Cyclosporine before Coronary Artery Bypass Grafting Does Not Prevent Postoperative Decreases in Renal Function

A Randomized Clinical Trial

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ABSTRACT

Background: Acute kidney injury is a common complication after cardiac surgery, leading to increased morbidity and mortality. One suggested cause for acute kidney injury is extracorporeal circulation–induced ischemia–reperfusion injury. In animal studies, cyclosporine has been shown to reduce ischemia–reperfusion injury in the kidneys. We hypothesized that administering cyclosporine before extracorporeal circulation could protect the kidneys in patients undergoing cardiac surgery.

Methods: The Cyclosporine to Protect Renal Function in Cardiac Surgery (CiPRICS) study was an investigator-initiated, double-blind, randomized, placebo-controlled, single-center study. The primary objective was to assess if cyclosporine could reduce acute kidney injury in patients undergoing coronary artery bypass grafting surgery with extracorporeal circulation. In the study, 154 patients with an estimated glomerular filtration rate of 15 to 90 ml · min^{-1} · 1.73 m^{-2} were enrolled. Study patients were randomized to receive 2.5 mg/kg cyclosporine or placebo intravenously before surgery. The primary endpoint was relative plasma cystatin C changes from the preoperative day to postoperative day 3. Secondary endpoints included biomarkers of kidney, heart, and brain injury.

Results: All enrolled patients were analyzed. The cyclosporine group (136.4 ± 35.6%) showed a more pronounced increase from baseline plasma cystatin C to day 3 compared to placebo (115.9 ± 30.8%), difference, 20.6% (95% CI, 10.2 to 31.2%, $P < 0.001$). The same pattern was observed for the other renal markers. The cyclosporine group had more patients in Risk Injury Failure Loss End-stage (RIFLE) groups R (risk), I (injury), or F (failure; 31% *vs.* 8%, $P < 0.001$). There were no differences in safety parameter distribution between groups.

Conclusions: Administration of cyclosporine did not protect coronary artery bypass grafting patients from acute kidney injury. Instead, cyclosporine caused a decrease in renal function compared to placebo that resolved after 1 month. **(Anesthesiology 2018; 128:710-7)**

ACUTE kidney injury (AKI) after coronary artery bypass grafting (CABG) with extracorporeal circulation (ECC) occurs in approximately one third of patients in most institutions, including our own,[1] and leads to increased long- and short-term morbidity and mortality.[1] The source for AKI in CABG is multifactorial, but renal ischemia–reperfusion injury induced by the use of ECC is at least part of the cause,[2,3] especially in the poorly oxygenated and metabolic active outer medulla. A suggested mechanism is induced mitochondrial damage through the opening of the mitochondrial permeability transition pore (mPTP) during reperfusion, leading to cell injury or death.[4,5] Animal

What We Already Know about This Topic

- Acute kidney injury is common after cardiac surgery with cardiopulmonary bypass
- Animal studies suggest that cyclosporine may be protective

What This Article Tells Us That Is New

- In a double-blind trial, 154 cardiac surgical patients were randomly assigned to 2.5 mg/kg cyclosporine or placebo
- Plasma cystatin C, a marker of renal injury, increased more in patients given cyclosporine
- Cyclosporine does not reduce the risk of acute renal injury after cardiac surgery

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studies demonstrate that mPTP opening may be inhibited in cyclophilin D knockout animals[6] and by the cyclophilin inhibitor cyclosporine[7] administered before the ischemic event, resulting in decreased ischemia–reperfusion injury in the kidneys,[8] heart,[9] and brain.[10]

Several clinical studies of cardiac patients have investigated cyclosporine's cytoprotective effects against ischemia–reperfusion injury in the heart.[11–16] The collection of safety data was structured, and none of these studies reported renal side effects. All these studies administered cyclosporine in the same dose, 2.5 mg/kg, as an intravenous bolus injection.

At the same time, cyclosporine is known for inducing renal insufficiency[17] when used as a continuous medication, caused by an imbalance of the vascular tone in the efferent and afferent arterioles.[18,19] This impairment is reported to be reversible after 3 months of continuous medication.[20–22] Importantly, this is a different pathway than the proposed renoprotective mechanism of cyclosporine.

In summary, a single pretreatment dose of cyclosporine has been demonstrated to have renoprotective effects against ischemia–reperfusion injury in the experimental setting. Clinical studies with cyclosporine in patients with cardiac disease, including cardiac surgery, have not shown any adverse renal effects.[11–16] Therefore, we raised the hypothesis that cyclosporine, administered as a single dose intravenously before CABG, may reduce the level of postoperative renal injury.

Materials and Methods

Trial Design

The Cyclosporine to Protect Renal Function in Cardiac Surgery (CiPRICS) trial was an investigator-initiated, clinical, double-blind, randomized, placebo-controlled, parallel-design, single-center clinical trial and was performed at Skåne University Hospital in Lund, Sweden.

The trial was performed according to the 1964 Declaration of Helsinki and its later amendments and the European Guidelines for Good Clinical Practice, and in accordance with Swedish laws and regulations. Informed consent was obtained from all individual participants included in the study. Permits were obtained from the local ethics committee (LU 2014/777) and the Swedish Medical Products Agency (Uppsala, Sweden). The trial was registered under EudraCT No. 2014-004610-29 and at ClinicalTrials.gov (NCT02397213). The rationale for and the design of the study have been published previously.[23]

Study Population

Men and women scheduled for nonemergent CABG as their sole procedure at Skåne University Hospital with a preoperative estimated glomerular filtration rate (eGFR) between 15 and 90 ml · min^{-1} · 1.73 m^{-2} were eligible for the study. Inclusion and exclusion criteria have been published in the protocol.[23]

The study dictated two predefined strata based on renal function with the aim to cover a sizeable number of patients with decreased renal function in the study. The two strata were preoperative eGFR 15 to 59 or 60 to 90 ml · min^{-1} · 1.73 m^{-2}.

Anesthesia and Surgery

Anesthesia was standardized using propofol, fentanyl, and rocuronium. Inhalation anesthetic agents were prohibited.

All patients underwent CABG with ECC, with blood cardioplegia or St. Thomas crystalloid cardioplegia using a single cross-clamp technique. ECC was performed with a pump flow of 2.2 l/m^2 and mean arterial pressure at 50 to 70 mmHg in mild hypothermia or normothermia and a nadir hematocrit at 25%. The left internal mammary artery was used in a majority of cases, and saphenous vein graft (open harvesting technique) as the other bypass grafts.

Experimental Protocol

A block randomization was performed (block size of four) in a 1:1 ratio by prepacking the drug vials with placebo or active substance in two batches (one for each stratum). Once the patient arrived at the operating ward, the next vial in line (in the correct stratum) was taken, thereby allocating the patient to a group. The investigational drug was a lipid emulsion of cyclosporine,[24] CicloMulsion 5 mg/ml (NeuroVive Pharmaceutical AB, Sweden). As placebo, a lipid emulsion provided by the same manufacturer was used. The only difference between the placebo and active drug formulation was the content of cyclosporine. After anesthetic induction and before surgery, the study drug/placebo was administered at 0.5 ml/kg, corresponding to a dose of 2.5 mg/kg cyclosporine, in a central venous catheter as a 10-min infusion.

Efficacy data were collected preoperatively and daily until postoperative day 4. The study was terminated after a follow-up phone call after day 30.

Endpoints

The primary endpoint was relative plasma cystatin C concentration change from preoperative concentrations to day 3 after surgery. Secondary endpoints to evaluate renal function were plasma concentrations of cystatin C, creatinine, urea, and eGFR according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[25] during the first 4 days. Incidence of AKI was assessed by the Risk Injury Failure Loss End-stage (RIFLE) criteria based on changes in plasma creatinine and without urine output criteria.[26] Blood cyclosporine concentrations were followed.[23] To evaluate the possible protective effect on the heart and brain, plasma creatinine kinase-MB, troponin T, and serum S100B[27] were followed.

Safety Measurements

According to protocol, an independent Drug Safety Monitoring Board (DSMB; Lund, Sweden) assessed the safety of

the study after 50 and 100 patients.[23] Adverse event (AE) and serious adverse event (SAE) data were collected daily from drug administration to postoperative day 4. The leg wound after the saphenous vein harvesting was assessed on day 4 using a standardized method.[28] A follow-up telephone call 30 days after surgery was made to determine if any new SAE had occurred, and to follow up ongoing AE/SAE. Events that could normally be attributed to the operation (bleeding, myocardial infarction, deep sternal wound infection, and atrial fibrillation) were not reported as AE/SAE. SAE and suspected unexpected serious adverse reaction data were reported according to the Swedish Medical Products Agency's instructions.

Statistical Analysis

The power calculation was based on a previous study in our department, in which we found cystatin C on day 3 to be 1.98 ± 0.67 mg/l.[29] To detect half a SD change (13%) in plasma cystatin C on day 3 with 80% power and an alpha of 5%, we estimated a sample size of 75 patients in each arm.

Noncompliance after enrollment depended primarily on rescheduled surgery (fig. 1). Therefore, the analysis was performed as an all-patients-treated/modified-intention-to-treat analysis.[30]

A linear mixed model with stratification according to preoperative eGFR as the covariate was used for testing of the primary endpoint and secondary endpoints. If the linear mixed model gave a significant result, individual testing was performed, and a Bonferroni–Holm correction was applied. A log-transformation was performed for skewed distributions (cystatin C, creatinine, and urea) before analysis. For testing of single measurements, Student's *t* test or the Mann–Whitney U test was performed depending on the distribution of data. Data are presented as mean ± SD, number (%), or median with interquartile range. A *P* value less than 0.05 was considered statistically significant.

All statistical analyses were performed according to a predefined statistical analysis plan by an independent statistician (Clinical Studies Sweden, Forum South, Unit for Medical Statistics and Epidemiology, Skåne University Hospital) with SAS Enterprise Guide 6.1 (SAS Institute Inc., USA) and SPSS Statistics 22 (IBM Corp., USA).

Results

Patient Characteristics

From April 2015 through June 2016, we assessed 456 patients for eligibility and enrolled 154 patients, with 75 patients assigned to the cyclosporine group and 79 to the placebo group (fig. 1). One patient met a predefined withdrawal criterion (decision to perform operation other than CABG during surgery) and was excluded from the modified-intention-to-treat group. One patient in the placebo group had a missing value for cystatin C on day 3 and was excluded from the analysis of the primary variable but was used in all other analyses.

Baseline characteristics were well balanced between the groups. The preoperative eGFR were similar, both in the entire group and in the two strata (table 1).

Primary Outcome

The cyclosporine group (136.4 ± 35.6%) had a more pronounced increase from baseline plasma cystatin C to day 3 compared to

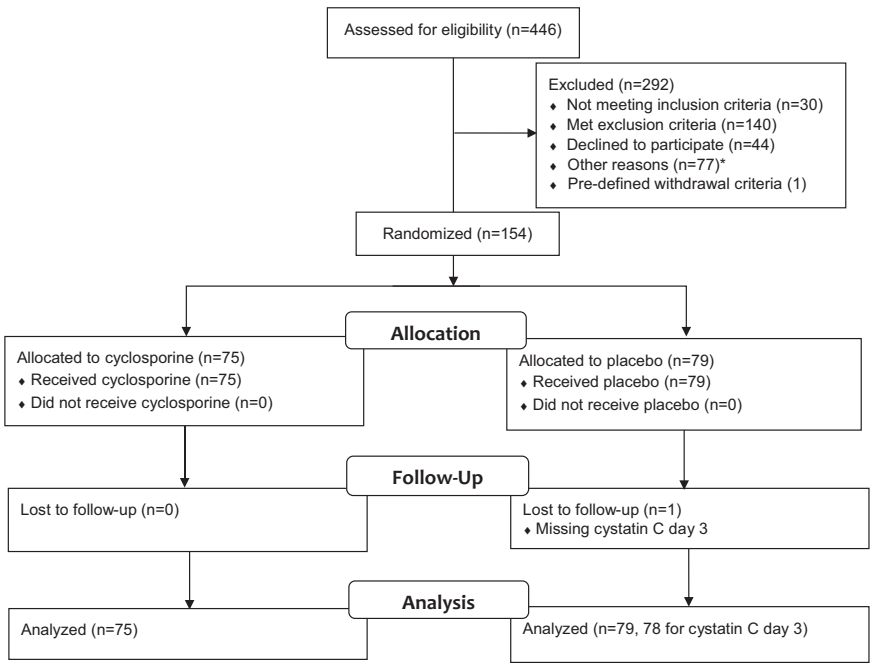

Fig. 1. Consolidated Standards of Reporting Trials flow chart for the Cyclosporine to Protect Renal Function in Cardiac Surgery study. *Mostly due to rescheduled surgery.

Table 1. Baseline Characteristics

Baseline Characteristics	Placebo (N = 79)	Cyclosporine (N = 75)
Male sex, No. (%)	68 (86.1)	62 (82.7)
Age (yr)	69 ± 8	69 ± 8
Height (cm)	175 ± 8	174 ± 9
Weight (kg)	86 ± 14	82 ± 13
Systolic blood pressure (mmHg)	137 ± 18	134 ± 17
Diastolic blood pressure (mmHg)	74 ± 8	72 ± 9
Medical history, No. (%)		
Hypertension	62 (78.5)	54 (72.0)
Congestive heart failure	15 (19.0)	10 (13.3)
LVEF < 30%	3 (3.8)	2 (2.7)
LVEF 30–50%	14 (17.7)	9 (12.0)
LVEF > 50%	59 (74.7)	62 (82.7)
COPD	0 (0)	4 (5.3)
Diabetes	26 (32.9)	14 (18.7)
Peripheral vascular disease	5 (6.3)	4 (5.3)
Previous CVI	5 (6.3)	6 (8.0)
Thyroid disease	8 (10.1)	3 (4.0)
Chronic AF	4 (5.1)	1 (1.3)
Paroxysmal AF	6 (7.6)	5 (6.7)
Medication use, No. (%)		
Diuretics	23 (29.1)	10 (13.3)
ACE/ARB	59 (76.0)	60 (78.7)
β-Blocker	64 (82.7)	62 (81.1)
Statins	76 (96.2)	69 (92.0)
Warfarin	2 (2.5)	1 (1.3)
ASA	73 (92.4)	68 (90.7)
Clopidrogel/prasurgel	3 (3.8)	5 (6.7)
Antithrombotic treatment	20 (25.3)	16 (21.3)
Antibiotics	4 (5.1)	1 (1.3)
Preop eGFR CKD-EPI ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)		
All patients	65.1 ± 18.9	69.0 ± 20.0
Subgroup eGFR 15–59 ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	51.1 ± 11.2	54.4 ± 11.9
Subgroup eGFR 60–90 ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	79.9 ± 10.0	81.5 ± 10.1

Values are presented as mean ± SD or No (%). ACE = angiotensin conversion enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaborative Group; COPD = chronic obstructive pulmonary disease; CVI = cerebrovascular incident; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction.

the placebo group (115.9 ± 30.8%). The difference between groups was 20.6% (95% CI, 10.2 to 31.2%, $P < 0.001$; fig. 2).

Secondary Outcome

The secondary renal outcomes, relative difference in plasma creatinine, and absolute values for plasma cystatin C and plasma creatinine were also significantly higher in the cyclosporine group (table 2; fig. 3). The classification according to RIFLE on postoperative day 3 also differed, as 7 patients (9%) in the placebo group were classified in RIFLE group R (risk), I (injury), or F (failure) compared to 23 (31%, $P < 0.001$) in the cyclosporine group (table 2), and 3 patients (4%) in the placebo group were classified as RIFLE R compared to 15 (20%, $P < 0.001$) in the cyclosporine group.

Because of the results in the primary variable, a *post hoc* investigation, not included in the study protocol, of plasma creatinine 1 to 3 months and 3 to 6 months after the end of study was performed by retrieving plasma creatinine from the patients' electronic medical records. We were able to obtain measurements from 86% of all study patients, revealing that plasma creatinine was normalized in both groups at both time intervals (fig. 3). There were no differences between the groups for troponin T, creatinine kinase-MB, or S100B (tables S1 and S2, Supplemental Digital Content, http://links.lww.com/ALN/B623, listing the result of cardiac injury markers and S100B, respectively, in this study).

Predefined Subgroups

In the subgroup with eGFR 15 to 59 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, the relative increase in plasma cystatin from preoperative to day 3 was 1.39 ± 0.35 (mean ± SD) for cyclosporine *versus* 1.11 ± 0.24 for placebo ($P < 0.001$). The corresponding figures for the subgroup with an eGFR 60 to 90 were 1.34 ± 0.36 (mean ± SD) for the cyclosporine group *versus* 1.18 ± 0.34 for the placebo group ($P = 0.011$). The stratification variable was included in the primary analyses, and there was no difference between groups ($P = 0.858$). The same pattern was observed for the dynamics of eGFR during the study days (fig. 4, depicting the dynamic of eGFR in the two strata in this study).

Pharmacokinetics

Mean blood cyclosporine concentrations were 4423 ± 887 ng/ml 5 min after end of infusion, 775 ± 180 ng/ml at the end of ECC, and 106 ± 32 ng/ml the next morning. No clear relationships were observed between the cyclosporine exposure and change from baseline in plasma cystatin C or creatinine.

Safety

A total number of 31 AE were reported, with 16 in the cyclosporine group and 15 in the placebo group. A total number of 26 SAE were reported, with 12 in the cyclosporine group and 14 in the placebo group (table S3, Supplemental Digital Content, http://links.lww.com/ALN/B623, listing the SAE in this study). All AE/SAE were resolved. Two patients, both in the placebo group, suffered a stroke. One of these patients died during the study period, which was the only death in the study. Safety biochemistry in this study is presented in table S3, Supplemental Digital Content (http://links.lww.com/ALN/B623). The cyclosporine group had both higher C-reactive protein concentrations on postoperative day 2 to 4 and higher leukocyte count on all 4 postoperative days compared with placebo. Also, plasma potassium was higher on day 2, thrombocytes were lower on days 3 and 4 and hemoglobin was lower on day 3 in the cyclosporine group as listed in table S4, Supplemental Digital Content (http://links.lww.com/ALN/B623). Two DSMB meetings after 50 and 100 patients recommended continuation of the study according to study protocol.

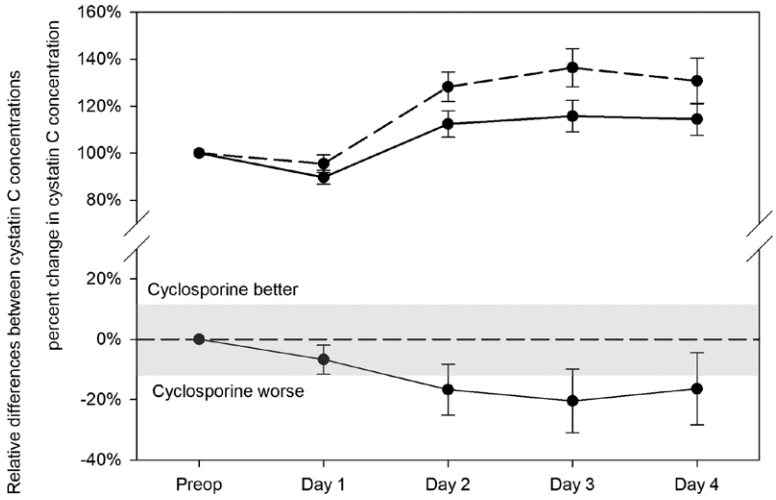

Fig. 2. Cystatin C changes expressed as percentage of baseline for the cyclosporine group (*dashed line*) and the placebo group (*solid line*) with 95% CI. Relative differences between cystatin C concentrations for the groups with 95% CI. *Gray area* reflects a ±13% change (number used in power calculations) in the primary endpoint. Preop = preoperative.

Clinical Outcome

There were few differences in clinical outcome between the groups. The cyclosporine group had more a positive fluid balance and received more diuretics on postoperative days 2 to 4 (table 3; table S5, Supplemental Digital Content, http://links.lww.com/ALN/B623, listing the use of diuretics in this study). The cyclosporine group had a shorter time until extubation, but time in the intensive care unit did not differ. No patient in either group was treated with continues renal replacement therapy. There were no differences in leg scoring on day 4 (table S5, Supplemental Digital Content, http://links.lww.com/ALN/B623, listing the leg scoring in this study).

Discussion

In this study, administration of 2.5 mg/kg cyclosporine as an intravenous bolus before CABG surgery with ECC resulted in decreased renal function postoperatively according to all measured renal parameters, compared with placebo. No protective effects were found.

The *post hoc* review found plasma creatinine for 86% of patients, while there were very few plasma cystatin C values. We found that plasma creatinine had normalized in both groups, and there was no difference between the groups, as depicted in figure 2. This supports previous findings that renal impairment induced by cyclosporine can be reversible.[20–22]

One explanation for our findings might be that the AKI induced by CABG surgery with ECC is not linked to ischemia–reperfusion injury with mPTP-mediated dysfunction. However, Lannemyr *et al.*[3] recently demonstrated reduced renal oxygenation both during and after ECC, in combination with signs of tubular injury, implying hypoxia is an important factor for AKI. In contrast to the clinical situation, animal models evaluating cytoprotective compounds typically use models in which the renal injury results in massive necrotic cell death,[31] perhaps not representative of a milder hypoxia during ECC.

Anesthesia may influence the results. Propofol[32] and anesthetic gases[33] may have renoprotective effects. We used a standardized protocol in which propofol was allowed, while use of anesthetic gas was prohibited. No protocol violations were reported.

In addition to the renal findings, we were unable to demonstrate any cytoprotective effects on the heart. This contrasts with the results of Chiari *et al.*[11] and Hausenloy *et al.*,[14] who both found improved myocardial protection, with the caveat that Hausenloy *et al.* observed this effect only in patients with longer cross-clamp times. The different results may be explained by the fact that our study had shorter perfusion times, did not use intermittent cross-clamp fibrillation, and had lower biomarkers for myocardial injury. In addition, Chiari *et al.*[11] studied patients with aortic valve stenosis who had left ventricle hypertrophy, which differs from our study. Our results also suggest that the two previous cardiac surgery studies were not statistically powered to detect renal side effects. In our study, the DSMB recommended continuing the study after 50 and 100 patients, but the final analysis revealed a clear negative renal effect, emphasizing the strength of prospective testing with adequate statistical power.

We also found a higher inflammatory response, measured with C-reactive protein and leukocyte count, in the cyclosporine group. An increase in leukocyte count was also found by Mazzeo *et al.*[34] in a traumatic brain injury study. Despite this, the AE/SAE did not imply an increased infection rate in the cyclosporine group.

The study was designed using two strata and prespecified subgroups according to preoperative eGFR in order to evaluate whether the potential protective effect or safety profile differed at lower or higher GFRs.[23] No clear differences in change in the fraction of plasma cystatin C or plasma

Table 2. Clinical Chemistry Renal Function

Clinical Chemistry Renal Function	Placebo (N = 79)	Cyclosporine (N = 75)	*P* Value
Plasma cystatin C (mg/l)			0.001*
Day –1	1.18 (0.31)	1.13 (0.30)	
Day 1	1.06 (0.38)	1.08 (0.36)	0.007†
Day 2	1.33 (0.48)‡	1.48 (0.64)	< 0.001†
Day 3	1.37 (0.51)‡	1.57 (0.69)	< 0.001†
Day 4	1.32 (0.45)‡	1.51 (0.79)	0.001†
Plasma creatinine (μmol/l)			< 0.001*
Day –1	91.9 (19.1)	89.3 (19.4)	
Day 1	88.6 (23.2)	91.8 (23.6)	0.009†
Day 2	107.9 (40.9)	122.0 (48.1)	0.001†
Day 3	106.2 (49.3)	123.9 (55.9)	< 0.001†
Day 4	102.1 (48.1)	112.5 (56.7)	0.019
1–3 months	93.4 (33.0)	89.9 (22.0)	0.498§
3–6 months	94.5 (29.0)	91.7 (24.1)	0.643§
Plasma urea (mmol/l)			0.006*
Day –1	6.9 (2.3)	6.4 (2.2)	
Day 1	5.3 (1.9)	5.4 (2.1)	0.026†
Day 2	6.4 (2.8)	7.1 (2.6)	< 0.001†
Day 3	7.1 (3.2)	8.6 (3.9)	< 0.001†
Day 4	7.4 (3.5)	8.8 (4.8)	0.002†
eGFR P-CystatinC/P-Creatinine (ml · min^{-1} · 1.73 m^{-2})			0.001*
Day –1	69.0 (17.5)	71.4 (17.0)	
Day 1	77.0 (22.3)	74.0 (21.0)	0.003†
Day 2	61.9 (21.4)	55.1 (21.1)	< 0.001†
Day 3	62.0 (21.8)	53.7 (22.0)	< 0.001†
Day 4	63.7 (21.5)	59.0 (22.6)	0.002†
RIFLE-creatinine classification, postoperative day 3 (%)			
No damage	72 (91.1)	52 (69.3)	0.001†‖
R	3 (3.8)	15 (20.0)	0.001†‖
I	2 (2.5)	5 (6.7)	0.192‖
F	2 (2.5)	3 (4.0)	0.522‖

Outcome in terms of clinical chemistry, renal function. eGFR (estimated glomerular filtration rate) calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for creatinine and cystatin C. Values are presented as mean (SD) or No. (%). *Linear mixed model. †Statistical significance ($P < 0.05$) after Bonferroni–Holm correction. ‡N = 78. §Data retrieved *post hoc* and not included in linear mixed model, but tested with *t* test. ‖Mann–Whitney test. Day –1 = preoperative measurement, usually the admission day; Day 1 = the first day after surgery, and so forth; F = failure; I = injury; R = risk; RIFLE = Risk Injury Failure Loss End-stage.

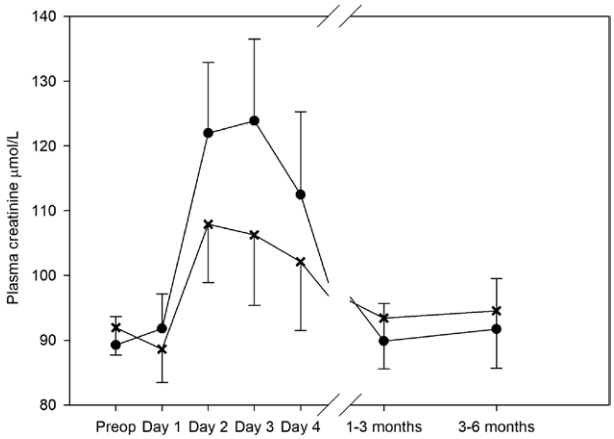

Fig. 3. Mean values with 95% CI for plasma creatinine in the cyclosporine (*dashed line*) and placebo (*solid line*) groups. The *broken axis* denotes that a *post hoc* analysis was performed in the period 1 to 6 months after operation. Preop = preoperative sampling, usually the day of admission. Days 1 to 4 = days after surgery.

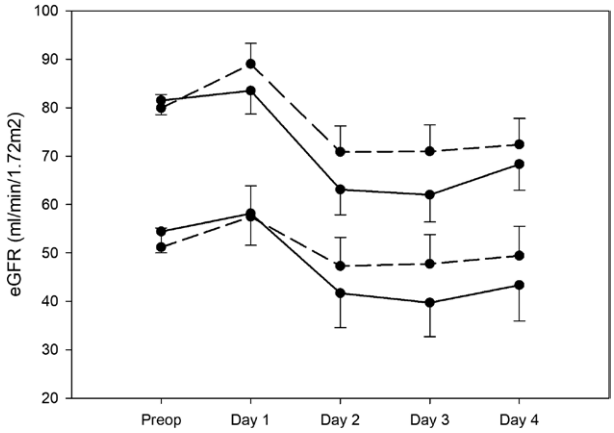

Fig. 4. The dynamics of eGFR (estimated glomerular filtration rate; based on cystatin C and creatinine according to Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) during the postoperative period for the two subgroups (eGFR 15 to 59 and 60 to 90 ml · min^{-1} · 1.73 m^{-2}) expressed as mean ± SD. The stratification variable is included in the primary analyses, and there are no differences between the stratification groups ($P = 0.858$). *Solid line* denotes cyclosporine and *dashed line*, placebo. Preop = preoperative.

creatinine from baseline between the two eGFR groups were observed. We chose to include patients with an eGFR as low as 15 ml · min^{-1} · 1.73 m^{-2}. On the other hand, we excluded patients with normal renal function (eGFR greater than 90 ml · min^{-1} · 1.73 m^{-2}), which is reflected in a higher baseline mean plasma creatinine compared to the other studies. In conclusion, we could not discern any difference in results for cyclosporine relating to preoperative renal function.

A limitation of the current study is the single-center design. However, the consistency of the results under the well-controlled study settings suggests that the main findings would likely be generalizable. Other doses, repeated doses, or different timings may have yielded other results. However, the tested single administration of 2.5 mg/kg is the same as in previous studies reporting positive outcomes. Furthermore, we did not observe any exposure-dependent effects in a *post hoc* pharmacokinetic–pharmacodynamic analysis. In contrast, the negative effects on renal function were consistent among all the measured endpoints, which emphasizes the strengths of a sufficiently powered, prospective, randomized, double-blinded trial in a well-defined study population.

In conclusion, despite promising animal data, pretreatment of patients with cyclosporine intravenously before CABG with ECC resulted in decreased renal function in the immediate postoperative period compared with placebo. Further studies on cyclosporine should take these findings into account when assessing the safety of the drug.

Table 3. General Outcome

General Outcome	Placebo (N = 79)	Ciclosporin (N = 75)	*P* Value
Surgical procedure			
Perfusion time, ECC (min)	74 (27)	77 (30)	0.423*
Aortic cross-clamp duration (min)	46 (16)	47 (20)	0.849*
Number of distal coronary grafts (n)	3.4 (0.9)	3.2 (0.9)	0.298*
Diuresis and fluid balance			
Diuresis before ECC (ml)	182 (198)	163 (142)	0.930*
Diuresis during ECC (ml)	168 (121)	165 (106)	0.723*
Diuresis 12 h (ml)	1723 (579)	1575 (581)	0.067*
Fluid balance during surgery	1933 (737)	2071 (709)	0.240†
Fluid balance until first morning after surgery (ml)	2540 (1157)	291 (1171)	0.050†
Postoperative outcome			
Time to extubation (min)	467 (794)	426 (214)	0.015*
ICU time (h)	29 (25)	32 (32)	0.261*
Bleeding 12 h (ml)	477 (244)	536 (310)	0.392*
Complications, No. (%)			
Reoperation for bleeding	3 (4.0)	2 (2.5)	0.675‡
Postoperative DSWI	1 (1.3)	0 (0.0)	1.000‡
Postoperative myocardial damage	0 (0)	2 (2.7)	0.235‡
Postoperative stroke	2 (2.5)	0 (0)	0.497‡
Postoperative heart failure	3 (3.8)	4 (5.3)	0.714‡
Postoperative atrial fibrillation	29 (36.7)	32 (42.7)	0.511‡
Leg scoring	4.9 (2.8)	5.6 (2.4)	0.057*
30-day mortality, No. (%)	1 (1.3)	0 (0)	1.000‡

Testing was done with *Mann–Whitney test, †*t* test, or ‡Fisher exact test. DSWI = deep sternal wound infection; ECC = extracorporeal circulation; ICU = intensive care unit.

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Competing Interests

Dr. Ederoth has received lecture fees from Orion Pharma AB (Danderyd, Sweden). Drs. Hansson and Elmér are employed by and are shareholders of NeuroVive Pharmaceutical AB, Lund, Sweden. The other authors declare no competing interests. Financial support for research staff, laboratory tests, and the study drug was granted by NeuroVive Pharmaceutical AB. NeuroVive Pharmaceutical AB was given the opportunity to comment on the drafting of both the protocol and the manuscript, but the final decision on the study design was made solely by the investigators. Data were analyzed according to the statistical analysis plan by an independent external statistician (Clinical Studies Sweden, Forum South, Lund, Sweden). The authors designed the trial, gathered the data, supervised statistical analysis, prepared the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data set and adherence of the study to the protocol.

Reproducible Science

Full protocol available at: henrik.bjursten@med.lu.se. Raw data available at: henrik.bjursten@med.lu.se.

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References

1. Dardashti A, Ederoth P, Algotsson L, Brondén B, Bjursten H: Incidence, dynamics, and prognostic value of acute kidney injury for death after cardiac surgery. J Thorac Cardiovasc Surg 2014; 147:800–7
2. Kumar AB, Suneja M: Cardiopulmonary bypass-associated acute kidney injury. Anesthesiology 2011; 114:964–70
3. Lannemyr L, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten SE: Effects of cardiopulmonary bypass on renal perfusion, filtration, and oxygenation in patients undergoing cardiac surgery. Anesthesiology 2017; 126:205–13
4. Crompton M: The mitochondrial permeability transition pore and its role in cell death. Biochem J 1999; 341(pt 2):233–49
5. Di Lisa F, Menabò R, Canton M, Barile M, Bernardi P: Opening of the mitochondrial permeability transition pore causes depletion of mitochondrial and cytosolic NAD+ and is a causative event in the death of myocytes in postischemic reperfusion of the heart. J Biol Chem 2001; 276:2571–5
6. Hu W, Chen Z, Ye Z, Xia D, Xia Z, Ma J, Zhu M, Chen G: Knockdown of cyclophilin D gene by RNAi protects rat from ischemia/reperfusion-induced renal injury. Kidney Blood Press Res 2010; 33:193–9
7. Crompton M, Ellinger H, Costi A: Inhibition by cyclosporin A of a Ca2+-dependent pore in heart mitochondria activated by

inorganic phosphate and oxidative stress. Biochem J 1988; 255:357–60

8. Singh D, Chander V, Chopra K: Cyclosporine protects against ischemia/reperfusion injury in rat kidneys. Toxicology 2005; 207:339–47
9. Oka N, Wang L, Mi W, Zhu W, Honjo O, Caldarone CA: Cyclosporine A prevents apoptosis-related mitochondrial dysfunction after neonatal cardioplegic arrest. J Thorac Cardiovasc Surg 2008; 135:123–30, 130 e1-2
10. Okonkwo DO, Melon DE, Pellicane AJ, Mutlu LK, Rubin DG, Stone JR, Helm GA: Dose-response of cyclosporin A in attenuating traumatic axonal injury in rat. Neuroreport 2003; 14:463–6
11. Chiari P, Angoulvant D, Mewton N, Desebbe O, Obadia JF, Robin J, Farhat F, Jegaden O, Bastien O, Lehot JJ, Ovize M: Cyclosporine protects the heart during aortic valve surgery. Anesthesiology 2014; 121:232–8
12. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guérin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De Poli F, Morice MC, Ider O, Dubois-Randé JL, Unterseeh T, Le Breton H, Béard T, Blanchard D, Grollier G, Malquarti V, Staat P, Sudre A, Elmer E, Hansson MJ, Bergerot C, Boussaha I, Jossan C, Derumeaux G, Mewton N, Ovize M: Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015; 373:1021–31
13. Ghaffari S, Kazemi B, Toluey M, Sepehrvand N: The effect of prethrombolytic cyclosporine-A injection on clinical outcome of acute anterior ST-elevation myocardial infarction. Cardiovasc Ther 2013; 31:e34–9
14. Hausenloy Dj, Kunst G, Boston-Griffiths E, Kolvekar S, Chaubey S, John L, Desai J, Yellon D: The effect of cyclosporin-A on peri-operative myocardial injury in adult patients undergoing coronary artery bypass graft surgery: A randomised controlled clinical trial. Heart 2014; 100:544–9
15. Ottani F, Latini R, Staszewsky L, La Vecchia L, Locuratolo N, Sicuro M, Masson S, Barlera S, Milani V, Lombardi M, Costalunga A, Mollichelli N, Santarelli A, De Cesare N, Sganzerla P, Boi A, Maggioni AP, Limbruno U; CYCLE Investigators: Cyclosporine A in reperfused myocardial infarction: The multicenter, controlled, open-label CYCLE Trial. J Am Coll Cardiol 2016; 67:365–74
16. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, André-Fouët X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M: Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 2008; 359:473–81
17. Issa N, Kukla A, Ibrahim HN: Calcineurin inhibitor nephrotoxicity: A review and perspective of the evidence. Am J Nephrol 2013; 37:602–12
18. Zhang W, Victor RG: Calcineurin inhibitors cause renal afferent activation in rats: A novel mechanism of cyclosporine-induced hypertension. Am J Hypertens 2000; 13:999–1004
19. Textor SC, Burnett JC Jr, Romero JC, Canzanello VJ, Taler SJ, Wiesner R, Porayko M, Krom R, Gores G, Hay E: Urinary endothelin and renal vasoconstriction with cyclosporine or FK506 after liver transplantation. Kidney Int 1995; 47:1426–33
20. Klintmalm GB, Iwatsuki S, Starzl TE: Nephrotoxicity of cyclosporin A in liver and kidney transplant patients. Lancet 1981; 1:470–1
21. Morris PJ, French ME, Dunnill MS, Hunnisett AG, Ting A, Thompson JF, Wood RF: A controlled trial of cyclosporine in renal transplantation with conversion to azathioprine and prednisolone after three months. Transplantation 1983; 36:273–7
22. Naesens M, Kambham N, Concepcion W, Salvatierra O Jr, Sarwal M: The evolution of nonimmune histological injury and its clinical relevance in adult-sized kidney grafts in pediatric recipients. Am J Transplant 2007; 7:2504–14
23. Ederoth P, Grins E, Dardashti A, Brondén B, Metzsch C, Erdling A, Nozohoor S, Mokhtari A, Hansson MJ, Elmér E, Algotsson L, Jovinge S, Bjursten H: Ciclosporin to Protect Renal function In Cardiac Surgery (CiPRICS): A study protocol for a double-blind, randomised, placebo-controlled, proof-of-concept study. BMJ Open 2016; 6:e012299
24. Ehinger KH, Hansson MJ, Sjövall F, Elmér E: Bioequivalence and tolerability assessment of a novel intravenous ciclosporin lipid emulsion compared to branded ciclosporin in Cremophor ® EL. Clin Drug Investig 2013; 33:25–34
25. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367:20–9
26. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, Schaff HV: Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011; 15:R16
27. Jönsson H, Johnsson P, Birch-Iensen M, Alling C, Westaby S, Blomquist S: S100B as a predictor of size and outcome of stroke after cardiac surgery. Ann Thorac Surg 2001; 71:1433–7
28. Elahi MM, Haesey AM, Graham KC, Battula NR, Manketlow B, Dhannapuneni RR, Hickey MS: Leg wound infections following cardiac surgery: A scoring system for assessment and management. J Wound Care 2005; 14:337–40
29. Dardashti A, Ederoth P, Algotsson L, Brondén B, Grins E, Larsson M, Nozohoor S, Zinko G, Bjursten H: Erythropoietin and protection of renal function in cardiac surgery (the EPRICS Trial). Anesthesiology 2014; 121:582–90
30. Group. IEW: ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Stat Med 1999; 18:1905–42
31. Lemoine S, Pillot B, Rognant N, Augeul L, Rayberin M, Varennes A, Laville M, Ovize M, Juillard L: Postconditioning with cyclosporine a reduces early renal dysfunction by inhibiting mitochondrial permeability transition. Transplantation 2015; 99:717–23
32. Yoo YC, Shim JK, Song Y, Yang SY, Kwak YL: Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. Kidney Int 2014; 86:414–22
33. Cai J, Xu R, Yu X, Fang Y, Ding X: Volatile anesthetics in preventing acute kidney injury after cardiac surgery: A systematic review and meta-analysis. J Thorac Cardiovasc Surg 2014; 148:3127–36
34. Mazzeo AT, Brophy GM, Gilman CB, Alves OL, Robles JR, Hayes RL, Povlishock JT, Bullock MR: Safety and tolerability of ciclosporin a in severe traumatic brain injury patients: Results from a prospective randomized trial. J Neurotrauma 2009; 26:2195–206