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Extracorporeal Blood Purification and Acute Kidney Injury in Cardiac Surgery
The SIRAKIO2 Randomized Clinical Trial

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IMPORTANCE Cardiac surgery–associated acute kidney injury (CSA-AKI) remains a significant problem following cardiopulmonary bypass (CPB). Various strategies are proposed to attenuate CSA-AKI, including extracorporeal blood purification (EBP), but little is known about the effect of EBP through an acrylonitrile-sodium methallylsulfonate/polyethyleneimine membrane during CPB.

OBJECTIVE To determine whether the use of an EBP device in a nonemergent cardiac surgery population reduces CSA-AKI after CPB.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, randomized clinical trial was conducted in 2 tertiary hospitals in Spain. Patients 18 years or older undergoing nonemergent cardiac surgery who were at high risk for CSA-AKI were enrolled from June 15, 2016, through November 5, 2021, with follow-up data through February 5, 2022. Of 1156 patients assessed, 343 patients were randomized (1:1) to either receive EBP or standard care.

INTERVENTION Nonselective EBP device connected to the CPB circuit.

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of CSA-AKI in the 7 days after randomization.

RESULTS Among 343 patients randomized (169 to receive EBP and 174 to receive usual care), the mean (SD) age was 69 (9) years and 119 were females. The rate of CSA-AKI was 28.4% (95% CI, 21.7%-35.8%) in the EBP group vs 39.7% (95% CI, 32.3%-47.3%) in the standard care group (P = .03), with an adjusted difference of 10.4% (95% CI, 2.3%-18.5%) using a log-binomial model (P = .01). No significant differences (P > .05) were observed in most of the predefined clinical secondary end points or post hoc exploratory end points. In a sensitivity analysis, EBP was found to be more effective in terms of CSA-AKI reduction in patients with chronic kidney disease, diabetes, hypertension, low left ventricular ejection fraction (<40%), and lower body mass index (<30). No differences were observed between the groups in adverse events tracking.

CONCLUSIONS AND RELEVANCE The use of a nonselective EBP device connected to the CPB circuit in a nonemergent population of patients undergoing cardiac surgery was associated with a significant reduction of CSA-AKI in the first 7 days after surgery.

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Supplemental content

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Acute kidney injury (AKI) after cardiac surgery is common, with an incidence between 10% and 40%. The development of mild to moderate cardiac surgery-associated AKI (CSA-AKI) is associated with a prolonged length of stay, increased cost, and increase in hospital mortality.[1,2] An international consensus conference defined CSA-AKI using the Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria and proposed the 7 postoperative days as the incidence period for CSA-AKI. Although most CSA-AKI resolves, studies suggest that approximately 11% of these patients will develop acute kidney disease and 6% will progress to chronic kidney disease (CKD) at 1 year.[3]

There are multiple mechanisms that lead to AKI after cardiac surgery. Common causes include hemodynamic instability due to hypovolemia or vasoplegia and/or exposure to nephrotoxic medications. Exposure to the CPB circuit also leads to complement activation, hemolysis, and systemic inflammation.[3] After restoration of the circulation, there is additional ischemia-reperfusion injury.[3,4] However, there are still knowledge gaps about the effects and mechanisms of cardiac surgery in CSA-AKI occurrence besides the complexity of interindividual risk factors that may predispose for this complication.[4]

The implementation of standardized protocols in high-risk patients has reduced the incidence and severity of CSA-AKI.[3,5] However, interventions targeted at the inflammatory response are less successful.[6] Extracorporeal techniques such as high-volume continuous venovenous hemofiltration or ultrafiltration (for volume removal) do not modify the rate of CSA-AKI.[7-9] Extracorporeal blood purification (EBP) devices may nonselectively remove inflammatory mediators from the circulation,[10] but, although some experimental studies have shown promising results, these have failed to demonstrate clinical benefit.[11,12] Specifically, a membrane composed of a copolymer of acrylonitrile and sodium methallyl sulfonate can adsorb cytokines together with a polyethylenimine surface to bind endotoxin.[13] It is unknown whether the addition of an EBP device to the CPB circuit during cardiac surgery will attenuate the inflammatory response and reduce CSA-AKI.

To address these knowledge gaps this study randomized patients at high risk for AKI undergoing cardiac surgery at 2 medical centers to receive a nonselective EBP membrane connected to the CPB circuit vs standard care to examine the effect on CSA-AKI at postoperative day 7.[13]

Key Points

Question Does the use of a nonselective extracorporeal blood purification (EBP) device connected to the cardiopulmonary bypass circuit reduce the incidence of acute kidney injury (AKI) in high-risk patients undergoing cardiothoracic surgery?

Findings In this randomized clinical trial that included 343 adults, a significant decrease in cardiac surgery–associated AKI was observed in those treated with EBP compared with those who were not (28.4% vs 39.7%).

Meaning In high-risk patients undergoing cardiac surgery, the use of a nonselective EBP device was associated with a significant reduction in AKI in the first 7 days after surgery.

Methods

Study Design

The SIRAKI02 study was an institutionally and commercially sponsored, double-blind, 2-center, randomized clinical trial performed in the operating rooms and intensive care units (ICUs) of 2 tertiary hospitals in Spain (Hospital Universitari de Bellvitge and Hospital Universitari Germans Trias i Pujol). Both hospitals have extensive cardiac surgery programs with more than 1000 patients undergoing cardiac surgery treated annually. The study protocol was approved by the ethical committee of both participating centers (PR 283/16). All interventions and analyses were done in accordance with the International Conference on Harmonization and Good Clinical Practice guidelines. The study is registered with ClinicalTrials.gov (NCT02518087) and is completed. The trial protocol is provided in Supplement 1 and the statistical analysis plan in Supplement 2.

Participants

Eligible patients were 18 years or older with no evidence of advanced (stage 4 or 5) CKD and scheduled for elective cardiac surgery with an expected CPB time of more than 90 minutes. In general, these patients were receiving double or triple valve replacement or coronary artery bypass grafting (CABG) plus valve replacement or ascending aortic replacement plus CABG/valve replacement. Written informed consent was obtained from all participants.

Randomization and Masking

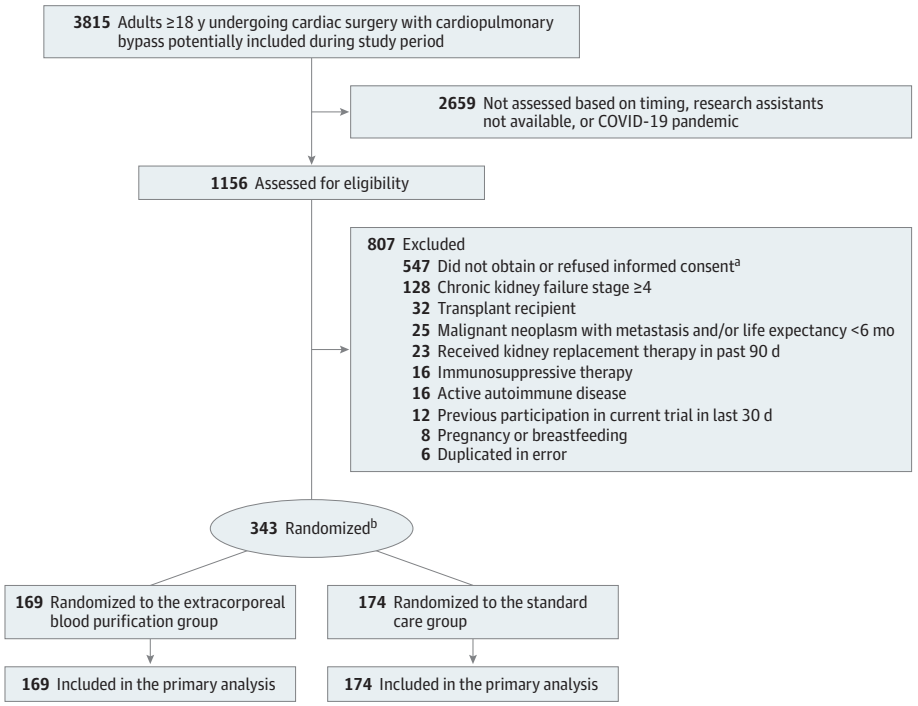
Enrollment was performed by the cardiac surgery team and was computer-generated, balanced by blocks of variable and undisclosed size (from 10 to 30) and stratified per center (2:1 ratio expecting recruitment rate differences). Patients were randomized in a 1:1 ratio to an intervention EBP group or a standard care group. Randomization concealment was achieved by means of sealed envelopes for each center (**Figure 1**) that were opened by a research assistant who was only involved in the operative phase. Although practitioners involved in the surgical intervention could not be blinded, intensivists assessing the outcomes were masked to group assignment.

Procedures

All patients were included in the study the day before the operation and preoperative blood specimens were collected. Documented comorbidities and calculated surgical risk scores (EuroSCORE II) were collected together with drug history and preoperative cardiac functional status, including left ventricular ejection fraction.

Patients randomized to the EBP group received treatment during the CPB time with a nonselective acrylonitrile-sodium methallylsulfonate/polyethylenimine membrane (oXiris; Baxter) connected to a continuous kidney replacement therapy (KRT) machine (Prismaflex System; Baxter) (eFigure 1 in Supplement 1). The continuous KRT modality used was

Figure 1. Flow of Patients in the Trial



[a]It was not possible to obtain consent on account of timing (failure to obtain consent the day before surgery because patients were admitted late in the afternoon when research assistants were not available) for 489 patients and 58 did not sign informed consent.

[b]Randomization was stratified by center (2:1) according to expected recruitment rates. In 6 cases, envelopes were opened by 2 different research fellows for the same patient, but that patient only received 1 group assignment. For clarity, these duplications have been excluded from the randomization in the flowchart.

slow continuous ultrafiltration and, although ultrafiltration was not included in the initial study protocol, perfusionists were allowed to remove fluid from the patient if clinically required (a polysulfone membrane Livanova with phosphorylcholine was used in the control group for this purpose). Technical EBP features (eg, blood flow) and possible complications related to the use of EBP in the operating room were collected (eg, platelet differences, blood product transfusion requirements).

On admission to the ICU, patients underwent hemodynamic and respiratory monitoring. Laboratory samples were taken every 8 hours during the first 24 hours and daily during ICU admission (or at least up to day 7). The Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were measured during the 24 hours of ICU admission (kidney function parameters were removed from the scores to avoid collinearity). Complications during ICU stay were also recorded, including transfusion requirements, additional emergent surgery, major bleeding events, and arrhythmias.

Serum creatinine was recorded daily for the first 7 days after cardiac surgery, with daily urine output monitored up to day 4 in most patients, because urinary catheters are routinely removed on discharge from the ICU. The initial hourly urine output at ICU admission was not considered because surgical interventions (eg, mannitol) could introduce bias. Kidney function and the need for KRT were determined at ICU discharge, hospital discharge, and 28 and 90 days after the operation. The worst CSA-AKI stage[14] within the first 7 days after the cardiac operation was recorded for each patient.

Outcomes

The primary outcome was the occurrence of CSA-AKI between randomization and day 7. There were several secondary outcomes, including 90-day survival after surgery, the length of ICU and hospital stay, the daily AKI stage during the first 7 days, and laboratory end points (circulatory cytokines) at baseline (0 hours), CPB end, ICU admission, and 24 hours. Post hoc analyses included several exploratory end points, such as the effect of ultrafiltration, rates of early/late CSA-AKI or transitory/persistent CSA-AKI, need for vasopressor support, mechanical ventilation, KRT during the first 28 days, time receiving CPB, and SOFA and APACHE II scores at ICU admission. Days free from vasopressor, mechanical ventilation, or KRT were calculated until 28 days or hospital discharge, whichever occurred first. Risk factors for CSA-AKI were also analyzed in a post hoc exploratory analysis. Safety events were also compared between the groups in the operating room and during ICU admission.

The study follows the CONSORT reporting guideline for randomized clinical trials.

Statistical Analysis

A clinically important difference in the primary end point was considered to be a 10% absolute reduction in CSA-AKI incidence at 7 days. Based on previous work, the incidence of CSA-AKI is nearly 25%.[15,16] Investigators estimated that a population of 320 patients was needed to detect a 10% difference with 80% power (α = 5%). Considering a dropout rate of 5% of the total sample, enrollment was planned for 340 patients.

Categorical variables were expressed as frequencies and percentages and continuous variables were expressed as the mean and SD or median and IQR, depending on the distribution.

The primary outcome was compared using the χ^2 test. Percentage differences and their 95% CIs were reported. Log-binomial models were adjusted for age, CPB time, and other relevant variables. Estimated adjusted percentage differences between the groups and risk ratios (RRs) with their 95% CIs were reported. The primary outcome analysis was repeated, stratifying CSA-AKI by the worst KDIGO classification (stages 1, 2, and 3) within the first 7 days after the surgical procedure and in subgroups for age, CPB time, and other relevant variables (sensitivity analysis).

Secondary outcomes were compared between study groups using *t* tests for symmetric continuous variables, Kruskal-Wallis tests for asymmetric continuous variables, and χ^2 or Fisher exact tests for categorical variables. Mean, median, or percent differences were reported. Variables measured at multiple points (baseline, CPB end, ICU admission, and 24 hours) were analyzed using 1-way repeated measures analysis of variance. To compare variables among more than 2 groups, analysis of variance or Kruskal-Wallis tests were used for continuous variables, depending on the data distribution. Categorical variables were compared using χ^2 tests or Fisher exact tests.

To assess factors associated with CSA-AKI, independent logistic regression analyses were performed for each factor, reporting odds ratios (ORs). Whenever mean, median, or percentage difference were reported, the 95% CI was computed with the *t* test, bootstrapping, and Wilson method with continuity correction, respectively. RRs and ORs were also reported with 95% CIs. Statistical analyses were all performed using R, version 3.3.1 (R Foundation).

Results

Between June 2016 and November 2021, a total of 3815 patients were screened, of whom 343 were randomized (169 to receive the EBP protocol and 174 to receive the standard care protocol; Figure 1). **Table 1** shows the main baseline characteristic distribution between both groups, in which balance was largely preserved with no differences in age, sex, left ventricular ejection fraction, or important comorbidities such as CKD and diabetes (eTable 1 and eTable 2 in Supplement 3). Surgical risk score (median [IQR] EuroSCORE II: 2.6 [1.7-4.1] in the EBP group vs 2.2 [1.5-3.9] in the standard care group) and the type of operation were also well distributed between both groups, with the highest percentage of patients receiving CABG plus valve replacement (40% in the EBP group vs 35% in the standard care group).

In the primary analysis, CSA-AKI within the first 7 days after the surgical procedure was present in 48 of 169 patients (28.4% [95% CI, 21.7%-35.8) in the EBP group vs 69 of 174 (39.7% [95% CI, 32.3%-47.3%]) in the standard care group (P = .03; **Table 2**). The adjusted between-group difference was 10.4% (95% CI, 2.3%-18.5%) in a log-binomial model (P = .01). A reduction in CSA-AKI was seen in all stages of

Table 1. Baseline Patient Characteristics

	Extracorporeal blood purification (n = 169)	Standard care (n = 174)
Age, mean (SD), y	68.8 (9)	68.6 (10)
Sex, No. (%)		
Female	56 (33)	63 (36)
Male	113 (67)	111 (64)
Weight, mean (SD), kg	75.1 (15)	75.3 (13)
Body mass index, mean (SD)	27.5 (4)	27.5 (4)
Medical history, No. (%)[a]		
High blood pressure	118 (70)	132 (76)
Dyslipidemia	86 (51)	80 (46)
Diabetes	56 (33)	48 (28)
Chronic heart failure	51 (30)	50 (29)
Chronic atrial fibrillation	44 (26)	43 (25)
Chronic obstructive pulmonary disease	27 (16)	42 (24)
Chronic kidney disease stage 1-3[b]	34 (20)	29 (17)
Currently smokes	24 (14)	37 (21)
Alcohol misuse	5 (3)	6 (3)
Chronic liver failure	2 (1)	4 (2)
Medications, No. (%)		
Statins	109 (65)	91 (52)
ACEI or ARB	98 (58)	100 (58)
Diuretics	79 (48)	88 (51)
Aspirin	62 (37)	46 (26)
β-Blockers	9 (5)	10 (6)
Baseline creatinine, mean (SD), mg/dL	1.02 (0.33)	1.04 (0.35)
Left ventricular ejection fraction, mean (SD), %	58 (11)	58 (10)
EuroSCORE II, median (IQR)[c]	2.62 (1.67-4.08)	2.22 (1.47-3.85)
Underwent surgical procedure, No. (%)[d]		
CABG and/or valve replacement and/or ascending aorta	68 (40)	61 (35)
Double valve replacement	45 (27)	55 (32)
Ascending aorta plus valve replacement	33 (20)	42 (24)
Single valve replacement	10 (6)	12 (7)
Triple valve replacement	13 (8)	4 (2)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft.

SI conversion: To convert creatinine to µmol/L, multiply by 88.4.

[a] Medical history was obtained from patient interview and the review of electronic medical records. See eTables 1 and 2 in Supplement 3 for baseline comorbidities and previous treatments.

[b] Chronic kidney disease (CKD) was classified according to Kidney Disease Improving Global Outcomes 2012 guidelines. The worst estimated glomerular filtration rate (eGFR) in the 6 mo before or at admission was used based on Cockcroft-Gault equation. Stage 1: eGFR ≥90 mL/min/1.73 m^2; stage 2: eGFR of 60-89 mL/min/1.73 m^2; stage 3: eGFR of 30-59 mL/min/1.73 m^2; stage 4: eGFR of 15-29 mL/min/1.73 m^2; stage 5: eGFR <15 mL/min/1.73 m^2 or receiving dialysis. Patients with eGFR <60 mL/min/1.73 m^2 for 3 mo are defined as having CKD.

[c] European System for Cardiac Operative Risk Evaluation (EuroSCORE) II represents and predicts the risk of in-hospital mortality after major cardiac surgery. For elective major cardiac surgery, scores range from 0.8% to hypothetically >90% in urgent major cardiac surgery with severe risk factors associated (with no study exclusion criteria).

[d] Overall, 90% of operations performed matched with the intended.

Table 2. Primary Outcome of Cardiac Surgery–Associated Acute Kidney Injury (CSA-AKI)

Outcome	Mean (SD)		Unadjusted		Adjusted	
	Extracorporeal blood purification (n = 169)	Standard care (n = 174)	Difference (95% CI)[a,b]	*P* value[c]	Difference (95% CI)[a,b]	*P* value[c]
Primary outcome						
Occurrence of CSA-AKI by day 7, No./total No. of patients (%)	48/169 (28.4)	69/174 (39.7)	11.25 (1.30 to 21.21)	.03	10.42 (2.34 to 18.49)	.01
Elements of primary outcome						
Peak serum creatinine, mg/dL[d]	1.26 (0.61)	1.39 (0.89)	0.13 (−0.03 to 0.30)	.11		
Oliguria >6 h[e]	22 (13)	35 (20)	7.14 (−0.83 to 15.10)	.08		
CSA-AKI						
I	26 (15)	35 (20)	4.73 (−3.34 to 12.80)			
II	17 (10)	24 (14)	3.73 (−3.11 to 10.58)			
III	5 (3)	1 (6)	2.79 (−1.51 to 7.09)			
II/III	22 (13)	34 (20)	6.52 (−1.25 to 14.30)	.08		
Post hoc exploratory analysis related to primary outcome						
Kidney replacement therapy, No./total No. of patients (%)	3/169 (1.8)	6/174 (3.5)	1.67 (−1.69 to 5.04)	.50		
Early CSA-AKI (first 48 h)	39 (23)	57 (33)	9.68 (0.25 to 19.11)	.05		
AKI						
Transitory (resolved <48 h)	23 (59)	35 (61)	2.43 (−7.93 to 12.79)	.98		
Persistent (>48 h)	16 (41)	22 (39)				

SI conversion: To convert creatinine to µmol/L, multiply by 88.4.

[a] Mean difference for continuous variables and percentage difference for categorical variables.

[b] Unadjusted results: *t* test for continuous variables and Wilson method with continuity correction for categorical variables. Adjusted results: log-binomial model.

[c] Unadjusted results: *t* test for continuous variables and χ^2 or Fisher exact test for categorical variables. Adjusted results: log-binomial model.

[d] Serum creatinine concentration during the first 7 days after cardiac surgery. Higher value during the first 7 days was used to classify CSA-AKI category.

[e] CSA-AKI categories represent the severity of acute kidney injury based on serum creatinine increase and/or urine output decrease and are determined by the worst AKI stage according to KDIGO (Kidney Disease Improving Global Outcome), identified within the first 7 days after cardiac surgery. Oliguria >6 hours defined as urine output <0.5 mL/kg/h for >6 hours.

CSA-AKI, although the difference was not statistically significant (*P* > .05). KRT was performed in 1.8% of patients in the EBP group vs 3.5% of patients in the standard care group (Table 2; eFigure 2 in Supplement 3). Subgroup analysis suggested potential benefit to EBP in patients with CKD, diabetes, hypertension, low LEVF (<40%), and lower body mass index (**Figure 2**). In a post hoc exploratory analysis, these results remained consistent when patients receiving ultrafiltration (18.1%) were removed from the primary analysis (*P* = .03) (eTable 3 in Supplement 3). Another post hoc exploratory analysis including all patients with CSA-AKI showed that early CSA-AKI (within 48 hours after the surgical procedure) was present in 96 patients (82%), with 39 patients (23% [95% CI, 17%-30%]) in the EBP group vs 57 (34% [95% CI, 27%-42%]) in the standard care group (*P* = .046). Among those with early CSA-AKI, there was no significant difference in persistent CSA-AKI (41% in the EBP group vs 39% in the standard care group; *P* = .98; Table 2).

No significant differences (*P* > .05) were observed in 4 of the 5 predefined clinical secondary end points (**Table 3**). The median (IQR) ICU length of stay (3 [2-6] days in the EBP group vs 3 [2-5] days in the standard care group) and median hospital length of stay (13 [10-20] days in the EBP group vs 13 [10-19] days in the standard care group) presented no significant differences between the groups (*P* > .05). Among patients in whom circulatory cytokines were measured (106 in the EBP group and 99 in the standard care group), significant reductions in tumor necrosis factor α and interleukin 8 plasma concentrations during the surgical procedure were found in the EBP vs standard care group (*P* < .05; Table 3 and eFigure 3 in Supplement 3). During ICU admission, biomarker concentrations were not significantly different between the groups (*P* > .05), except for C-reactive protein at day 3 (*P* = .01) (Table 3; eTable 4 in Supplement 3).

In a multivariable regression analysis, EBP group assignment (OR, 0.72 [95% CI, 0.55-0.92]; *P* = .007), age, body mass index, CKD, and SOFA score were independently associated with CSA-AKI within the first 7 days after the cardiac operation (eTables 5 and 6 in Supplement 3).

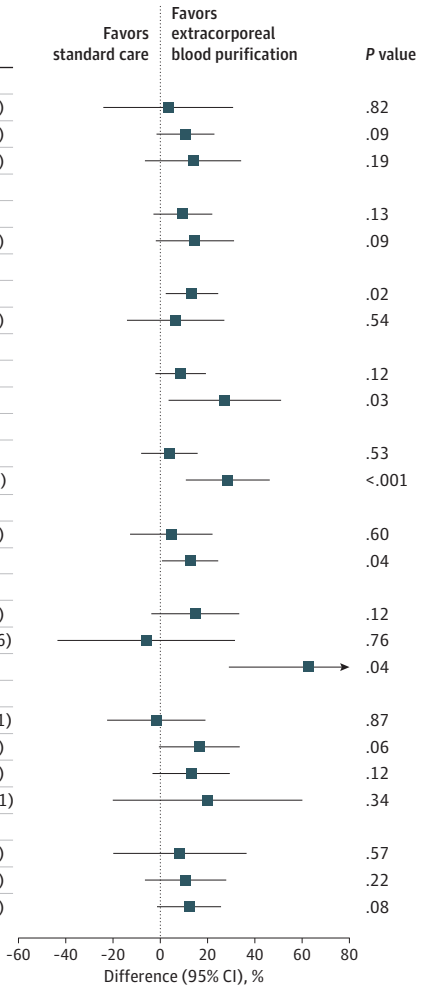
No differences were observed between the groups in surgical complications related to the use of EBP (eTable 7 in Supplement 3) or complications occurring during ICU stay (eTable 8 in Supplement 3).

Discussion

Among patients undergoing cardiac surgery at high risk of AKI, a nonselective EBP device within the CPB circuit reduced the rate of CSA-AKI within 7 days of randomization. These results were consistent when a sensitivity analysis was performed with subgroup differences for CKD, diabetes, and low

Figure 2. Risk Factors for Cardiac Surgery–Associated Acute Kidney Injury (CSA-AKI) Within 7 Days

Subgroup	No. of patients with CSA-AKI/total No. (%)		Between-group difference (95% CI), %	P value
	Extracorporeal blood purification (n = 169)	Standard care (n = 174)		
Age, y				
<55	2/12 (16.7)	4/20.0 (20)	3.3 (-24.1 to 30.8)	.82
55-75	30/117 (25.6)	37/102 (36.3)	10.6 (-1.6 to 22.9)	.09
>75	16/40 (40.0)	28/52 (53.8)	13.8 (-6.5 to 34.2)	.19
Sex				
Male	34/113 (30.1)	44/111 (39.6)	9.6 (-2.9 to 22.0)	.13
Female	14/56 (25.0)	25/63 (39.7)	14.7 (-1.9 to 31.2)	.09
Body mass index				
<30	28/123 (22.8)	47/130 (36.2)	13.4 (2.3 to 24.5)	.02
≥30	20/46 (43.5)	22/44 (50.0)	6.5 (-14.1 to 27.1)	.54
Chronic kidney disease				
No	35/135 (25.9)	50/145 (34.5)	8.6 (-2.1 to 19.3)	.12
Yes	13/34 (38.2)	19/29 (65.5)	27.3 (3.5 to 51.1)	.03
Diabetes				
No	36/113 (31.9)	45/126 (35.7)	3.9 (-8.1 to 15.8)	.53
Yes	12/56 (21.4)	24/48 (50.0)	28.6 (10.8 to 46.3)	<.001
Hypertension				
No	11/51 (21.6)	11/42 (26.2)	4.6 (-12.8 to 22.1)	.60
Yes	37/118 (31.4)	58/132 (43.9)	12.6 (0.7 to 24.5)	.04
Left ventricular ejection fraction, %				
>50	17/51 (33.3)	26/54 (48.1)	14.8 (-3.8 to 33.4)	.12
40-50	5/12 (41.7)	5/14 (35.7)	-6.0 (-43.5 to 31.6)	.76
<40	3/8 (37.5)	4/4 (100)	62.5 (29 to 96)	.04
Surgical procedure				
Ascending aorta plus valve replacement	10/33 (30.3)	12/42 (28.6)	-1.7 (-22.5 to 19.1)	.87
Double or triple valve replacement	16/58 (27.6)	26/59 (44.1)	16.5 (-0.6 to 33.6)	.06
CABG plus valve replacement and/or aorta	19/68 (27.9)	25/61 (41.0)	13.0 (-3.3 to 29.4)	.12
Endocarditis	3/10 (30.0)	6/12 (50.0)	20.0 (-20.1 to 60.1)	.34
Cardiopulmonary bypass duration, min				
<90	7/21 (33.3)	10/24 (41.7)	8.3 (-19.9 to 36.5)	.57
90-120	15/56 (26.8)	21/56 (37.5)	10.7 (-6.5 to 27.9)	.22
>120	26/92 (28.3)	38/94 (40.4)	12.2 (-1.4 to 25.7)	.08



CABG indicates coronary artery bypass graft.

left ventricular ejection fraction. No increase in adverse events was observed.

Most previous studies of EBP techniques have focused on patients with sepsis and do not consistently demonstrate an impact on organ dysfunction. This absence of clinical benefit often correlates with an ineffective decrease of the proposed molecular targets.[17,18] There are several potential reasons for this, not least the heterogeneous nature of the patients together with differences in the timing of the intervention, which is often much later than the original injury in patients with sepsis. However, some previous observational studies in patients undergoing cardiac surgery have shown encouraging results with the use of nonselective EBP devices when evaluating the elimination of cytokines or even possible damage-associated molecular patterns, such as free hemoglobin.[11,19,20] A 2022 trial showed no benefit in decrease of postoperative organ dysfunction despite a temporary reduction in cytokine concentrations during the cardiac operation.[11] Amidst these variable results, EBP devices connected to CPB are widely used in many cardiac surgery centers.[21]

The primary end point of the study was CSA-AKI within 7 postoperative days, as defined by consensus criteria.[14] Most of the observed CSA-AKI was early (within the first 48 hours after surgical procedure), transitory (recovered within 2 days), and mild (KDIGO stage 1). Of interest, the reduction in CSA-AKI with EBP was observed in the first 24 hours after the cardiac surgical procedure and maintained during the first week. This early, but persistent, effect of EBP suggests further consideration of the technique during the CPB and not after the procedure.[12,21] Oliguria in the first hours after the surgical procedure may be confounded by related changes in volume status, which could lead to misclassification of CSA-AKI.[22] To avoid this potential bias, immediate postoperative urine output was not included as CSA-AKI criteria.

No differences were found in secondary end points. However, patients with CSA-AKI in this study had longer (though not statistically significant) ICU and hospital length of stay and increased hospital mortality. The intervention effect was corroborated in an exploratory multivariable analysis and, by the trends of interleukin-8 and tumor necrosis

Table 3. Secondary and Post Hoc Exploratory Outcomes

	Median (IQR)		
	Extracorporeal blood purification (n = 169)	Standard care (n = 174)	Unadjusted difference (95% CI)[a,b]
Prespecified secondary outcomes[c]			
ICU length of stay, d[d]	3 (2 to 6)	3 (2 to 5)	0 (−1 to 1)
Hospital length of stay, d	13 (10 to 20)	13 (10 to 19)	0 (−3 to 0)
Survival at day 7, No. (%)	167 (99)	172 (99)	0.03 (−2.27 to 2.34)
Survival at day 28, No. (%)	163 (96)	169 (97)	0.68 (−3.64 to 4.99)
Survival at day 90, No. (%)	160 (95)	167 (96)	1.30 (−3.75 to 6.36)
Cytokine variation during surgery [(T1 − T0)/T0][e]			
IFN-γ	−31.3 (−51.0 to −12.1) [n = 106]	−24.2 (−45.3 to −5.7) [n = 99]	7.2 (−5.0 to 19.2)
IL-2	−29.6 (−52.1 to −9.3) [n = 106]	−21.6 (−42.3 to −4.4) [n = 99]	8.1 (−5.5 to 18.6)
IL-6	642 (208 to 1655) [n = 106]	514 (154 to 1982) [n = 99]	−128.4 (−506.8 to 172.9)
IL-8	135 (64.7 to 350) [n = 106]	241 (133 to 639) [n = 99]	106.2 (−3.8 to 213.1)
IL-10	4486 (1391 to 12 376) [n = 106]	4100 (976 to 12 920) [n = 99]	−386.8 (−3305.6 to 2864.6)
TNF	−2.5 (−21.3 to 42.3) [n = 106]	25.3 (0 to 91.8) [n = 99]	27.7 (9.0 to 47.4)
Post hoc exploratory outcomes			
Cardiopulmonary bypass duration, mean (SD), min	132 (46.7)	127 (39.2)	1 (−8 to 9)
SOFA ICU[f]	6 (5 to 7) [n = 161]	6 (5 to 7) [n = 172]	0 (−1 to 0)
APACHE II ICU[g]	13 (11 to 16) [n = 132]	14 (11 to 16) [n = 150]	1 (−1 to 2)
Days free from vasopressor/inotrope support[h]	11 (8 to 17)	11 (8 to 16)	0 (−2 to 1)
Use of vasopressor/inotrope support, No. (%)[h]	143 (85)	145 (83)	−1.28 (9.04 to 6.48)
Days free from IMV[h]	13 (9 to 19)	13 (9 to 17)	0 (−2 to 0)
Days free from KRT[h]	13 (10 to 20)	13 (10 to 19)	0 (−3 to 0)
Laboratory values			
Serum creatinine at 7 d, mg/dL	0.85 (0.69 to 1.06) [n = 159]	0.86 (0.72 to 1.05) [n = 165]	0.01 (−0.08 to 0.09)
Serum creatinine at 28 d, mg/dL	0.93 (0.77 to 1.13) [n = 124]	0.93 (0.76 to 1.13) [n = 123]	−0.01 (−0.12 to 0.04)
Serum creatinine at 90 d, mg/dL	0.89 (0.79 to 1.16) [n = 127]	0.97 (0.76 to 1.18) [n = 125]	0.08 (−0.03 to 0.14)
Lactate at ICU admission, mmol/L	1.40 (1.10 to 1.90) [n = 167]	1.40 (1.00 to 1.90) [n = 170]	0 (−0.2 to 0.1)
Lactate 8 h after admission, mmol/L	1.80 (1.27 to 2.40) [n = 155]	1.85 (1.30 to 2.60) [n = 158]	0.05 (−0.2 to 0.3)
C-reactive protein (day 3), mg/L[i]	215 (156 to 287) [n = 81]	237 (172 to 302) [n = 85]	22 (3.2 to 45)
GPT (day 1), U/L	19 (15 to 30) [n = 148]	19 (13 to 28) [n = 145]	−0.1 (−3.6 to 3)
Troponin T (8 h), ng/L[j]	884 (522 to 1586) [n = 99]	944 (586 to 1648) [n = 110]	60.5 (226.16 to 385.7)
Troponin I (24 h), ng/L[k]	662 (387 to 1148) [n = 106]	636 (412 to 1125) [n = 111]	−26 (−214.63 to 136.5)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; GPT, glutamic-pyruvic transaminase; ICU, intensive care unit; IFN, interferon; IMV, invasive mechanical ventilation; KRT, kidney replacement therapy; SOFA, Sequential Organ Failure Assessment; T0, baseline; T1, end of surgery; TNF, tumor necrosis factor.

[a] Median difference for continuous variables and percentage difference for categorical variable.

[b] CI: boostraping for continuous variables and Wilson method with continuity correction for categorical variables.

[c] Krukall-Wallis for continuous variables and χ^2 or Fisher exact test for categorical variable.

[d] Patients who left and returned to the ICU (10 [3%]) were considered as not being discharged from the ICU if readmission was within 48 hours (2 patients [0.5%]). For the other 8 patients, ICU days were calculated as the sum of both admissions.

[e] See extended information on cytokine variation in eFigure 3 in Supplement 3.

[f] SOFA evaluates 6 organ functions ranging from 0 (normal function) to 4 (organ failure). Total scores range from 0 to 24.

[g] APACHE II estimates ICU mortality based on laboratory values and patient signs, taking both acute and chronic disease into account. It is calculated within the first 24 hours of ICU admission. Range, 0-71; higher scores indicate an increasing risk of hospital death.

[h] Days free of organ support (vasopressor, mechanical ventilation, and kidney replacement therapy) are considered until hospital discharge or 28 days, whichever takes place first.

[i] C-reactive protein kinetics are represented in eTable 3A in Supplement 3 and had a peak at 72 hr after cardiac surgery.

[j] Troponin T kinetics are represented in eTable 3B in Supplement 3 and had a peak at 24 hours after cardiac surgery.

[k] Troponin I kinetics are represented in eTable 3C in Supplement 3 and had a peak at 8 hours after cardiac surgery.

factor α while receiving CPB, compared with the standard care group in a subset of patients with biospecimens collected. Additional hypothesis-generating results included the consistency of the treatment effect among patients with CKD, reduced LEVF, or diabetes. Because the EBP technique performed was safe, further work should substantiate the heterogeneity of EBP treatment among different patient subtypes.

Limitations

This study has several limitations. First, the true rate of CSA-AKI among patients transferred out of the ICU is unknown because urine output was not accurately collected during the full 7 postoperative days. Second, changes in serum creatinine can be influenced by volume status during ICU stay, and this may contribute to CSA-AKI.[23] Third, post hoc exploratory analyses suggested that CSA-AKI was primarily early and transitory during intensive care, and these results may not be generalizable to future patients in whom AKI may be late and persistent. Fourth, blinding in the operating room was not possible, and this could have influenced some decisions such as fluid administration or ultrafiltration use. Fifth, missing data were present in some of the variables specified in the study protocol (eg, cytokines or creatinine after ICU discharge). Sixth, the case-mix effect of having only 2 recruiting centers could be a limitation to the generalizability of the study results.

Conclusions

The use of a nonselective EBP device connected to the CPB circuit in a nonemergent population of patients undergoing cardiac surgery was associated with a significant reduction of CSA-AKI in the first 7 days after the surgical procedure.

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