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Original Article

Center-mediated Differences in Postoperative Acute Kidney Injury Rates: A Post Hoc Analysis of the PROTECTION Trial

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Objectives: The recently published PROTECTION trial (Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery) demonstrated that, in adult cardiac surgery patients, preoperative amino acid (AA) administration has a protective effect on renal function. However, large differences were observed within the participating centers. We aimed to investigate whether such center effects would remove the impact of AA on the prevention of cardiac surgery-associated acute kidney injury (CSA-AKI).

Design: A post hoc analysis of data from the PROTECTION trial was performed.

Setting: Multi-institutional data from centers that participated in the PROTECTION trial.

Participants: Adult patients undergoing cardiac surgery enrolled in the PROTECTION trial.

Interventions: Two centers showed a significantly lower rate of CSA-AKI with respect to the pooled rate in all centers (low-rate centers) and 3 centers had a significantly higher rate (high-rate centers [HR-C]). These centers were compared for preoperative and intraoperative variables.

Results: Patients in the HR-C were significantly ($p = 0.001$) older, with lower left ventricular ejection fraction and hemoglobin values, a higher rate of class III and IV New York Heart Association functional class, arterial hypertension, previous myocardial infarction, diabetes, peripheral vascular disease, and more frequently received myocardial revascularization. During surgery, patients in the HR-C group had a longer aortic cross-clamp time, higher temperature on cardiopulmonary bypass, and received diuretics and hemofiltration at a lower rate. Additionally, a greater number of patients in the HR-C group required norepinephrine. However, once corrected for such a center effect, AA remained significantly independently associated with a reduction in CSA-AKI (relative risk, 0.79).

Conclusions: HR-Cs treated patients with greater severity (unmodifiable risk factors) and received different operative and perioperative management. Taking into account such center effects, however, AA therapy remained independently associated with CSA-AKI prevention.

Key Words: acute kidney injury; amino acids; cardiac surgery; cardiopulmonary bypass; perioperative care

IN THE RECENTLY PUBLISHED PROTECTION trial (Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery), cardiac surgery patients were randomized to receive either an intravenous infusion of a balanced mixture of amino acids (AAs) or placebo from the induction of anesthesia for up to a maximum of 3 postoperative days.[1,2] The study showed that the treatment arm had a significantly ($p = 0.002$) lower rate of cardiac surgery-associated acute kidney injury (CSA-AKI), with a relative risk (RR) of 0.85 and a 95% confidence interval (CI) of 0.35 to 0.87. The exact mechanisms of action of AAs on renal function remain unclear, but several hypotheses have been raised, including the recruitment of renal function reserve.[3–6]

This important result was obtained in a sample size of 3511 patients recruited at 22 centers located in Europe, Asia, and Australia. Overall, 10 centers contributed with fewer than 30 patients; 5 centers with 31 to 100 patients; and the 7 top-recruiting centers contributed with more than 100 patients. The overall incidence of CSA-AKI (treatment and control arm pooled together) was 29.3%. However, when analyzed by a single center, it ranged from 9% to 56%. Even excluding institutions with a low sample size ($\leq$30), the CSA-AKI incidence ranged from 20% to 51%. These data suggest a potential center effect on the incidence of CSA-AKI and introduce the need for including the recruiting center within the risk factors for CSA-AKI.

The present post hoc analysis of the PROTECTION trial is aimed to (i) verify and quantify the impact of the treatment (AAs) after correction for the recruiting center and (ii) investigate the differences between centers with a low vs high CSA-AKI, in terms of patient risk factors.

Methods

Patient Population and Definitions

For the purposes of the present post hoc analysis, we used the original database of the PROTECTION trial.[1] Patient data were originally collected as part of the main trial using standardized case report forms in accordance with the study's predefined protocols and data quality control procedures. No changes or amendments were made to the original dataset and all variables from the original dataset were included in the present analysis. No imputation for missing data was applied.

Statistics

The overall CSA-AKI rate was calculated by pooling together data from the treatment and placebo arms in the whole patient population. Subsequently, the CSA-AKI rate of each center was compared with the overall CSA-AKI rate using a RR analysis with 95% CI. Centers with a significantly ($p < 0.05$) lower rate of CSA-AKI with respect to the overall CSA-AKI rate were identified and labeled as low-rate centers (LR-Cs), whereas centers with a significantly ($p < 0.05$) higher CSA-AKI rate with respect to the overall CSA-AKI rate were labeled as high-rate centers (HR-Cs). LR-Cs and HR-Cs were

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pooled in a LR-C group and an HR-C group. Centers with a CSA-AKI rate comparable with the mean value observed in all centers (ie, 29%) were excluded from the present comparative analysis, which focused on LR-C ie HR-C groups only. These 2 groups were analyzed for patient or procedure-related factors using parametric and non-parametric tests as appropriate, in order to investigate the factor(s) being associated with a low or high CSA-AKI rate.

The normality of the sample distributions was verified using the Shapiro-Wilks test. Continuous variables are presented either as means with standard deviations (SD) or as medians with interquartile ranges, based on their distribution. For these continuous variables, comparisons were conducted using the Wilcoxon rank-sum test for skewed distributions and the t-test for those that were normally distributed. Categorical variables were represented as counts and relative proportions, with comparisons made using either a 2-tailed chi-square test or Fisher's exact test, as appropriate. Differences between groups for secondary outcomes were quantified as RR or mean differences, along with their respective 95% CI, for binary and continuous variables respectively.

The interaction between the experimental variable (AAs vs placebo) and the covariate (centers) as determinants of CSA-AKI was investigated using logistic regression analysis with CSA-AKI as the dependent (binary) variable and treatment and center as the independent (categorical) variables. Odds ratios with 95% CI were produced.

To identify predictors for the primary outcome, univariable logistic regression analyses were performed. Baseline variables that demonstrated a probable association with the primary outcome ($p < 0.1$) in the univariable analysis were subsequently included in a multivariable logistic regression model, using backward stepwise selection. The treatment allocation and a comparison between LR-Cs and HR-Cs were included in the model.

A p value of less than 0.05 was considered to indicate statistical significance. For the purposes of the present post hoc analysis, SAS (Statistical Analysis System Inc, Cary, NC, release 9.4) and R software, version 4.4.1 (R-project) were used, and a MedCalc (Ostend, Belgium) computerized package was implemented.

Results

The overall rate of CSA-AKI (all centers, treatment and control arms) was 29.3% (95% CI, 27.8%–30.8%). The CSA-AKI rate for each participating center is reported in Fig 1. On a multivariable logistic regression analysis, AA treatment had an odds ratio of 0.79 (95% CI, 0.68–0.92; p = 0.002) and the center had a p value for association with CSA-AKI of less than 0.001. The individual rate of CSA-AKI for each center was compared with an overall rate of 29.3% using a RR analysis. The results are reported in Fig 2. There were 2 centers with a CSA-AKI rate significantly lower than the overall rate (LR-C, 1983 patients), and 3 centers with a CSA-AKI rate significantly higher (HR-C, 923 patients). These 2 groups were compared for preoperative (patient-related) and operative

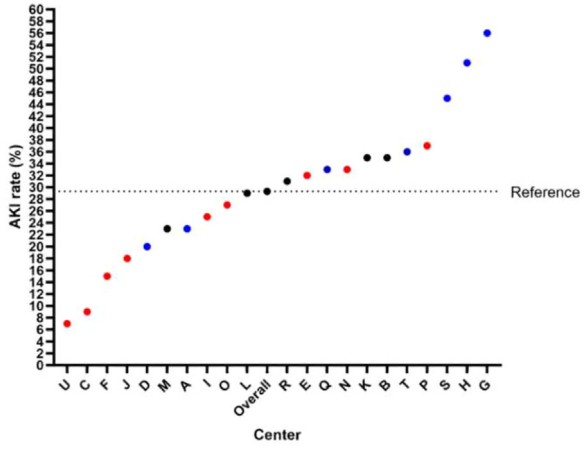

Fig 1. Acute kidney injury (AKI) rate in each center. The reference line is the overall (all centers, treatment, and control arms) AKI rate. *Red dots* are low (≤30 patients) recruiting centers, *black dots* are medium (31–100 patients) recruiting centers, and *blue dots* are high (>100 recruiting centers).

(procedure-related) factors. The results are shown in Tables 1 and 2.

The patients' profile was generally that of at a higher risk in the HR-C group, with a significantly older age and greater number of comorbidities including anemia, arterial hypertension, previous myocardial infarction, diabetes, and peripheral vascular disease. The cardiac function pattern was worse in the HR-C group, with a lower left ventricle ejection fraction and a higher New York Heart Association functional class. Patients operating in the HR-C received more preoperative medications, in particular statins, antiplatelet agents, and diuretics.

The procedural factors (Table 2) showed additional significant between-group differences. Patients in the HR-C group had a higher rate of redo operations, a longer aortic cross-clamp time, were more likely to receive coronary surgery than valve surgery, were treated at a higher temperature on cardiopulmonary bypass (CPB), and received less loop diuretics and hemofiltration during CPB.

An important difference pertains to the intraoperative use of catecholamines: patients receiving epinephrine were 10 times more likely to be in the LR-C group than in the HR-C group; conversely, the number of patients in the HR-C group who received norepinephrine was more than double that in the LR-C group.

The general outcome of the patients in the 2 groups greatly differed (Table 3). Patients in the HR-C group had a mortality rate that was about 3 times higher than patients in the LR-C (at any observation time). They were weaned from mechanical ventilation in a significantly ($p < 0.001$) shorter time, but remained in the intensive care unit and in the hospital for significantly longer ($p = 0.014$ and $p < 0.001$, respectively).

Univariable and multivariable analyses of the association of baseline variables, trial intervention, and center with the rate of AKI are shown in Table 4 and confirm the independent association of AA infusion with reduced AKI with an odds ratio of 0.80 (95% CI, 0.69–0.96). In a sensitivity analysis, we

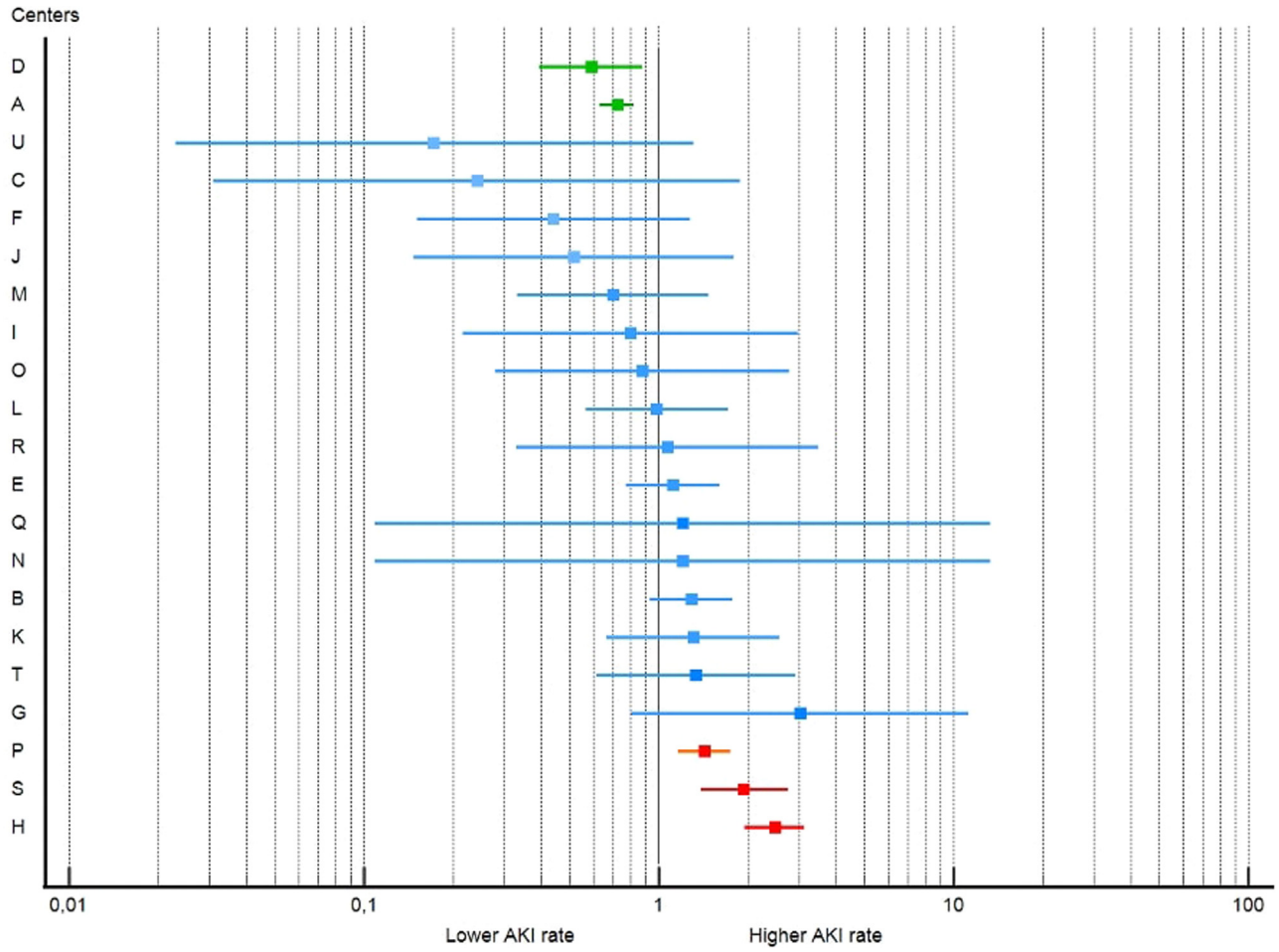

Fig 2. Reference values. (1) Overall AKI rate (all centers, treatment and control arm). *Green dots* are centers with an AKI rate significantly lower than reference (LR-C). *Red dots* are centers with an AKI rate significantly higher than reference (HR-C). *Blue dots* are centers with an AKI rate not significantly different from the overall rate. AKI, acute kidney injury.

performed a direct comparison between the AKI rate in LR-Cs vs HR-Cs according to treatment arm (ie, AAs vs placebo). Notably, a significant reduction in the AKI rate was observed in LR-Cs but not in HR-Cs (Supplementary Material, Supplementary Fig 1).

Discussion

Key Findings

The main results of our study are that there was significant heterogeneity in the CSA-AKI rate in the 22 centers that took part in the PROTECTION study and that, after correction for center, the AAs maintain their beneficial effects. Moreover, centers with a CSA-AKI rate significantly higher than the overall pooled rate had a patient profile of higher severity compared with patients belonging to centers at a significantly lower CSA-AKI rate; as expected, the outcome of patients in the HR-C group was significantly worse than that observed in patients in the LR-C group. Notably, in centers at a low AKI rate (ie, LR-Cs), the effect of AA treatment induced a significant containment of the AKI rate, whereas it did not in centers at a high AKI rate (ie, HR-Cs). Although the distribution of CSA-AKI across participating institutions was already reported in the PROTECTION trial,[1] the present post hoc analysis specifically focused on center-based differences and modifiable factors with clear clinical relevance that could guide anesthesia strategies for intraoperative AKI prevention. Notably, even after adjustment for multiple confounders, including more complex patient profiles, being treated in an LR-C remained independently associated with a lower CSA-AKI risk, suggesting that additional modifiable, center-related factors play a decisive role.

Relationship to Previous Studies

The heterogeneity of the CSA-AKI rate is commonly found in registries and clinical studies. A recent multicenter, international, randomized, controlled trial with CSA-AKI as the outcome showed CSA-AKI rates ranging from 9% to 30%.[7] This heterogeneity is justified by differences in patient population, type of surgery, surgical technique, CPB conduct, perioperative use of drugs, and, of course, differences in technical and human skills. The first 2 items can be considered unmodifiable risk factors, whereas the others can be modified. In our study,

Table 1
Baseline Characteristics of the Patient Population

	LR-C (n = 1983)	HR-C (n = 923)	p Value
Amino acids arm	991 (50)	464 (50.3)	0.88
Placebo arm	992 (50)	459 (49.7)	
Age (years)	65 (55–72)	69 (62–74)	<0.001
Female sex	641 (32.3)	263 (28.5)	0.038
Body mass index	25 (23–28)	26 (24–29)	<0.001
Preoperative serum creatinine (mg/dL)	0.96 (0.83–1.11)	0.92 (0.78–1.09)	<0.001
Preoperative hemoglobin concentration (g/dL)	14.1 (13.0–15.1)	13.3 (12.1–14.4)	<0.001
Left ventricular ejection fraction (%)	60 (55–64)	55 (50–60)	<0.001
New York Heart Association functional class			
I	466 (23.5)	228 (24.7)	<0.001
II	1290 (65.1)	380 (41.2)	
III	222 (11.2)	277 (30)	
IV	5 (0.3)	38 (4.1)	
Current smoker	261 (13.2)	159 (17.2)	0.005
Race or ethnicity			0.15
White	1961 (98.9)	906 (98.2)	
Hispanic	8 (0.4)	9 (1.0)	
Other	14 (0.7)	8 (0.9)	
Medical condition			
Arterial hypertension on medical treatment	1040 (52.5)	699 (75.7)	<0.001
Previous myocardial infarction	167 (8.4)	237 (25.7)	<0.001
Atrial fibrillation	389 (19.6)	126 (13.7)	<0.001
Previous stroke or transient ischemic attack	82 (4.1)	52 (5.6)	<0.001
Cardiac catheterization in the past 48 hours	500 (25.2)	58 (6.3)	<0.001
Diabetes in medical treatment	233 (11.8)	270 (29.3)	<0.001
Peripheral vascular disease	258 (13.0)	242 (26.2)	<0.001
Previous cardiac surgery	186 (9.4)	61 (6.6)	0.01
Preoperative medical therapy			
Beta-blockers	993 (50.1)	474 (51.4)	0.53
ARBs or ACE inhibitors	1000 (50.4)	465 (50.4)	0.98
Statin	683 (34.4)	564 (61.1)	<0.001
Antiplatelet	590 (29.8)	476 (51.6)	<0.001
Diuretics	669 (33.7)	385 (41.7)	<0.001
Anticoagulant	390 (19.7)	189 (20.5)	0.62

NOTE. Data are presented as number (%) or median (interquartile range).
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin renin blocker; HR-C, high-risk centers; LR-C, low-risk centers.

Table 2
Intraoperative Parameters of the Two Groups

	LR-C (n = 1983)	HR-C (n = 923)	p Value
Aortic cross-clamp time (min)	90 (71–115)	96 (75–121)	<0.001
Surgery type			
CABG	475 (24)	497 (53.9)	<0.001
Mitral valve	930 (46.9)	198 (21.5)	<0.001
Aortic valve	704 (35.5)	394 (42.7)	<0.001
Other	183 (9.2)	50 (5.4)	<0.001
Intraoperative loop diuretics	1074 (54.2)	197 (21.3)	<0.001
Lowest temperature during CPB	30 (29–32)	32 (30–34)	<0.001
Use of hemofiltration during CPB	194 (9.8)	47 (5.1)	<0.001
Intraoperative vasoactive and inotropic drugs (any kind)	1277 (64.4)	579 (62.7)	0.41
Epinephrine	1104 (55.7)	47 (5.1)	<0.001
Norepinephrine	340 (17.2)	401 (43.5)	<0.001
Dobutamine	0 (0)	187 (20.3)	<0.001
Other	13 (0.7)	24 (2.6)	<0.001

NOTE. Data are number (%) or median (interquartile range).
Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; HR-C, high-risk centers; LR-C, low-risk centers.

many unmodifiable risk factors were more common in the HR-C group.

There are different risk factors that predict CSA-AKI, and many of the factors differentiating HR-Cs from LR-Cs are risk factors for CSA–AKI.[8-11] They include age, left ventricular ejection fraction, New York Heart Association functional class, recent myocardial infarction, diabetes, peripheral vascular disease, and preoperative use of diuretics.[8–11] Even preoperative anemia is a risk factor for CSA-AKI, and patients in the HR-C group had lower preoperative hemoglobin levels.[12] Therefore, the preoperative condition of patients treated at HR-Cs justify an increased risk for CSA-AKI in the HR-C. It may appear surprising that patients in the HR-Cs had significantly ($p < 0.001$) lower preoperative values of serum creatinine than patients in the LR-Cs. Actually, this is not uncommon.

Our group previously demonstrated an inverse relationship between preoperative serum creatinine levels and the likelihood of developing stage 1 CSA-AKI, where lower baseline creatinine levels are associated with a higher risk of a 50% increase in creatinine levels, meeting the diagnostic threshold for stage 1 CSA-AKI.[13] Conversely, higher preoperative creatinine levels are linked to an increased likelihood of requiring renal replacement therapy, indicative of more severe kidney injury (ie, CSA-AKI stage 3).

However, there were differences in the intraoperative factors that are of interest, because they are modifiable in many cases. The longer aortic cross-clamp time is not surprising given the patient characteristics in the HR-Cs and CPB duration is a recognized risk factor for CSA-AKI.[14] However, other factors differentiated the HR-C from the LR-C group. We are lacking data on the nadir hematocrit and the nadir oxygen delivery and the mean arterial pressure on CPB. All these factors are recognized as additional CPB-related risk factors for CSA-AKI.[15]

Of great interest, there are some technical aspects that differ between the HR-C and the LR-C groups in the conduct of surgery, CPB, and anesthesia. The patients in the HR-C group were treated at a higher (2°C higher) core temperature; they received intraoperative loop diuretics at a lower rate; and the

Table 3
Postoperative Outcome of the Patient Population

Primary Outcome	LR-C (n = 1983)		HR-C (n = 923)		Relative Risk, Absolute Mean Difference (95% CI)	p Value
	Value	No. With Missing Data	Value	No. With Missing Data		
Incidence of in-hospital AKI (any stage)	451 (22.7)	1	397 (43.1)	0	0.53 (0.47 to 0.59)	<0.001
Stage 1	427 (21.5)	–	347 (37.6)	–	0.57 (0.51 to 0.64)	<0.001
Stage 2	1 (0.05)	–	18 (1.9)	–	0.03 (0.003 to 0.19)	0.03
Stage 3	23 (1.2)	–	32 (3.5)	–	0.33 (0.20 to 0.57)	<0.001
Secondary outcomes						
Use of renal replacement therapy	20 (1.0)	0	24 (2.6)	1	0.39 (0.22 to 0.70)	0.002
Mechanical ventilation duration (hours)	14 (10 to 18)	37	6 (4 to 12)	16	−8.4 (−12.03 to 4.70)	<0.001
Length of stay in intensive care unit (hours)	24 (21 to 65)	8	42 (21 to 69)	10	10.1 (2.1 to 18.1)	0.014
Length of stay in hospital (days)	6 (5 to 8)	1	7 (6 to 12)	0	2.5 (1.77 to 3.23)	<0.001
Mortality in intensive care unit	24 (1.2)	0	41 (4.4)	0	0.27 (0.17 to 0.45)	<0.001
Mortality at 30 days	35 (1.8)	0	52 (5.6)	0	0.31 (0.21 to 0.48)	<0.001
Mortality at 90 days	39 (2.0)	24	58 (6.3)	3	0.32 (0.21 to 0.47)	<0.001
Mortality at 180 days	50 (2.6)	35	70 (7.6)	7	0.34 (0.24 to 0.48)	<0.001

NOTE. Data are number (%) or median (interquartile range).
Abbreviations: AKI, acute kidney injury; CI, confidence interval; HR-C, high-risk centers; LR-C, low-risk centers.

rate of hemofiltration on CPB was one-half that in the LR-C group. Finally, the number of patients who received norepinephrine was significantly ($p < 0.001$) higher (more than double) than in the LR-C.

We can speculate about the mechanisms underlying this pattern, which seems to be attributable to a condition of low mean arterial pressure on CPB: patients in the HR-C group had lower preoperative hemoglobin values, so it is likely that the hematocrit on CPB was lower as well, determining a decrease in viscosity and hence in mean arterial pressure. They were treated at a higher core temperature (32°C), with consequent lower peripheral resistances as compared with the LR-C group (30°C). It is likely that, under this condition, the anesthesiologists/perfusionists were inclined to administer norepinephrine to correct hypotension. The intraoperative use of norepinephrine is associated with CSA-AKI and is probably responsible for the higher CSA-AKI rate in the HR-C group.[16] Based on our results, it seems that hemofiltration on CPB and a liberal use of loop diuretics may be protective of, or at least associated with, a lower CSA-AKI rate.

The clinical outcome in the HR-C group was significantly worse than in the LR-C group, with a severe effect in terms of mortality at any follow-up time. This finding confirms the association between CSA-AKI and morbidity and mortality after cardiac surgery. The association of CSA-AKI with bad outcomes has been found even for minor increases in serum creatinine.[17,18] This finding is confirmed by our study, wherein the great majority (92%) of CSA-AKI events were stage 1.

Additionally, our findings suggest that the beneficial effects of AA treatment become more evident in centers with lower rates of CSA-AKI. In interpreting this result, we must, however, consider that the sample size is larger in these centers (1983 patients) than in HR-Cs (923 patients), thus increasing the significance of small differences. Additionally, HR-Cs tend to manage patients with greater disease severity and perform more complex procedures compared with LR-Cs. We can, therefore, speculate that the greater prevalence of confounding variables and CSA-AKI risk factors in HR-Cs may attenuate the measurable clinical benefits of AA treatment. In contrast, in LR-Cs—where the baseline CSA-AKI risk is lower and patient populations may be more homogeneous—the protective effects of AA treatment may be observed more readily.

Study Limitations

Our study has several limitations. Whereas the preoperative profile of the patients is almost complete for the analysis of CSA-AKI risk factors, there is not a specific CSA-AKI risk stratification according to the existing models.[9–11] Most important, we lack data regarding some procedural risk factors. These include the nadir hematocrit on CPB, the nadir oxygen delivery on CPB, the time of exposure to low oxygen delivery, and the red blood cell transfusion rate on CPB. All these factors have been identified as being associated with CSA-AKI.[14] Such confounders could account for the differences observed and may remove the center effect we report. Nevertheless, HR-Cs had lower preoperative hemoglobin (by nearly 1 g/dL), likely leading to lower intraoperative oxygen content and DO_2, indirectly supporting evidence that a low hemoglobin and reduced oxygen distribution on CPB increase CSA-AKI risk.

Although a single center in the PROTECTION trial enrolled 50% of the study population, which may introduce some bias, the 2 LR-Cs—among the largest institutions—applied distinct

Table 4
Univariate Analysis Between Baseline Variables and Acute Kidney Injury and Multiple Logistic Regression Analysis*: Independent Predictors of In-Hospital AKI

Variable	Unadjusted OR (95% CI)	p Value	Adjusted odds Ratio (95% CI)	p Value
Randomization to amino acids group	0.84 (0.71–0.98)	0.03	0.80 (0.69–0.96)	0.0125
Enrollment in a low-rate center	0.39 (0.33–0.46)	<0.001	0.41 (0.34–0.50)	<0.001
Age	1.05 (1.04–1.06)	<0.001	1.04 (1.03–1.04)*	<0.001
Female sex	0.90 (0.75–1.07)	0.22	–	–
Body mass index†	1.05 (1.03–1.07)	<0.001	–	–
Baseline serum creatinine	1.49 (1.39–1.59)	<0.001	1.44 (1.34–1.54)‡	<0.001
Preoperative hemoglobin concentration	0.88 (0.84–0.91)	<0.001		
Left ventricular ejection fraction	0.96 (0.95–0.97)	<0.001	0.98 (0.97–0.99)§	0.0008
New York Heart Association functional classes III and IV	2.19 (1.81–2.66)	<0.001	–	–
Current smoker	1.04 (0.83–1.30)	0.74	–	–
Medical condition				
Arterial hypertension on medical treatment	1.81 (1.53–2.15)	<0.001	–	–
Previous myocardial infarction	1.59 (1.28–1.98)	<0.001	–	–
Atrial fibrillation	1.74 (1.42–2.12)	<0.001	1.42 (1.14–1.78)	0.002
Previous stroke or transient ischemic attack	1.97 (1.39–2.80)	<0.001	1.49 (1.01–2.19)	0.042
Cardiac catheterization in the past 48 hours	0.65 (0.53–0.81)	<0.001	–	–
Diabetes on medical treatment	2.44 (2.00–2.98)	<0.001	1.65 (1.32–2.06)	<0.001
Peripheral vascular disease	1.87 (1.53–2.28)	<0.001	1.78 (1.32–2.41)	0.0002
Previous cardiac surgery	1.58 (1.20–2.06)	<0.001	–	–
Preoperative medical therapy				
Beta-blockers	1.19 (1.01–1.39)	0.037	–	–
ARB or ACE inhibitor	1.32 (1.13–1.55)	<0.001	–	–
Statin	1.77 (1.50–2.08)	<0.001	–	–
Antiplatelet	1.57 (1.33–1.85)	<0.001	–	–
Diuretics	1.74 (1.48–2.05)	<0.001	–	–
Anticoagulant	1.64 (1.35–1.99)	<0.001	–	–

NOTE. For this multiple logistic regression analysis, we used preoperative variables, the randomization group (amino-acids vs placebo) and the center (low-rate centers vs high-rate centers).
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; NYHA, New York Heart Association; OR, odds ratio.
* For a 1-year increase.
† The body mass index is the weight in kilograms divided by the square of the height in meters.
‡ For an 0.20-mg/dL increase.
§ For a 1-percentage increase.

management strategies, including lower CPB temperatures, more loop diuretics and hemofiltration, and preferential use of epinephrine. These center-specific, modifiable factors further strengthen the findings of our study, suggesting that such interventions may help mitigate the risk of CSA-AKI.

These results remained robust after adjustment for confounders: despite the higher prevalence of risk factors in HR-Cs, patients in LR-Cs still had an approximately 50% lower CSA-AKI rate. This finding indicates that the preoperative patient profile alone does not fully explain center-related differences and highlights the important role of modifiable factors in AKI prevention.

Conclusions

Our study highlights the role of preoperative patient conditions, but also of intraoperative management, as risk factors for CSA-AKI. Within this setting, and after correction for the center-mediated effects, we confirm that AA infusion remains associated with a 20% RR reduction in the rate of CSA-AKI rate. In this context, considering the low cost (ie, approximately 80 Euros) of a 48-hour AA infusion, we advocate for the widespread implementation of this protective strategy to further maximize its potential clinical benefits.

Study registration

ClinicalTrials.gov NCT03709264.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Marco Ranucci: Supervision, Conceptualization. **Fabrizio Monaco:** Supervision, Conceptualization. **Nikola Bradic:** Writing – original draft, Formal analysis. **Maria Venditto:** Writing – review & editing, Investigation, Data curation. **Giuseppe Neri:** Writing – review & editing, Methodology. **Gaia Barucco:** Writing – original draft, Investigation, Data curation. **Lian Kah Ti:** Writing – review & editing, Software, Formal analysis. **Sabrina Porta:** Writing – original draft,

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2025.10.022.

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