Erythropoietin and Protection of Renal Function in Cardiac Surgery (the EPRICS Trial)

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ABSTRACT

Background: To date, there are no known methods for preventing acute kidney injury after cardiac surgery. Increasing evidence suggests that erythropoietin has renal antiapoptotic and tissue protective effects. However, recent human studies have shown conflicting results. The authors aimed to study the effect of a single high-dose erythropoietin preoperatively on renal function after coronary artery bypass grafting in patients with preoperative impaired renal function.

Methods: This single-center, randomized, double-blind, placebo-controlled study included 75 patients scheduled for coronary artery bypass grafting with preexisting renal impairment estimated glomerular filtration rate based on p-cystatin C (<60 and >15 ml/min). The patients either received a single high-dose erythropoietin (400 IU/kg) or placebo preoperatively. The primary endpoint was renal protection evaluated by p-cystatin C at the third postoperative day compared to the preoperative values. Incidence of acute kidney injury and other renal biomarker changes were among secondary endpoints.

Results: There was no statistically significant difference on the third postoperative day for relative p-cystatin C level changes from baseline between the groups, 131 ± 31% (mean ± SD) for the study group and 125 ± 24% for the control group ($P = 0.31$; 95% CI, −0.6 to 20% for the difference). There were no statistically significant differences in other renal biomarkers or measures between the groups (p-neutrophil gelatinase–associated lipocalin, p-creatinine, p-urea, and estimated glomerular filtration rate). There were no other differences in outcome variables between the groups.

Conclusion: Intravenous administration of a single high-dose (400 IU/kg) erythropoietin did not have a renal protective effect on patients with reduced kidney function undergoing coronary artery bypass surgery. **(Anesthesiology 2014; 121:582-90)**

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ACUTE kidney injury (AKI) is an ominous complication after cardiac surgery, and incidence statistics between 5 and 40% have been reported depending on definition.[1–4] Several studies have shown that decreased renal function after cardiac surgery is associated with a prolonged hospital stay and decreased long-term survival.[1,2,4,5] Therefore, effective renal protection during cardiac surgery is highly desired, and several drugs have been proposed. However, none have shown promising results to date.[6]

Erythropoietin is an endogenous hormone and the primary regulator of erythropoiesis. It is mainly produced in the kidneys with its production controlled through the hypoxia-inducible factor system.[7] In recent years, additional tissue/organ protective properties of erythropoietin against ischemia and reperfusion injury have become apparent.[8] The cytoprotective, preconditioning, and antiapoptotic effects of erythropoietin on kidneys have been shown in both experimental[9–15] and a few human studies.[16–18] Available evidence suggests that these pleiotropic effects of erythropoietin are mediated by a tissue protective receptor that is distinct from the receptor responsible for erythropoiesis.[19] Activation of the tissue protective receptor requires a higher concentration of erythropoietin than is needed for maximal erythropoiesis.[19] Doses between 100 and 500 U/kg have been used in human studies to attain the pleiotropic effects of erythropoietin, with no adverse events reported.[17,20–24] However, in a study by Ehrenreich *et al.*[25] using erythropoietin for the treatment of ischemic stroke, an increased mortality was reported in the erythropoietin-treated group, and thus the safety profile of erythropoietin must be considered.

What We Already Know about This Topic

- Acute kidney injury after cardiac surgery is associated with prolonged hospital stay and decreased long-term survival
- Although recombinant human erythropoietin has been reported to have renal protective effects in experimental ischemia and reperfusion injury, its ability to prevent acute kidney injury after cardiac surgery is uncertain

What This Article Tells Us That Is New

- In a double-blind, randomized, placebo-controlled study of patients with preexisting impaired renal function undergoing coronary artery bypass grafting, preoperative administration of a high dose of recombinant human erythropoietin had no renal protective effects

Despite the promising renoprotective effects of recombinant human erythropoietin (rHuEPO) in experimental studies against ischemia and reperfusion injury, recent clinical studies have shown conflicting results[17,23] on the incidence of AKI after cardiac surgery.[17,21–23] This could be dependent on patient inclusion, choice of renal outcome marker, and/or

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dosage administered. Traditional renal biomarkers (*i.e.*, creatinine, urea, and urinary output) have serious limitations.[26] P-cystatin C has been found superior to p-creatinine in estimating glomerular filtration rate (GFR) for the diagnosis of AKI.[27–31] Moreover, previous studies have not focused on a homogeneous group of patients undergoing cardiac surgery with impaired renal function who have increased risk of AKI.[32]

Accordingly, we hypothesized that a single high-dose (400 U/kg) rHuEPO administered preoperatively in patients with preexisting impaired renal function undergoing coronary artery bypass grafting (CABG) has a renoprotective effect, as evaluated by postoperative changes in p-cystatin C in the third postoperative day. We tested the hypothesis in a double-blind, placebo-controlled pilot trial.

Materials and Methods

This prospective single-center, randomized, double-blind, placebo-controlled study was conducted between October 2011 and January 2013 at Skåne University Hospital in Lund, Sweden, and was registered with ClinicalTrials.gov in August 2011 (no. NCT01423955). The study protocol was approved by the ethics committee for clinical research at Lund University, Lund, Sweden, and the Swedish Medical Product Agency (EUDRACT no. 2011-00167-70). One of the authors (H.B.) served as a principal investigator for the study. Written and oral consent was obtained from all patients before inclusion in the study.

Quality control and monitoring were delegated to Skåne's Competence Centre for Research at Skåne University Hospital, Lund, Sweden, an independent organization that performed on-site monitoring before, during, and after the study to ensure that the study complied with Good Clinical Practice guidelines and the Helsinki declaration. According to their recommendation, no separate Data Safety Monitoring Board was setup. Instead, we continuously reported serious adverse events to the drug supplier, and if the number of complications were deemed too high by the investigators, company, or other physicians, we would unblind patients with serious adverse events.

Patient Selection

Patients scheduled for surgery were screened for the study, and if determined to be suitable, they were informed about the study and asked to participate (usually 1 to 3 days before the operation) by a physician not responsible for their immediate care. Inclusion criteria were nonemergent CABG, preoperative estimated GFR (eGFR) less than 60 and greater than 15 ml/min (based on p-cystatin C), and written and oral consent. Exclusion criteria (fig. 1) were uncontrolled hypertension (defined as previously undetected hypertension with no antihypertensive therapy), hypersensitivity to the active drug, pregnancy, fertile women (<50 yr old), treatment with erythropoietin up to 4 weeks before the surgery, ongoing dialysis, planned off-pump CABG surgery, known malignancy, inclusion in other ongoing clinical trial, or clinical judgment by the investigators that the patient could not participate in the study due to inability to assimilate information such as linguistic barriers.

Endpoints

The primary endpoint of this study was renal function measured by p-cystatin C level changes measured at the third postoperative day compared to the preoperative p-cystatin C level.

The secondary endpoints were other renal biomarkers including the changes in plasma neutrophil gelatinase–associated lipocain (p-NGAL), p-creatinine, p-urea, and incidence of AKI according to the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria[5,33] and based on eGFR calculated by the Modification of Diet in Renal Disease formula.[34]

Additional secondary endpoints were cardiac and cerebral organ injury assessed by p-troponin-I, plasma-creatine kinase muscle and brain, plasma-brain natriuretic peptide, p-S100B, time in ventilator, time in cardiothoracic intensive care unit (ICU), postoperative bleeding, transfusion requirement during days 0 to 4, and overall outcome after surgery.

Study Drug/Placebo

The study drug rHuEPO supplied in a 1-ml ampoule containing 40,000 units of rHuEPO (Retacrit® with ATC code B03XA01; Hospira Nordic AB, Stockholm, Sweden) was stored according to factory recommendations. As placebo, 0.9% NaCl was used (NaCl 0.9% 20 ml with ATC code V07AB00; Fresenius Kabi AB, Uppsala, Sweden).

Randomization, Study Drug Preparation, and Administration

Patients were randomly allocated to either the rHuEPO or the control group in a 1:1 ratio according to simple randomization using sequentially numbered, sealed, and opaque envelopes. Three experienced anesthesia nurses, independent from the study team, were trained and delegated to randomize and prepare the study drug. For the intervention group, a 20-ml syringe containing rHuEPO diluted in saline to a concentration of 2,000 U/ml was prepared. The volume equivalent to 400 U/kg rHuEPO was left in the syringe. For the placebo group, an equivalent volume of saline was prepared. The syringes were delivered to the operation theater blinded and administered in a central venous line by the anesthesiologists in charge of the patients. Patients and the medical staff responsible for the care of the patient were thus blinded to randomization.

Data Collection, Blood Sampling, and Analysis

Demographic and baseline characteristics of included patients were collected after enrollment. Other data included preoperative p-cystatin C, p-creatinine, hemoglobin level, platelet count, and p-urea acquired 1 to 3 days before the

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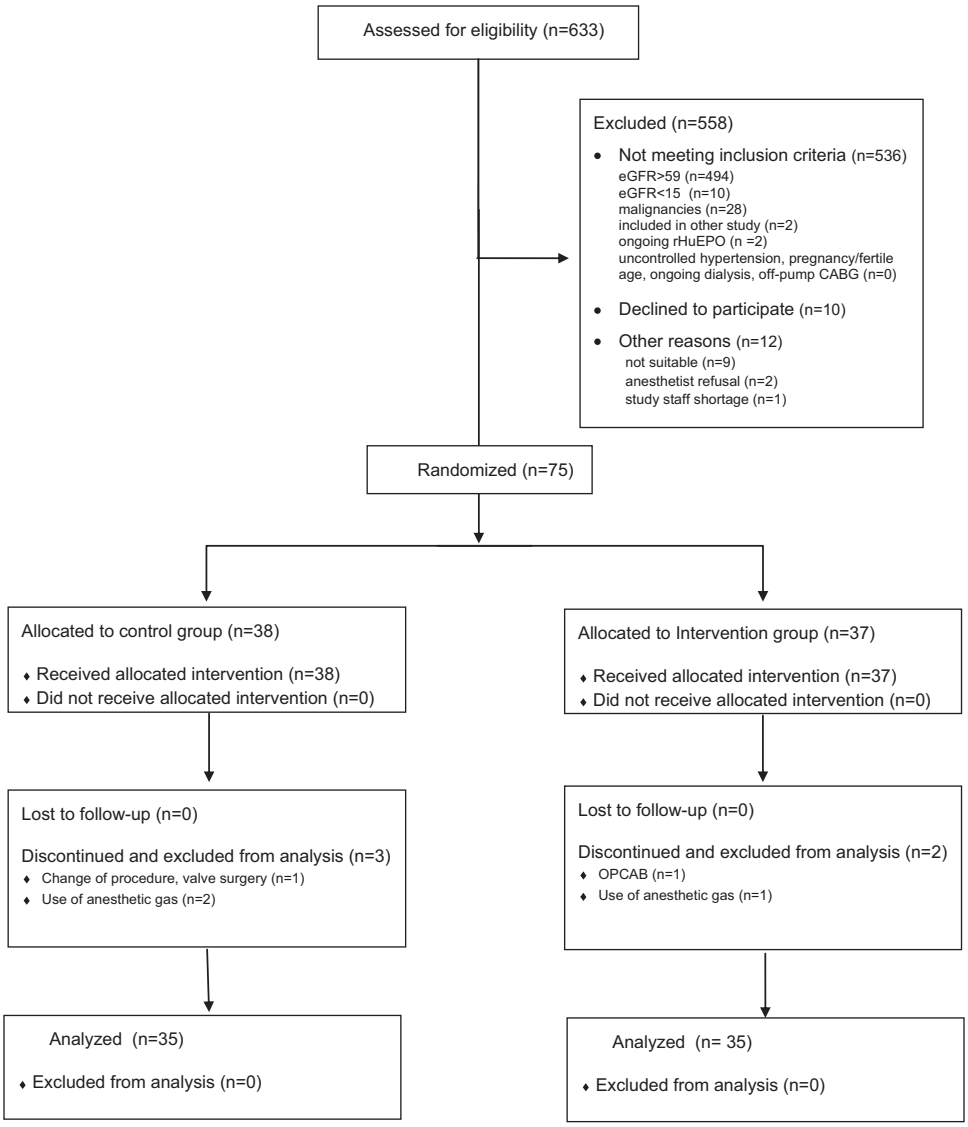

Fig. 1. Flow chart. CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; OPCAB = off-pump coronary artery bypass; rHuEPO = recombinant human erythropoietin.

surgery. P-creatinine and p-cystatin C concentrations were determined with enzymatic colorimetric method[35] and immunometric method, respectively.

Baseline p-NGAL was acquired preoperatively after arterial line insertion and before anesthesia induction. Postoperative p-NGAL sampling and analysis were performed 4 h after patient arrival to the ICU by a point-of-care analyzing device (Biosite Bedside analyzer; Nordic Biosite AB, Stockholm, Sweden). Hemoglobin, platelets, p-cystatin C, p-creatinine, and p-urea were sampled days 1 to 4 postoperatively. The urinary output was assessed perioperatively, and 12 and 24 h postoperatively. Other postoperative data included time on ventilator, ICU time, bleeding during the first 12 h, and total bleeding until chest tube removal. Preoperative transfusions and postoperative transfusion (days 1 to 4) of erythrocytes, plasma, and platelets were recorded. In addition, all adverse events were recorded continuously during the 4 postoperative days and assessed 30 days postoperatively by telephone interview. However, four patients could not be reached for the postoperative telephone interview. Nonetheless, all patient charts were reviewed 30 days postoperatively for hospital visits and registration of possible adverse events.

Anesthesia and Study Drug Administration

All patients received standardized anesthetic care. Induction was according to routine clinical practice using fentanyl, midazolam, and propofol. Maintenance of anesthesia was performed with propofol infusion and fentanyl. An acetated Ringer's solution was infused continuously from induction until initiation of cardiopulmonary bypass (CPB) and restarted after termination of CPB. After induction, a central line was placed in the internal jugular vein. The prepared study drug/placebo was administered as a single intravenous bolus dose after induction when the patient was in a

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stable circulatory state but always before the skin incision. The study drug/placebo was given in the central venous line without concomitant administration of other drugs in this line. The line was then flushed with 0.9% saline after administration of the study drug.

All patients received standardized surgical and CPB management. CPB was instituted with a membrane oxygenator primed with 1.2 l of priming solution, including 1,000 ml acetated Ringer's solution, 200 ml mannitol (150 mg/ml), and 10,000 IU heparin. Nonpulsatile pump flow was maintained at a rate of 2.0 to 2.4 l min^{-1} m^{-2}. During the perioperative period, including CPB, mean arterial pressure was maintained at 50 to 80 mmHg with norepinephrine or glyceryl trinitrate.

Sample Size

The study was designed to identify the superiority of rHuEPO in protecting renal function after cardiac surgery in comparison with placebo. The power calculation was based on the following: the primary endpoint was renal function measured by changes in p-cystatin C levels preoperatively compared to the third postoperative day. Based on data from a previous institutional study assessing postoperative changes in p-cystatin C,[31] it was estimated that with the (two-tailed) α error set at 0.05, there would be a 90% power to detect a 15% difference and a 70% power to detect a 10% difference in p-cystatin C levels at the third postoperative day between the groups if 70 patients (35 patients per treatment group) were included.

Statistical Analysis

Results are presented as mean ± 1 SD, median (interquartile ranges [25th to 75th]), or number of patients (%). Continuous variables were compared using independent Student *t* test or Mann–Whitney U test when appropriate. Continuous repeated measure variables were compared using a two-way repeated measures ANOVA model (group × time and group). The tests were two-tailed, and a P- value of 0.05 was considered statistically significant. All statistical analysis was performed using Statistica software version 9.0 (StatSoft Inc., Tulsa, OK).

Results

A total of 633 patients were screened in the study. Noneligibility was mainly due to an eGFR of greater than 59 ml/min (fig. 1). A total of 75 patients met the inclusion criteria and were enrolled. Five patients were withdrawn due to protocol violation, and the remaining 70 patients completed the study per protocol with 35 patients randomized to receive rHuEPO and 35 patients to receive saline (table 1). In a two-way repeated measurements ANOVA (group and group × time), there were no significant differences in the primary outcome or other renal outcome (*i.e.*, p-cystatin C, p-NGAL, p-creatinine, p-urea, and Modification of Diet in Renal Disease eGFR), between the two groups (table 2 and fig. 2). The relative p-cystatin C level changes from baseline between the groups were 132 ± 43% (mean ± SD) for the study group and 122 ± 23% for the control group on day 2, 131 ± 31% and 125 ± 24% on day 3, and 124 ± 35% and 113 ± 21% on day 4 (fig. 2). In addition, there was no difference in the incidence of postoperative AKI according to RIFLE criteria. All data were complete to 100%, except for one p-cystatin C value on the second postoperative day in the placebo group and one p-cystatin C value on the fourth postoperative day in the rHuEPO group.

No patient in either group required renal replacement therapy postoperatively. The overall incidence of AKI was 31% (n = 22 of 70), as defined by the RIFLE classification based on p-creatinine and the Modification of Diet in Renal Disease formula, where 24% (17 of 70) were classified as RIFLE Risk, 6% (4 of 70) classified as RIFLE Injury, and 1% (1 of 70) classified as RIFLE Failure. The overall postoperative outcomes measures were also similar, with no statistically significant difference between the two groups (table 3). Transfusions of erythrocyte, plasma, and platelets did not differ during the perioperative period and 4 days after surgery (table 3). There were no statistically significant differences in

Table 1. Preoperative Characteristics

Variable	rHuEPO	Placebo
Female	7 (20%)	8 (23%)
Age	72.4 ± 8.1	72.5 ± 10.5
Weight	82.9 ± 14.2	82.8 ± 15.6
Height	174.3 ± 10.1	174.6 ± 8.0
Systolic blood pressure	142.7 ± 19.7	135.1 ± 18.9
Diastolic blood pressure	73.7 ± 7.9	75.5 ± 12.8
Hypertension	29 (83%)	30 (86%)
Chronic heart failure	15 (43%)	15 (43)%
LVEF <30%	4 (11%)	4 (11%)
LVEF 30–50%	11 (31%)	11 (31%)
LVEF >50%	20 (57%)	20 (57%)
COPD	1 (3%)	2 (6%)
Diabetes	12 (34%)	15 (43%)
PVD	4 (11%)	4 (11%)
Previous CVI	6 (17%)	5 (14%)
Thyroid disease	4 (11%)	8 (23%)
CAF	1 (3%)	1 (3%)
PAF	5 (14%)	2 (6%)
Previous PCI	6 (17%)	5 (15%)
Preoperative IABP	0	0
Diuretics	17 (49%)	18 (51%)
ACE-i/ARB	24 (69%)	22 (86%)
β-blocker	29 (80%)	33(94%)
Statins	32 (91%)	32 (91%)
Vitamin K antagonist	6 (17%)	1 (3%)
ASA	32 (91%)	32 (91%)
Other antithrombotic drug	10 (29%)	7 (20%)

ACE-i = angiotensin converting enzyme-inhibitor; ARB = angiotensin receptor blocker; ASA = acetyl salicylic acid; CAF = chronic atrial fibrillation; COPD = chronic obstructive pulmonary disease; CVI = cerebrovascular insult; IABP = intraaortic balloon pump; LVEF = left ventricular ejection fraction; PAF = paroxysmal atrial fibrillation; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; rHuEPO = recombinant human erythropoietin.

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Table 2. Renal Outcome

	rHuEPO (n = 35)	Placebo (n = 35)	*P* Value
Preop CyC	1.6 ± 0.4	1.5 ± 0.2	
CyC day 1	1.6 ± 0.6	1.4 ± 0.5	
CyC day 2	2.1 ± 0.8	1.8 ± 0.5	0.35*
CyC day 3	2.1 ± 0.8	1.9 ± 0.5	
CyC day 4	1.9 ± 0.8	1.7 ± 0.5	
Preoperative creatinine	119.2 ± 33.6	115.4 ± 34.7	
Creatinine day 1	121.2 ± 47.8	108.4 ± 45.5	
Creatinine day 2	150.5 ± 75.0	131.7 ± 60.2	0.38*
Creatinine day 3	149.6 ± 75.6	132.7 ± 61.0	
Creatinine day 4	139.0 ± 66.5	123.7 ± 55.0	
MDRD eGFR preoperative	56.3 ± 14.4	58.0 ± 14.5	
MDRD eGFR day 3	49.4 ± 20.5	53.8 ± 19.0	0.60*
RIFLE 0 MDRD eGFR	24 (66%)	25 (71%)	0.61
RIFLE R MDRD eGFR	8 (23%)	9 (26%)	0.78
RIFLE I MDRD eGFR	3 (9%)	1 (3%)	0.31
RIFLE F MDRD eGFR	1 (3%)	0	0.32
Preoperative NGAL	105.7 ± 32.7	94.5 ± 12.7	0.51*
Postoperative NGAL	165.5 ± 98.7	167.7 ± 105.0	

Values are presented as mean ± SD or number (%). MDRD eGFR represents GFR estimated by MDRD formula. All eGFR are standardized to 1.73 m^2 body surface. P-CyC unit is mg/l; P-creatinine unit is μmol/l, and p-NGAL unit is ng/ml. RIFLE categorization is based on the third postoperative eGFR according to the MDRD formula. Days 1–4 represent the first to fourth day after surgery.

* Statistical testing was performed with repeated-measures ANOVA (*P* value for group × time), otherwise a Student *t* test was performed.

Creatinine = plasma creatinine; CyC = plasma cystatin C; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease formula; p-NGAL = plasma neutrophil gelatinase–associated lipocain; rHuEPO = recombinant human erythropoietin; RIFLE = Risk, Injury, Failure, Loss, End-stage criteria.

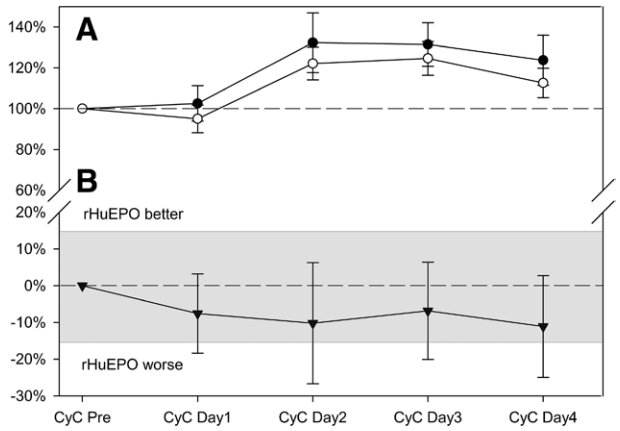

Fig. 2. (*A*) Cystatin C (CyC) changes expressed as percentage of baseline for the recombinant human erythropoietin (rHuEPO) group (*solid dots*) and placebo (*open dots*) with 95% CI. (*B*) Relative differences between cystatin C levels for the groups (*triangles*) with 95% CI. *Gray area* in *B* reflects a ±15% change in the primary endpoint. Days 1–4 = days after surgery.

the other secondary endpoints between the two groups (table 3). BNP on day 1 was 305 ± 215 for the placebo group and 346 ± 318 for the rHuEPO group (*P* = 0.48). The CKMB levels for the placebo group at the first postoperative day was 14.0 ± 15.0 for the placebo group and 20.1 ± 28.4 for the rHuEPO group (*P* = 0.46). S100B levels on the second postoperative day were 0.13 ± 0.06 for the placebo group and 0.13 ± 0.06 for the rHuEPO group (*P* = 0.94). There was no statistically significant difference in the incidence of predefined adverse events (*i.e.*, postoperative mediastinitis, atrial fibrillation, periprocedural acute myocardial infarction, chest tube drainage, and reoperation for bleeding) or other adverse events. One patient in the control group experienced a postoperative stroke. The total number of reported adverse events was 24, with 13 events in the placebo group and 11 events in the rHuEPO group (*P* = 0.62), none of which were deemed to be associated with the drug.

Discussion

In this single-center, double-blinded, randomized, placebo-controlled trial, we aimed to study if a single high-dose (400 IU/kg) rHuEPO preoperatively could reduce renal function impairment after cardiac surgery, in a group of patients with preexisting impaired renal function and, therefore, at high risk of developing postoperative AKI.[32] Several renal outcome measures were used, and as primary endpoint, cystatin C was chosen since it is considered a highly accurate surrogate for GFR.[27–31] The salient finding of this study was that rHuEPO had no renoprotective effects, measured by p-cystatin C, p-creatinine, p-NGAL, or incidence of AKI according to the RIFLE criteria.

Our human study could not reproduce previous positive experimental studies, which have shown promising data on the renoprotective effects of rHuEPO against ischemia–reperfusion injury.[11,36–38] Furthermore, our results contrast with two recent human studies, where renoprotective effects of rHuEPO in conjunction with cardiac surgery were found.[17,18] Song *et al.*[17] administered a dose of 300 U/kg rHuEPO after anesthesia induction, and they reported a reduction in the incidence of postoperative AKI from 29 to 8% within 5 days postoperatively. Tasanarong *et al.*[18] assessed the effect of a two-dose regimen of preoperative rHuEPO, first 200 U/kg 3 days before CABG surgery and 100 U/kg after anesthesia induction. They demonstrated statistically significant differences in eGFR 24, 48, and 72 h postoperatively in the rHuEPO group, and a decline in AKI from 38 to 14% in the rHuEPO group. They also reported statistically significant lower postoperative urine NGAL levels in the rHuEPO group.[18] However, other studies on cardiac surgery patients have failed to show this renoprotective effect.[21–23] The diverging results may be due to patient selection, time point, and dose of administered rHuEPO. In the EARLYARF study, Endre *et al.*[21] assessed the renoprotective effect of rHuEPO in a double-blind controlled study of 162 general ICU patients with severe illness. The patients with the risk of AKI were included by a predefined cutoff value of two proximal tubular enzymes in the urine. Two doses of 500 U/kg IV rHuEPO were given, and there were no differences reported in p-creatinine changes between the two

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Table 3. General Outcome

Variable	rHuEPO (n = 35)	Placebo (n = 35)	*P* Value
ICU time (h)†	23 (22–48)	25 (21–46)	0.67
Ventilator time (min)†	300 (215–420)	255 (210–400)	0.30
Fluid balance day 1 (l)†	2.9 (2.2–3.7)	3.0 (2.3–3.9)	0.93
Diuresis 12 h postoperative (ml)	1,715 ± 732	1,725 ± 667	0.96
Bleeding 12 h postoperative (ml)†	450 (340–600)	450 (360–620)	0.95
Total bleeding (ml)†	650 (500–980)	450 (500–940)	0.54
Weight postoperative day 3 (kg)	84.4 ± 15.4	84.3 ± 13.8	0.96
Reoperation for bleeding	2 (6%)	1 (3%)	0.56
ECC time (min)†	64 (49–82)	71 (42–90)	0.92
Postoperative mediastinitis	1 (3%)	1 (3%)	1.00
Postoperative atrial fibrillation	10 (29%)	11 (31%)	0.80
Peri procedural myocardial damage	2 (6%)	0	0.16
Postoperative heart failure	0	2 (6%)	0.16
Reoperation for bleeding	0	2 (6%)	0.15
Postoperative transient cerebral insult	1	0	0.33
Postoperative permanent stroke	0	0	
RRT/dialysis	0	0	
Erythrocyte transfusion	22 (63%)	16 (45%)	0.15
Plasma transfusion	3 (9%)	4 (11%)	0.40
Platelet transfusion	2 (6%)	4 (11%)	0.70
Hb preoperative	129.1 ± 14.6	133.6 ± 14.8	
Hb day 1	108.8 ± 13.2	112.0 ± 13.2	
Hb day 2	98.9 ± 14.4	101.8 ± 12.3	0.09*
Hb day 3	98.1 ± 15.2	99.1 ± 8.3	
Hb day 4	103.1 ± 12.4	100.3 ± 10.9	

Values are presented as mean ± SD or number of patients (%).

* Statistical testing was performed with repeated-measures ANOVA (*P* value for group × time), otherwise a Student *t* test was performed. † Outcome variables that are skewed are presented as median (interquartile range) and tested with Mann–Whitney U test.

ECC = extra corporeal circulation; ICU = intensive care unit; rHuEPO = recombinant human erythropoietin; RRT = renal replacement therapy.

groups within 7 days from baseline.[21] In the EARLYARF study, rHuEPO was administered during or after the renal insult and in a heterogeneous critically ill group of patients, which may differ from a cardiac surgical patient population.[21] In another randomized controlled study, de Seigneux *et al.*[22] assessed different cardiac surgical patients. Two different doses of rHuEPO (40,000 and 20,000 U) were administered postoperatively after patient admission to ICU. The primary outcome was levels of urine NGAL 48 h postoperatively compared to baseline. The study did not show any renoprotective effect.[22] However, it could be argued that late administration of rHuEPO may impede the renoprotective effects of rHuEPO. Recently, Kim *et al.*[23] published a study where they administered 300 U/kg rHuEPO preoperatively in a high-risk heterogeneous cardiac surgical cohort, but mostly with normal GFR. Erythropoietin was administered in a similar timing and dosing as the study by Song *et al.*,[17] and renal outcome was measured also by cystatin C and NGAL. Kim *et al.*[23] could not show any renoprotective effect of rHuEPO. Our study could also not detect any beneficial effect of rHuEPO. Most of the experimental evidence regarding the renoprotective role of EPO stems from direct renal ischemia–reperfusion models. Renal injury after CPB is more complex, and both hypoperfusion and inflammation are considered important factors. In addition, there is no overt mechanical renal ischemia–reperfusion. It has indeed been shown that rHuEPO may not be effective in animal models of renal injury from inflammation (and not overt ischemia–reperfusion).[39] It has also recently been shown that rHuEPO was not able to attenuate the increase in some of the key inflammatory markers related to renal injury in patients undergoing complex valvular heart surgery.[23] Whether erythropoietin has a role in surgery requiring suprarenal aortic cross-clamping is yet to be shown. All taken together, there are accumulating data suggesting that rHuEPO has no prophylactic effect to prevent AKI after cardiac surgery.

Study Strengths and Limitations

Two important strengths in this study are a homogeneous patient population undergoing only CABG with CPB and that all patients had preoperative renal dysfunction, which is considered one of the strongest predictors for developing AKI after cardiac surgery.[32] This makes the study more relevant for clinical implementation. In addition, we chose a wide variety of markers for renal function to accurately find any relevant differences. Another strength is that anesthetic drugs during surgery were standardized to clinic routine, with no use of volatile agents or remifentanil, shown to have preconditioning effects.[40–42] The fact that this was a single-center

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study should be viewed as a strength as it contributes to limiting heterogeneity and confounding factors. A few limitations could be discussed. First, although the suggested time frame to assess the potential development of AKI has been agreed on to be 7 days for greater than 50% creatinine increase, we chose to evaluate the renal function at 72 h based on previous data indicating p-creatinine and p-cystatin C peak at 48 to 72 h.[28,31,43,44] Given the results of this study, the smallest variation in difference in cystatin C was on the third day, supporting this timing as a primary endpoint. However, larger differences could be seen the second and fourth day, but with a larger variation, increasing the risk of type II errors. Second, patients were not selected on the underlying mechanism of renal dysfunction, and, therefore, there was heterogeneity in this aspect. Another limitation is that only a single dosage of rHuEPO was evaluated in this study. Tasanarong *et al.*[18] could show positive effect with a two-dose regimen.[18] However, the single preoperative dose of a single 400 U/kg in this study was chosen because of the documented efficacy and safety aspects of this dose in previous studies.[17,20,45–47] Furthermore, a similar dose has shown efficacy in other studies both in preventing postoperative renal injury[17] and in other settings.[45,46]

This study was a phase II equivalent and was conducted as a pilot trial in a larger program of AKI prevention. The safety aspects of a single high-dose EPO was also considered, given that in a study by Ehrenreich *et al.*[25] using EPO for the treatment of ischemic stroke, increased mortality in the EPO group was reported. We could not observe statistically significant difference or any trends between the two groups regarding the adverse effects of the drug; however, the trial was not designed and powered to study the safety aspects of rHuEPO in this context. Furthermore, we could not observe any statistically significant difference in the secondary and general outcomes. Although it seems reasonable that the study was adequately powered for the primary endpoint, it was probably underpowered to detect AKI, other relevant clinical endpoints, or side effects of the drug.

Given the frequency and severity of AKI after cardiac surgery, there is an undisputed need for an efficient prophylactic treatment. Both animal and human data indicated that rHuEPO was a promising and inexpensive candidate that could meet this demand. We designed Erythropoietin and Protection of Renal Function in Cardiac Surgery trial including patients with the largest risk of developing AKI after CABG surgery, but we found no renoprotective effect of rHuEPO in this setting.

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Competing Interests

Henrik Bjursten has a vested interest in ErySave AB (Lund, Sweden). Lars Algotsson lectures for Orion Pharma AB (Sollentuna, Sweden) and Abbott Scandinavia AB (Solna, Sweden). The other authors declare no competing interests.

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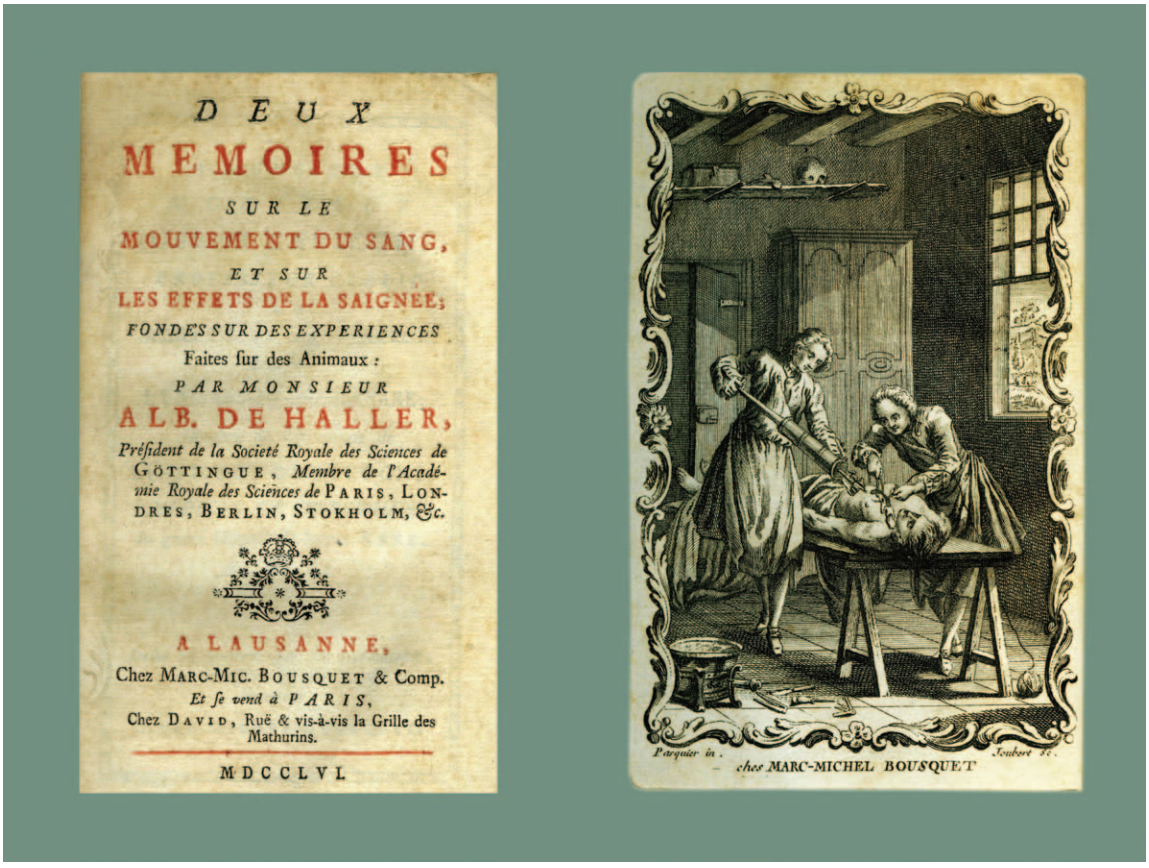

This French language title page (*left*), from *Two Memoirs of the Movement of Blood and the Effects of Bleeding: Based on Experiments on Animals*, was printed in Lausanne, Switzerland, in 1756 by publisher Marc-Michel Bousquet and Company. The author, Victor Albrecht von Haller (1708–1777), helped pioneer the concept that capillaries lack contractility. An eccentric Swiss botanist, anatomist, physiologist, and physician, Haller had a genius for languages as well as sciences. Opposite the unusual choice for a frontispiece (*right*), Haller proudly listed his memberships in the "Royal Academies of Science in Paris, London, Berlin, Stockholm, *etc*." (Copyright © the American Society of Anesthesiologists, Inc.)

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