Corticosteroids for the Prevention of Atrial Fibrillation After Cardiac Surgery
A Randomized Controlled Trial

Atrial fibrillation (AF) is the most common arrhythmia to occur after cardiac surgery. An exaggerated inflammatory response has been proposed to be one etiological factor.

Objective To test whether intravenous corticosteroid administration after cardiac surgery prevents AF after cardiac surgery.

Design, Setting, and Patients A double-blind, randomized multicenter trial (study enrollment August 2005–June 2006) in 3 university hospitals in Finland of 241 consecutive patients without prior AF or flutter and scheduled to undergo first on-pump coronary artery bypass graft (CABG) surgery, aortic valve replacement, or combined CABG surgery and aortic valve replacement.

Intervention Patients were randomized to receive either 100-mg hydrocortisone or matching placebo as follows: the first dose in the evening of the operative day, then 1 dose every 8 hours during the next 3 days. In addition, all patients received oral metoprolol (50-150 mg/d) titrated to heart rate.

Main Outcome Measure Occurrence of AF during the first 84 hours after cardiac surgery.

Results The incidence of postoperative AF was significantly lower in the hydrocortisone group (36/120 [30%]) than in the placebo group (58/121 [48%]; adjusted hazard ratio, 0.54; 95% confidence interval, 0.35–0.83; \( P = .004 \); number needed to treat, 5.6). Compared with placebo, patients receiving hydrocortisone did not have higher rates of superficial or deep wound infections, or other major complications.

Conclusion Intravenous hydrocortisone reduced the incidence of AF after cardiac surgery.

Trial Registration clinicaltrials.gov Identifier: NCT00442494

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METHODS
Study Design and Participants
Our study took place in 3 university hospitals in Finland: University Hospital of Kuopio, University Hospital of Oulu, and University Hospital of Tampere. Study enrollment occurred between August 2005 and June 2006. The study protocol was approved by the Kuopio University ethical committee, and all patients gave written informed consent.

We enrolled 241 consecutive ethnic Finnish patients aged between 30 and 85 years scheduled to undergo their first on-pump CABG surgery, aortic valve replacement, or combined CABG surgery and aortic valve replacement (FIGURE 1). We excluded patients with previous episodes of AF or flutter, uncontrolled diabetes mellitus, systemic bacterial or mycotic infection, active tuberculosis, Cushing syndrome, psychotic mental disorder, herpes simplex keratitis, or renal insufficiency (serum creatinine concentration >20 mg/dL [>1768 µmol/L]). We also excluded patients with a history of peptic ulcer or thrombophlebitis.

Patients underwent cardiac surgery on standard cardiopulmonary bypass. Intermittent blood or cold crystalloid cardioplegia solution was administered via the antegrade or retrograde route. The cardioplegia solution consisted of 32 mEq/L of magnesium, and no extra magnesium substitution was administered.

After surgery, patients were followed up in the intensive care unit and were weaned off mechanical ventilation when they fulfilled the following criteria: hemodynamic stability, peripheral temperature of more than 32°C, cooperativity, and no major bleeding. Chest drains were removed on the first postoperative day and patients were referred to the surgical ward.

All patients were connected to 3 channel ward monitors for continuous electrocardiographic monitoring for the whole study period. The ward monitor stored 24-hour electrocardiographic recordings for subsequent analysis, and 12-lead electrocardiographic recording was performed if necessary to confirm the rhythm. The rhythm was defined as AF when there were no consistent P waves before each QRS complex and ventricular rate was irregular. Atrial fibrillation episodes lasting longer than 5 minutes were recognized.

Perioperative myocardial infarction was defined as the development of new Q waves. A stroke was defined as a new neurological symptom verified by correlative changes in computed tomography. A psychotic mental disorder was defined as a new psychotic symptom diagnosed by the psychiatrist. Mediastinitis was defined as deep sternal infection requiring resternotomy and operative revision. Superficial infections were defined as wound infections in the sternotomy or leg wounds, which were treated without surgical intervention.

Study Protocol
Randomization lists were produced by a biostatistician (P.H.). The groups were block-randomized with block sizes of 6, separately in each hospital. Randomization lists were sent to each hospital’s department of pharmacy, where study drugs were prepared. The investigator sent the name and date of birth by telefax to the pharmacy each time a new patient had given written informed consent. Randomization was performed on the operation day. The pharmacy personnel selected the next number on the randomization list, labeled the drug container with the patient’s name, and sent the container to the department where the patient was treated. The study group remained unknown to all caring nurses and physicians. The randomization codes were opened after the end of the study. It was not necessary to break the code for any of the patients, so blinding was ensured.

The study drugs were prepared in each hospital’s department of pharmacy. Solutions were prepared by using aseptic techniques under a laminar flow hood. Reconstituted solutions of hydrocortisone sodium succinate (Solu-Cortef; Pfizer Manufacturing, Puurs, Belgium) in 0.9% sodium chloride solution (Na-tri umklorid Braun, 9 mg/mL) were prepared by transferring 100 mg per 2 mL of hydrocortisone sodium succinate into polyethylene infusion containers containing 100 mL of 0.9% sodium chloride solution. Placebo solutions were prepared by transferring 2 mL of 0.9% sodium chloride solution (Natri umchlorid Braun, 9 mg/mL) into polyethylene infusion containers containing 100 mL of 0.9% sodium chloride solution. Both the active drug and the placebo preparations were identical regarding color and other characteristics.

Each patient was administered either hydrocortisone or placebo as follows: the first dose in the evening of the operative day, then 1 dose every 8 hours during the next 3 days. In addition, all patients were administered oral metoprolol according to heart rate (if heart rate was 60-70/min, the metoprolol dose was 25 mg 2 times a day; if heart rate was 71-80/min, the metoprolol dose was 50 mg 2 times a day; and if heart rate was >80/min, the metoprolol dose was 50 mg 3 times a day). The study period was 84 hours in both groups.

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Main Outcome Measure
The primary end point of our study was the occurrence of AF during the first 84 hours after cardiac surgery. All patients in the hydrocortisone and placebo groups had complete courses of the intended treatment until designated end points, so intention to treat was the same as actual treatment. After the first episode of AF, the study protocol was discontinued. Investigators telephoned the patients 2 to 4 weeks after the surgery. If the patient reported that he or she had had contact with a physician due to suspected infection, patient charts were ordered to verify and check the event. In addition, the patient charts were checked 6 months after the surgery to assess the incidence of major postoperative complications (mediastinitis or other complications requiring hospitalization).

The sample size determination was based on the assumption that the incidence of AF can be diminished from 30% to 15% with intravenous hydrocortisone treatment. At a level of \( \alpha = .05 \) with a power of more than 80%, the sample size calculation was 120 patients in each group.

Statistical Analysis
The difference in continuous variables was analyzed using unpaired \( t \) test. Differences in categorized variables were tested using the \( \chi^2 \) test. Kaplan-Meier curves were depicted for non-AF. In addition, a multivariable Cox proportional hazards regression analysis model was performed to adjust for age, sex, left ventricular ejection fraction, type of operation, unstable angina pectoris, chronic obstructive pulmonary disease, and right coronary artery bypass. The assumptions of Cox proportional hazards regression analysis were verified with log minus log plots.

We performed a meta-analysis of randomized controlled trials of corticosteroid therapy on the prevention of postoperative AF after cardiac surgery. We selected the trials from the PubMed database. The selection criteria included a randomized, placebo-controlled trial and the primary outcome was AF; the incidence of AF was reported either in percentages or in numbers together with the total number of patients in the treatment and placebo groups. We found 4 studies that fulfilled these criteria.15-18 In a thorough examination, we discerned that 2 studies did not define AF as a primary outcome16,18; these studies were excluded from the meta-analysis. Thus, 2 studies15,17 remained in the meta-analysis together with the present study. We used fixed-effects test. The 3 studies were homogeneous (heterogeneity test: \( Q_2 = 4.12; P = .13 \)).

The limit for statistical significance was \( P < .05 \). All statistical procedures were performed with SPSS version 11.5.1 (SPSS Inc, Chicago, Ill). The meta-analysis was performed with Comprehensive Meta-Analysis version 2.2.021 (Biostat TM, Englewood, NJ).

### Table 1. Characteristics of the Patient Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 121)</th>
<th>Hydrocortisone (n = 120)</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>66.1 (9.5)</td>
<td>64.4 (8.4)</td>
<td>.16</td>
</tr>
<tr>
<td>Male sex</td>
<td>89 (73.6)</td>
<td>96 (80.0)</td>
<td>.24</td>
</tr>
<tr>
<td>LVEF, mean (SD), %</td>
<td>61.4 (11.3)</td>
<td>60.3 (13.1)</td>
<td>.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (67.8)</td>
<td>70 (58.3)</td>
<td>.13</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (15.7)</td>
<td>19 (15.8)</td>
<td>.98</td>
</tr>
<tr>
<td>History of COPD</td>
<td>3 (2.5)</td>
<td>4 (3.3)</td>
<td>.72</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.7 (4.0)</td>
<td>27.9 (4.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (28.9)</td>
<td>26 (21.7)</td>
<td>.19</td>
</tr>
<tr>
<td>CCS class†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (0.8)</td>
<td>2 (1.7)</td>
<td>.53</td>
</tr>
<tr>
<td>II</td>
<td>46 (38.3)</td>
<td>39 (32.5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>52 (43.3)</td>
<td>62 (51.7)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>21 (17.5)</td>
<td>17 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Preoperative use of ( \beta )-blockers</td>
<td>103 (86.6)</td>
<td>99 (82.5)</td>
<td>.39</td>
</tr>
<tr>
<td>History of stroke or TIA</td>
<td>7 (5.8)</td>
<td>9 (7.5)</td>
<td>.59</td>
</tr>
<tr>
<td>History of Claudication</td>
<td>6 (5.0)</td>
<td>4 (3.3)</td>
<td>.75</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>27 (22.3)</td>
<td>20 (16.7)</td>
<td>.27</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>90 (75.0)</td>
<td>85 (71.4)</td>
<td>.53</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; \( \beta \)-blockers, \( \beta \)-blockers; TIA, transient ischemic attack.

*Data are expressed as absolute No. (%) unless otherwise indicated. Because of rounding, percentages may not total 100.
†CCS classes defined as follows: I, no angina pectoris during ordinary physical activity; II, slight limitations of ordinary physical activity due to angina; III, marked limitations of ordinary physical activity due to angina; IV, inability to carry on any physical activity.

### Table 2. Perioperative Characteristics of the Patient Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 121)</th>
<th>Hydrocortisone (n = 120)</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of operation, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated CAGB surgery</td>
<td>96 (79.3)</td>
<td>100 (83.3)</td>
<td>.49</td>
</tr>
<tr>
<td>Isolated AVR</td>
<td>17 (14.0)</td>
<td>11 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Combined CAGB surgery and AVR</td>
<td>8 (6.6)</td>
<td>9 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery bypass, No. (%)</td>
<td>87 (71.9)</td>
<td>77 (64.2)</td>
<td>.20</td>
</tr>
<tr>
<td>Pump time, min</td>
<td>93.0 (37.2)</td>
<td>97.9 (41.4)</td>
<td>.33</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>77.6 (31.1)</td>
<td>80.0 (31.7)</td>
<td>.55</td>
</tr>
<tr>
<td>No. of peripheral anastomoses</td>
<td>3.4 (1.7)</td>
<td>3.5 (1.6)</td>
<td>.60</td>
</tr>
<tr>
<td>First postoperative creatine kinase-MB mass, mg/L</td>
<td>24.8 (12.2)</td>
<td>29.2 (45.1)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Abbreviations: AVR, aortic valve replacement; CAGB, coronary artery bypass graft.
*Data are expressed as mean (SD) unless otherwise indicated. Because of rounding, percentages may not total 100.
RESULTS

Preoperative characteristics of study patients according to randomized treatment assignment are shown in Table 1. In general, the groups were well-matched, although patients randomized to the hydrocortisone group tended to be male and not have hypertension or unstable angina. Perioperative characteristics are shown in Table 2. Again, groups were similar, although patients randomized to the hydrocortisone group were less likely to undergo right coronary artery bypass.

There were 94 patients who had AF during the first 84 hours after cardiac surgery. Patients randomized to the hydrocortisone group were significantly less likely to have AF than patients randomized to the placebo group (36/120 [30%] vs 58/121 [48%]; hazard ratio [HR], 0.54; 95% CI, 0.36-0.82; P=.01; number needed to treat, 5.6) (Table 3). The relative risk reduction was 37%. The first AF episode occurred later in patients randomized to the hydrocortisone group (P=.003) (Figure 2). After adjusting for potential imbalanced confounders, the association between randomization to hydrocortisone and postoperative AF was unchanged (adjusted HR, 0.54; 95% CI, 0.35-0.83; P=.004). The incidence of in-hospital AF was also significantly lower in the hydrocortisone group than in the placebo group (risk ratio, 0.74; 95% CI, 0.56-0.97; P=.02) (Table 3). The concentrations of C-reactive protein on the first, second, and third postoperative days were significantly lower in the hydrocortisone group than in the placebo group (Table 3).

One patient in the hydrocortisone group died during the study period (from cardiac failure), and 1 patient in the placebo group died during the study period (from multiorgan failure). There were no statistically significant differences between the groups with respect to postoperative infection, mediastinitis, stroke, myocardial infarction, conduction disturbances, or resternotomy caused by bleeding. There was no psychotic disorder in either study group.

In a meta-analysis that combined results from our trial with 2 other similar trials and included a total of 621 patients, corticosteroid therapy was associated with a lower incidence of postoperative AF (risk ratio, 0.67; 95% CI, 0.54-0.84; P=.001) (Figure 3).

COMMENT

We reported the results of the first, to our knowledge, prospective, double-blind, randomized multicenter trial investigating the effects of corticosteroid treatment on the incidence of postoperative AF after cardiac surgery. We found that intravenous hydrocortisone reduced the relative risk of postoperative AF by 37% compared with placebo in patients undergoing CABG surgery, aortic valve replacement, or combined CABG surgery and aortic valve replacement. In addition, a meta-analysis in which all randomized controlled trials, including our study, were included confirmed the beneficial effect of corticosteroid treat-
Corticosteroid and Prevention of Atrial Fibrillation

Table 3. Meta-analysis of Randomized Controlled Trials of Corticosteroid Therapy on the Prevention of Atrial Fibrillation After Cardiac Surgery

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydrocortisone</th>
<th>Placebo</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halvorsen et al, 2003</td>
<td>40/147</td>
<td>47/147</td>
<td>0.85 (0.60-1.21)</td>
</tr>
<tr>
<td>Prasongsukarn et al, 2005</td>
<td>9/43</td>
<td>22/43</td>
<td>0.41 (0.21-0.78)</td>
</tr>
<tr>
<td>Halvorsen et al, 2007</td>
<td>36/120</td>
<td>58/121</td>
<td>0.63 (0.45-0.87)</td>
</tr>
<tr>
<td>Combined</td>
<td>Hydrocortisone</td>
<td>Placebo</td>
<td>0.67 (0.54-0.85)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. Size of data markers indicates the weight of the study (proportional to sample sizes).

The effects of corticosteroid treatment on postoperative AF have been addressed earlier in 2 randomized controlled trials with postoperative AF as the primary end point. The study by Prasongsukarn et al studied 86 patients scheduled for CABG surgery who were administered 1000 mg of methylprednisolone or placebo before surgery and 4 mg of dexamethasone or placebo every 6 hours for 24 hours after surgery. Postoperative incidence of AF was significantly lower (21%) in the corticosteroid group than in the placebo group (51%). Halvorsen et al administered 4 mg of dexamethasone or placebo after induction of anesthesia and on the first postoperative morning in 300 patients undergoing CABG surgery. The incidence of postoperative AF was lower among patients randomized to the dexamethasone group vs the placebo group (27% vs 32%, respectively). These disparate findings suggest that corticosteroids are effective in preventing postoperative AF.

However, the anti-inflammatory effect was highest in the study by Prasongsukarn et al, lowest in the study by Halvorsen et al, and in the middle range in our study. Finally, there was a relatively low incidence of postoperative AF in the placebo group in the study by Halvorsen et al (32%) compared with the study by Prasongsukarn et al (51%) and our study (48%).

Two other prior studies deserve mention. The study by Rubens et al enrolled 68 patients undergoing CABG surgery and randomized them to 1000 mg intravenous infusion of methylprednisolone or placebo before surgery. Methylprednisolone was found to have a statistically significant inhibitory effect on the incidence of postoperative AF vs placebo (12% vs 34%, respectively). Yared et al studied 235 patients scheduled for CABG or valve surgery. The patients were administered a single dose of 0.6 mg/kg of dexamethasone or placebo after induction of anesthesia. Compared with the placebo group, the dexamethasone group had a lower incidence of postoperative AF (19% vs 32%). The results of these studies are interesting, it is difficult to compare them with our study. In these trials, postoperative AF was not a primary end point, with no prospective definitions of AF. These studies were not primarily designed to address the effect of corticosteroids on postoperative AF but on the activation of inflammatory and coagulation pathways and recovery from cardiac surgery.

Previous studies have found several predictors of AF after cardiac surgery. To adjust for these confounding factors, we performed a multivariable analysis in which independent predictors such as age, sex, left ventricular ejection fraction, type of operation, unstable angina pectoris, chronic obstructive pulmonary disease, and right coronary artery bypass were taken into account. After adjustment for these factors, corticosteroid treatment remained a significant independent predictor of absence of postoperative AF.

The mechanisms by which corticosteroids prevent postoperative AF are not entirely clear. The concentration of complement C-reactive protein complex, the number of white blood cells, and the concentration of inflammatory cytokines—all markers of increased inflammatory reaction concentration—are higher in patients with postoperative AF than in patients who remain in sinus rhythm. Corticosteroids have anti-inflammatory activity and reduce exaggerated inflammatory reaction. We observed that the concentration of C-reactive protein was significantly lower postoperatively in the hydrocortisone group than in the placebo group. The study by Derrnells and Panaretou also found that corticosteroid therapy reduces both C-reactive protein values and the risk of recurrent and permanent AF in nonoperative patients.

Corticosteroids reduce postoperative nausea, vomiting, and anorexia. Thus, corticosteroid therapy may improve absorption of oral medications, such as β-blockers, and thereby reduce the incidence of AF.

Increased risk of wound infections and gastrointestinal bleeding (stress ulcer) can be a concern with corticosteroid therapy. In our study, no adverse effects were related to hydrocortisone therapy. In the study by Prasongsukarn et al, no difference was found between the corticosteroid and placebo.
Corticosteroid and Prevention of Atrial Fibrillation

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 cebo groups in major complications, but the corticosteroid group had more minor complications. In our trial, there were no more complications (minor or major) in the hydrocortisone group than in the placebo group. The different result in regard to complication between this and our studies may be explained by the administration of different corticosteroid preparations (methylprednisolone and dexamethasone vs hydrocortisone) and different dosages.

Although we found that intravenous administration of hydrocortisone was well tolerated, our study was underpowered to assess the safety of corticosteroid therapy. This is an important limitation and we acknowledge that a much larger trial is needed to demonstrate the non inferiority of corticosteroid treatment compared with placebo. Another important limitation of our trial is that we excluded patients undergoing mitral valve surgery.

One might argue that the incidence of postoperative AF in our study was high (48%). The incidence of postoperative AF depends on the definition of an AF episode. We defined AF as an episode lasting longer than 5 minutes, regardless of whether it was asymptomatic or required therapy. In a recent trial with an almost identical end point to that in our study, a 57% incidence of postoperative AF was reported. In addition, in another study, the incidence of AF in the placebo group was 51%.

Although hydrocortisone was effective in reducing the incidence of AF, 30% of the patients who received corticosteroid treatment had postoperative AF. Earlier studies have reported that intravenous metoprolol, amiodarone, bi-atrial pacing, and magnesium reduce the incidence of AF after cardiac surgery. Further studies are warranted to clarify whether the administration of corticosteroids in combination with other preventive measures will further reduce the risk of postoperative AF after cardiac surgery.

We conclude that intravenous administration of hydrocortisone is efficacious and well tolerated in the prevention of AF after cardiac surgery.

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Acknowledgment: We thank Paula Hyvonen, RN, Kuopio University Hospital, for assisting in the collection of the data. Ms Hyvonen was compensated as a study nurse by the hospital.

REFERENCES


5. Halonen J, Hakala T, Auvinnen T, et al. Intravenous administration of metoprolol is more effective than peroral administration in the prevention of AF, regardless of whether it was asymptomatic or required therapy. In a recent trial with an almost identical end point to that in our study, a 57% incidence of postoperative AF was reported. In addition, in another study, the incidence of AF in the placebo group was 51%.

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We conclude that intravenous administration of hydrocortisone is efficacious and well tolerated in the prevention of AF after cardiac surgery. Larger trials will be needed to confirm our findings and determine short- and long-term safety of corticosteroids to prevent postoperative AF and other arrhythmias.

Author Contributions: Dr J. Halonen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: J. Halonen, Auvinnen, Tarkka, Hippeläinen, Hartikainen, Hakala.

Acquisition of data: J. Halonen, Järvinen, Taskinen, Hippeläinen, Juvenon.

Analysis and interpretation of data: J. Halonen, P. Halonen, Hippeläinen, Hakala.

Drafting the manuscript: J. Halonen, P. Halonen, Järvinen, Hippeläinen, Hartikainen, Hakala.

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Obtained funding: J. Halonen, Hippeläinen.

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Study supervision: Hippeläinen, Hartikainen, Hakala.

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