands because of the additional requirements to comply with local research directives. This novel design could be adopted in future clinical trials evaluating currently used treatments that vary by clinician or across centers in an extremely cost-efficient manner. The broad eligibility criteria and high proportion of patient enrollments should more readily demonstrate real-world effectiveness.

Limitations

This study has several limitations. First, absence of blinding of anesthesiologists administering dexamethasone may have introduced bias in some endpoint monitoring. Second, the trial was pragmatic and included a heterogenous range of cardiac surgical procedures, aiming for generalizability. Third, there were many secondary outcomes (including ICU stay), and some findings may be spurious (type I error) as a result. Fourth, the planned sample size (aiming for 2,500 evaluable participants) was not achieved because of the COVID-19 pandemic (type II error). Nevertheless, the point estimate and 95% CI of the difference in home days precluded a clinically meaningful difference. Fifth, 22% of participants did not have measurements of CK-MB or troponin before and after surgery, and so detection of myocardial injury or infarction will be lessened.

Conclusions

Among patients undergoing cardiac surgery, high-dose dexamethasone, compared with control, reduced ICU stay but did not increase the number of home days after cardiac surgery. Dexamethasone did not reduce the risk of major complications but did result in a small increase in the need for insulin to control perioperative hyperglycemia. Prespecified subgroup analyses indicated high-dose dexamethasone led to a possible increase in home days after cardiac surgery among women.

Research Support

The study was financially supported by the Department of Anesthesiology and Perioperative Medicine, Monash University, Melbourne, Australia.

Competing Interests

Dr. Myles is supported by an Australian National Health and Medical Research Council (Canberra, Australia) investigator grant (ID2008079). Dr. Dieleman is a consultant for MicuRx (Foster City, California). The other authors declare no competing interests.

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Full protocol available at: p.myles@alfred.org.au. Raw data available at: p.myles@alfred.org.au.

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Supplemental Digital Content

Supplemental Digital Content 1. Assessment of pragmatic features of the DECS-II trial using the PRECIS-2 tool, https://links.lww.com/ALN/D613
Supplemental Digital Content 2. Trial protocol, https://links.lww.com/ALN/D614
Supplemental Digital Content 3. Statistical analysis plan, https://links.lww.com/ALN/D615
Supplemental Digital Content 4. Appendices, https://links.lww.com/ALN/D616
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Appendix

The authors thank collaborators contributing to the dexamethasone for cardiac surgery (DECS-II) trial: Australia: P. S. Myles, S. Wallace, M. Ueoka, M. Dutton, S. Robertshaw, M. Clarris, A. Neylan, J. Smith, A. Hulley, S. Warwarek, T. Painter, K. Heyman, R.-L. Falland, J. Pieterse, R. Fiddes, A. Marriott, J. Dieleman, J. Cope, E. Clark-Mackay. The Netherlands: K. E. Munting, L. P. J. Verheijen, D. van Dijk, N. .E Wietsma, N. P. Monteiro de Olivieira, L. W. L. Oey.

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