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Amino Acid Infusion for Kidney Protection in Cardiac Surgery Patients with Chronic Kidney Disease: A Secondary Analysis of the PROTECTION Trial

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ABSTRACT

Background: In the PROTECTION trial (Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery), intravenous amino acids decreased the occurrence of acute kidney injury in cardiac surgery patients with cardiopulmonary bypass. Recruitment of renal functional reserve may be responsible for such protection. However, patients with chronic kidney disease have diminished renal functional reserve, and amino acids may be less protective in such patients. Thus, a separate investigation of such patients is warranted.

Methods: For this study chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2}, and patients with estimated glomerular filtration rates greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2} served as controls. The primary outcome was the occurrence of acute kidney injury. Secondary outcomes included severity of acute kidney injury, need for and duration of renal replacement therapy, and all-cause mortality.

Results: Among chronic kidney disease patients (n = 812), compared with placebo, amino acids significantly decreased the rate of acute kidney injury (43.1% *vs* 50.3%; relative risk, 0.86; 95% CI, 0.74 to 0.99; $P = 0.041$; number needed to treat = 14) with a median percentage increase in estimated glomerular filtration rate from baseline to postoperative day 3 of 12.7% *versus* 6.5% ($P = 0.002$). In estimated glomerular filtration rate–based chronic kidney disease subgroups (30 to 39, 40 to 49, and 50 to 59 ml · min^{-1} · 1.73 m^{-2}), the amino acid effect was similar (interaction $P = 0.50$). Finally, amino acid infusion decreased the occurrence of severe (stage 3) acute kidney injury (2.7% *vs.* 5.6%; relative risk 0.48; 95% CI, 0.24 to 0.98; $P = 0.038$).

Conclusions: Amino acid infusion protected chronic kidney disease patients undergoing cardiopulmonary bypass from developing acute kidney injury, with an absolute risk reduction of 7% and a number needed to treat of 14 in a cohort with a greater than 45% rate of acute kidney injury. Moreover, it delivered a greater than 50% relative risk reduction in severe acute kidney injury.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Acute kidney injury is common in patients undergoing cardiac surgery with cardiopulmonary bypass and is associated with increased postoperative morbidity and mortality.
- The PROTECTION trial (a multinational randomized trial) recently reported that initiating intravenous amino acid infusion starting in the operating room before cardiac surgery with cardiopulmonary bypass and continuing the infusion for up to 72 h after surgery resulted in a significant reduction in acute kidney injury after surgery in the amino acid infusion group *versus* the placebo group.
- Amino acid infusions are thought to prevent acute kidney injury after cardiac surgery by recruiting renal functional reserve. Patients with chronic kidney disease have lower functional renal reserve than patients who have normal kidney function. Preventing cardiac surgery–associated acute kidney injury in patients who present with chronic kidney disease is important for avoiding further decline in kidney function.

What This Article Tells Us That Is New

- This article is a secondary analysis of the PROTECTION Trial data. The hypothesis of this secondary analysis is that in patients who have chronic kidney disease before cardiac surgery, amino acid infusion will still be associated with reduced acute kidney injury when compared to the placebo group.
- The authors found that in patients who had chronic kidney disease before surgery, postoperative acute kidney injury occurred significantly less in the amino acid infusion group *versus* the placebo group, with a magnitude of effect similar to the patients who did not have preoperative chronic kidney disease.

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Acute kidney injury (AKI) is common in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB)[1] and is associated with increased morbidity and mortality.[2–4] The PROTECTION trial (Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery) investigated the role of intravenous amino acid infusion on AKI in adult patients undergoing on-pump cardiac surgery,[5] showing, for the first time, to our knowledge, a 5% absolute and 15% relative risk reduction for AKI with amino acids infusion compared to placebo.[6]

The underlying physiologic mechanism of short-term amino acids infusion is thought to mainly rely on the recruitment of renal functional reserve,[7–10] which in turn leads to an increase in the glomerular filtration rate.[11] However, the amino acids protective effect on kidneys is likely multifactorial, involving the enhancement in renal blood flow, renal medullary and cortical oxygenation, and estimated glomerular filtration rate.[12]

Given its relevance in terms of morbidity and mortality, any effort to prevent AKI is valuable. However, in patients with CKD, prevention of acute or chronic kidney injury may be particularly important. This is because CKD patients are at greater risk of reaching lower levels of estimated glomerular filtration rate and of progressive loss of function after an episode of AKI.[13–15] Indeed, because the action of amino acids to protect glomerular filtration rate is, at least in part, dependent on renal functional reserve recruitment, CKD patients, who have a diminished renal functional reserve,[11] may fail to benefit from their administration. Thus, renal protection may not occur in such patients and/or may become progressively less with greater CKD severity.

Accordingly, we investigated the effect size of amino acids on postoperative renal protection in patients with preoperative CKD recruited in the PROTECTION study. We aimed to test the primary hypothesis that the protective effect of amino acids would still take place, even in the presence of baseline CKD.

Materials and Methods

Study Design

This is a preplanned secondary analysis of a multinational, double-blind, randomized, placebo-controlled trial (PROTECTION trial) conducted in 22 centers in three

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countries.[5] The study was registered at ClinicalTrials.gov (NCT03709264). From October 2019 through January 2024, 3,511 adult patients undergoing elective on-pump cardiac surgery were randomized 1:1 either to receive a continuous infusion of a balanced mixture of amino acids (isopuramin 10%; Baxter, USA) at a dose of 2 g/kg of ideal body weight per day (up to a maximum of 100 g/day) or an equivalent dose of placebo (Ringer's solution; Baxter).

The study drug infusion started at operating room admission and continued up to 72 h, intensive care unit (ICU) discharge, or initiation of renal-replacement therapy, whichever occurred first. The primary outcome was the incidence of AKI, defined in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria.[16] The trial protocol was approved by the ethics committee at each participating center, and all patients provided written informed consent before randomization. The PROTECTION trial was funded by the Italian Ministry of Health.

Population

In this analysis, we included all 3,511 patients randomized in the PROTECTION trial between October 28, 2019, through January 17, 2024. We defined CKD as a baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2}. Therefore, we compared patients with a baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2} (at least mildly to moderately decreased estimated glomerular filtration rate) with those with baseline estimated glomerular filtration rate greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2}.[17]

We used the Cockcroft–Gault equation to estimate estimated glomerular filtration rate, considering the baseline serum creatinine value, which was the most recently available measurement before randomization, obtained either during the current hospitalization or within 365 days before the current hospitalization. We also performed several sensitivity analyses using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation to estimate estimated glomerular filtration rate.[18]

Outcomes

The primary outcome was to investigate the occurrence of AKI in patients with CKD (estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2}). The overall population was divided into two groups according to baseline estimated glomerular filtration rate: less than 60 ml · min^{-1} · 1.73 m^{-2} (CKD patients) or greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2} (patients without CKD). Each group was further subdivided into amino acids and placebo groups, based on randomization assignment.

First, we aimed to investigate the effect of amino acids in preventing AKI through an interaction model. Thus, we performed a subgroup analysis of the incidence of AKI in the amino acids and placebo groups, according to baseline estimated glomerular filtration rate, with values expressed as relative risk and 95% CI. Moreover, patients with baseline CKD were further divided into three estimated glomerular filtration rate subgroups (30 to 39, 40 to 49, and 50 to 59 ml · min^{-1} · 1.73 m^{-2}) based on the severity of their baseline kidney dysfunction to assess whether the effect of the study intervention correlates with the decline in renal function.

Second, we estimated and compared the percentage changes in estimated glomerular filtration rate between groups (amino acids *vs.* placebo) in CKD patients and in those with preoperative preserved kidney function. We assessed these changes from baseline to postoperative day 3, as well as from baseline to each day (days 1, 2, and 3), analyzing the trends over time. The choice of 3 days was related to the maximum duration of the study drug infusion in the PROTECTION trial, which extended up to 72 h. We excluded day 0 from the analyses of variance to avoid the confounding effect of CPB pump prime, cardioplegia, and intraoperative fluids, which can dilute serum creatinine levels.

Further analyses were performed to evaluate the mean changes in estimated glomerular filtration rate from the placebo to the amino acids group, in patients with a baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2} and in those with baseline estimated glomerular filtration rate greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2}, thereby comparing the absolute mean differences between the two subgroups.

The secondary outcomes included the investigation of the two subgroups (less than 60 ml · min^{-1} · 1.73 m^{-2}; greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2}) in terms of severity of AKI as defined by the KDIGO AKI guidelines,[13] the application and duration of renal-replacement therapy during hospital stay, duration of ICU and hospital stay, duration of mechanical ventilation, all-cause mortality at different time points (30-day mortality, ICU discharge, 90 and 180 days after randomization), and quality of life at 180 days, evaluated by European Quality of Life–5, which measures quality of life across five domains, using a subjective rating scale from 0 to 100, where a higher score indicates a better quality of life.

Statistical Analysis

Dichotomous variables were compared using the two-tailed chi-square test or Fisher's exact test, as appropriate, and relative risks with 95% CIs were also calculated. Continuous variables are expressed as medians and interquartile ranges, compared using the Wilcoxon Mann–Whitney test, or as means and SDs, compared using the *t* test. Between-group differences were reported as mean differences with 95% CIs. We calculated means and 95% CIs of estimated glomerular filtration rate for each group at each time point (baseline, day 1, day 2, and day 3) and presented measures by analysis of variance. We performed time-to-event analyses of AKI, stage 3 AKI, and renal-replacement therapy. The hazard ratio and corresponding 95%

CI were calculated and used for a stratified log-rank test. A two-sided P value of < 0.05 was considered statistically significant. The data were analyzed using Stata software (version 18; StataCorp, USA) and SAS (release 9.4; Statistical Analysis System Inc., USA).

Results

In the PROTECTION trial, 812 patients had an estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2} (404 in the amino acids group *vs.* 408 in the placebo group) at randomization, whereas 2,699 patients had an estimated glomerular filtration rate greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2} (1,355 in the amino acids group *vs.* 1,344 in the placebo group; supplemental fig. S1, https://links.lww.com/ALN/D785). The baseline demographic and clinical characteristics, as well as surgical interventions and intraoperative management, are presented in table 1, showing a balance between the amino acids and control groups at randomization. In contrast to patients with

Table 1. Baseline and Intraoperative Characteristics of Study Patients with Chronic Kidney Disease at Baseline

Characteristics	Amino Acids Group (N = 404)	Placebo Group (N = 408)
Median age [interquartile range], yr	74.0 [69.0, 77.0]	74.0 [70.0, 78.0]
Sex, no. (%)		
Female	207 (51.2)	192 (47.1)
Male	197 (48.8)	216 (52.9)
Median body mass index [interquartile range]*	24.2 [21.5, 26.4]	24.1 [21.6, 26.4]
Median preoperative serum creatinine [interquartile range], mg/dl	1.15 [0.97, 1.35]	1.17 [0.99, 1.36]
Median left ventricular ejection fraction [interquartile range], %	58.0 [51.0, 62.0]	60.0 [54.0, 63.0]
New York Heart Association class, no. (%)		
I	56 (13.9)	55 (13.5)
II	241 (59.7)	238 (58.5)
III	97 (24.0)	106 (26.0)
IV	10 (2.5)	8 (2.0)
Current smoker, no. (%)	42 (10.5)	45 (11.1)
Race or ethnic group, no. (%)		
White	399 (98.8)	401 (98.3)
Asian	3 (0.7)	5 (1.2)
Other	2 (0.5)	2 (0.5)
Medical condition, no. (%)		
Arterial hypertension on medical treatment	276 (68.5)	281 (68.9)
Previous myocardial infarction	59 (14.6)	67 (16.5)
Atrial fibrillation	129 (31.9)	109 (26.7)
Previous stroke or transient ischemic attack	23 (5.8)	29 (7.2)
Cardiac catheterization in the past 48 h	67 (16.6)	73 (17.9)
Diabetes on medical treatment	80 (19.9)	81 (19.9)
Peripheral vascular disease	97 (24.2)	99 (24.3)
Previous cardiac surgery	44 (10.9)	35 (8.6)
Preoperative medical therapy, no. (%)		
Beta blockers	240 (59.6)	245 (60.6)
Angiotensin receptor blocker or angiotensin-converting enzyme inhibitor	221 (54.8)	224 (55.4)
Statin	204 (50.6)	196 (48.5)
Antiplatelet	160 (39.7)	159 (39.4)
Diuretics	213 (52.9)	199 (49.3)
Anticoagulant	130 (32.3)	129 (32.0)
Median duration of on-pump procedure [interquartile range], min	92.0 [71.0;120]	93.0 [70.0;120]
Surgery type, no. (%)		
Coronary artery bypass graft	125 (31.0)	157 (38.7)
Mitral valve	193 (47.9)	161 (39.7)
Aortic valve	146 (36.4)	148 (36.6)
Other	27 (6.7)	26 (6.4)
Intraoperative loop diuretics, no. (%)	171 (42.6)	153 (38.0)
Use of hemofiltration during cardiopulmonary bypass, no. (%)	51 (12.8)	45 (11.2)
Intraoperative vasoactive and inotropic drugs, no. (%)	312 (77.2)	289 (71.5)
Epinephrine	170 (42.1)	165 (40.8)
Norepinephrine	150 (37.2)	127 (31.6)
Dobutamine	55 (13.7)	41 (10.1)
Other	11 (2.7)	17 (4.2)

To convert the values for serum creatinine to millimoles/liter, multiply by 88.4%. Ages may not total 100 because of rounding. The New York Heart Association class for heart failure ranges from I to IV, where class I is a patient asymptomatic for heart failure, and class IV is a patient with symptoms of heart failure at rest.

*The body mass index is the weight in kilograms divided by the square of the height in meters.

normal baseline renal function, those with CKD were older, predominantly male, with fewer active smokers, lower body mass index, higher New York Heart Association class,[19] and higher prevalence of hypertension, atrial fibrillation, stroke/transient ischemic attach, and peripheral vascular disease. Additionally, the CKD group more often used beta blockers, renin angiotensin aldosterone system inhibitors, anticoagulants, and diuretics. Intraoperatively, compared to those with normal renal function, the CKD group had a higher rate of patients undergoing mitral surgery, receiving ultrafiltration during CPB, and needing vasoactive or inotropic drugs (74% *vs.* 62%; $P < 0.001$; supplemental table S1, https://links.lww.com/ALN/D785).

Primary Outcome

Among patients presenting with CKD, we observed a statistically significant reduction of AKI in the amino acids group compared to placebo (43.1% *vs.* 50.3%; relative risk, 0.86; 95% CI, 0.74 to 0.99; $P = 0.041$; number needed to treat = 14; supplemental fig. S2, https://links.lww.com/ALN/D785; table 2). Similar magnitude and direction of effect were found among patients without baseline CKD (22.1% *vs.* 26.0%; relative risk, 0.85; 95% CI, 0.74 to 0.97; $P = 0.02$; number needed to treat = 26; supplemental fig. S2 and table S2, https://links.lww.com/ALN/D785), with an interaction P value of 0.65.

When considering narrow estimated glomerular filtration rate subgroups (30 to 39, 40 to 49, and 50 to 59 ml · min^{-1} · 1.73 m^{-2}) of the CKD cohort, the effect of the study intervention on AKI was similar (interaction $P = 0.50$; supplemental fig. S2, https://links.lww.com/ALN/D785). A Kaplan–Meier time-to-event plot is presented in figure 1, showing the proportion of CKD patients who developed AKI within 7 days after randomization.

Both the median and the mean percentage increase in estimated glomerular filtration rate from baseline to

Table 2. Outcomes for Patients with a Baseline Estimated Glomerular Filtration Rate of Less than 60 ml · min^{-1} · 1.73 m^{-2}

	Amino Acid Group (n = 404)		Placebo Group (n = 408)			
Outcomes	**Value**	**No. with Missing Data**	**Value**	**No. with Missing Data**	**Relative Risk, Absolute Mean Difference (95% CI)**	***P* Value**
Primary outcome: Incidence of in-hospital AKI, no. (%)*	174 (43.1)	0	205 (50.3)	0	0.86 (0.74 to 0.99)	0.041
Stage 1 AKI	155 (38.4)		180 (44.1)		0.87 (0.74 to 1.03)	0.10
Stage 2 AKI	8 (2.0)		2 (0.5)		4.04 (0.86 to 18.91)	0.054
Stage 3 AKI	11 (2.7)		23 (5.6)		0.48 (0.24 to 0.98)	0.038
Secondary outcomes						
Use of renal-replacement therapy, no. (%)	9 (2.2)	0	15 (3.7)	1	0.60 (0.27 to 1.37)	0.22
Median duration of renal-replacement therapy [interquartile range], h	55 (18 to 106)	1	43 (22 to 266)	1	75.57(–77.87 to 229.00)†	0.32
Mean duration of renal-replacement therapy (± SD), h	71 ± 66	1	147 ± 200	1		
Median duration of mechanical ventilation [interquartile range], h	15 (9 to 19)	8	12 (8 to 19)	15	–1.71 (–7.41 to 3.99)†	0.56
Mean duration of mechanical ventilation (± SD), h	23 ± 38	8	22 ± 43	15		
Median duration of stay in intensive care unit [interquartile range], h	42 (22 to 73)	2	43 (22 to 70)	6	–4.31 (–17.87 to 9.24)†	0.53
Mean duration of stay in intensive care unit (± SD), h	70 ± 102	2	66 ± 94	6		
Median duration of stay in hospital [interquartile range], nights	7 (6 to 11)	0	7 (6 to 10)	0	–0.26 (–1.79 to 1.28)†	0.74
Mean duration of stay in hospital (± SD), nights	11 ± 11	0	10 ± 11	0		
Mortality before intensive care unit discharge, no. (%)	15 (3.7)	0	17 (4.2)	0	0.89 (0.45 to 1.76)	0.74
Mortality at 30 days, no. (%)	21 (5.2)	0	21 (5.2)	0	1.01 (0.56 to 1.82)	0.97
Mortality at 90 days, no. (%)	26 (6.4)	4	22 (5.4)	8	1.18 (0.68 to 2.05)	0.55
Mortality at 180 days, no. (%)	33 (8.3)	5	27 (6.8)	11	1.22 (0.75 to 1.98)	0.43
Quality of life at 180 days [interquartile range]	80 (70 to 90)	166	80 (70 to 90)	169	–1.23 (–5.24 to 2.77)†	0.55

The data are presented as relative risks for dichotomous outcomes and as absolute mean differences for continuous outcomes. The 95% CIs presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible. The quality of life at 180 days was measured by the European Quality of Life–5 Dimensions, which considers a five-domain questionnaire and a subjective rating scale from 0 to 100, which indicates excellent quality of life.

*Acute kidney injury is defined according to Kidney Disease: Improving Global Outcomes 2012 guidelines.

†The data are presented as absolute mean difference.

AKI, acute kidney injury.

postoperative day 3 were significantly higher in the amino acids group compared to the placebo group. This effect was present both in patients with a baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2} (median values, 12.7% *vs.* 6.5%, $P = 0.002$; mean values, 12.7% *vs.* 6.1%, $P = 0.005$) and in patients with a baseline estimated glomerular filtration rate greater than or equal to 60 ml · min^{-1} · 1.73 m^{-2} (median values, 13.8% *vs.* 10.0%, $P < 0.001$; mean values, 13.8% *vs.* 8.6%, $P < 0.001$; table 3).

The absolute mean differences in the percentage changes in estimated glomerular filtration rate from baseline to postoperative day 3, between amino acids and placebo were 6.59% (95% CI, 2.00 to 11.19) for CKD patients, and 5.18% (95% CI, 3.18 to 7.18) for patients without CKD at baseline. The absolute change in estimated glomerular filtration rate did not differ between the two groups ($P = 0.58$). Moreover, the median amino acids-induced estimated glomerular filtration rate increase was 12.7% in patients with CKD and 13.8% in patients without CKD ($P = 0.44$).

In a sensitivity analysis, we examined mean changes in estimated glomerular filtration rate over time, from baseline to days 1, 2, and 3 (fig. 2; supplemental fig. S3, https://links.lww.com/ALN/D785). These analyses confirmed the beneficial role of amino acids, compared to placebo, in increasing the estimated glomerular filtration rate in both patients with moderate to severe CKD at baseline ($P = 0.049$) and patients with normal baseline kidney function ($P < 0.001$).

Secondary Outcomes and Sensitivity Analyses

Among CKD patients, we observed a lower rate of severe (stage 3) AKI in the amino acids group (2.7% *vs.* 5.6%; relative risk, 0.48; 95% CI, 0.24 to 0.98; $P = 0.038$; table 2; fig. 3), compared with a rate of 1.3% *vs.* 2.2% (relative risk, 0.62; 95% CI, 0.34 to 1.11; $P = 0.10$) in patients without CKD (supplemental table S2, https://links.lww.com/ALN/D785). There were no significant differences in other secondary outcomes. However, we observed a 40% relative risk reduction of the use of renal replacement therapy, which was coherent with the changes in stage 3 AKI (table 2; supplemental table S2 and fig. S4, https://links.lww.com/ALN/D785). The results for primary and secondary outcomes were confirmed in multiple sensitivity analyses (supplemental table S3 and figs. S5 and S6, https://links.lww.com/ALN/D785).

Discussion

Key Findings

We conducted a secondary analysis of the PROTECTION trial[6] to investigate whether the effect of amino acids to prevent AKI relative to placebo also applied to patients with CKD at randomization. In CKD patients, we observed a statistically significant reduction of AKI in the amino acids group compared to placebo, with similar magnitude and direction to that of patients without CKD. However, because patients with CKD had a higher rate of AKI, the number needed to treat decreased from 26 to 14. Moreover, we found that, by postoperative day 3, amino acids increased the median estimated glomerular filtration rate by 12.7% compared to 6.5% with placebo. In addition, amino acids more than halved the rate of severe (stage 3) AKI. Finally, these findings were robust to multiple sensitivity analyses.

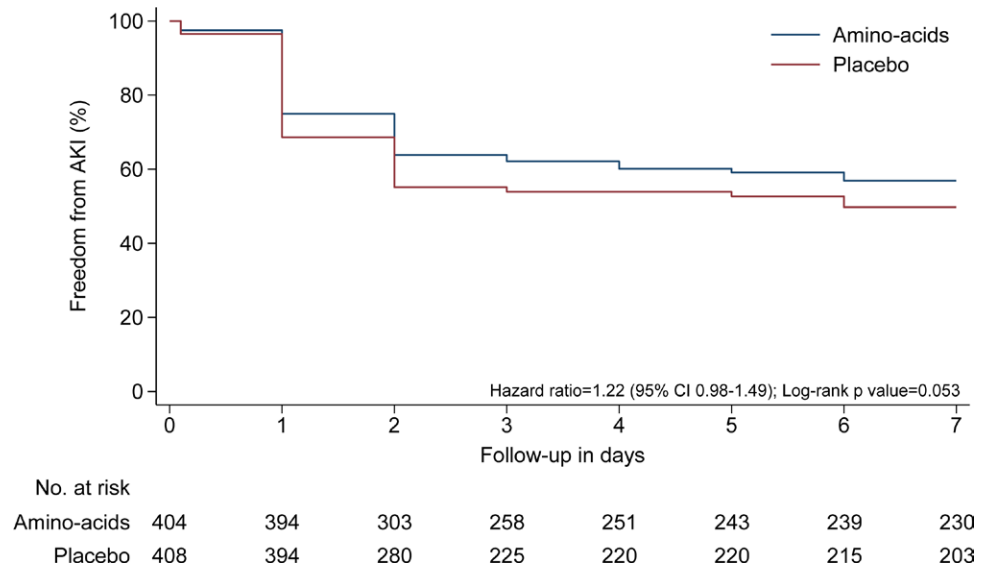

Fig. 1. Kaplan–Meier time-to-event plot for acute kidney injury (AKI) in patients with baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2}. CI, confidence interval.

Table 3. Median and Mean Estimated Glomerular Filtration Rate (mL · min^{-1} · 1.73 m^{-2}) Percentage Changes According to Chronic Kidney Disease Severity

Characteristic	Amino Acids Group		Placebo Group		
	Value	Patients, No.	Value	Patients, No.	*P* Value
Patients with baseline estimated glomerular filtration rate less than 60, %		404		408	
Median [interquartile range]	12.7 [–6.9 to 32.9]		6.5 [–13.0 to 22.2]		0.002
Mean ± SD	12.7 ± 33.6		6.1 ± 31.8		0.005
Patients with baseline estimated glomerular filtration rate greater than or equal to 60, %		1,355		1,344	
Median [interquartile range]	13.8 [0.0 to 28.6]		10.0 [–4.1 to 23.7]		< 0.001
Mean ± SD	13.8 ± 26.6		8.6 ± 24.7		< 0.001

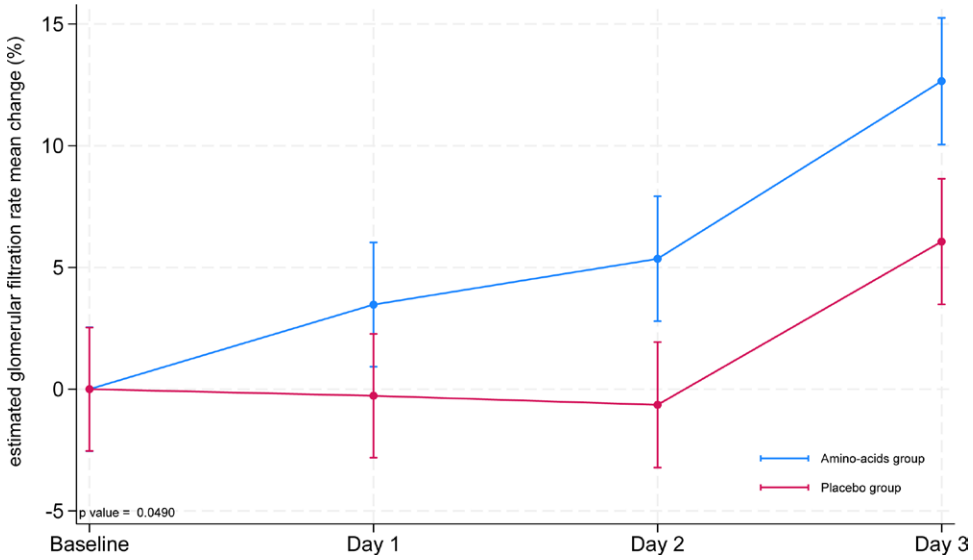

Fig. 2. Mean change in estimated glomerular filtration rate from baseline to postoperative day 3 (patients with baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2}).

Relationship to Previous Studies

To the best of our knowledge, no previous studies have investigated whether the protective effect of amino acids applies to patients with CKD. Previous studies, however, have shown that renal functional reserve is decreased in patients with CKD.[11] In an amino acids pilot randomized study by Pu *et al.*,[20] no separate analysis was performed for CKD patients. However, CKD made up almost half the study population, suggesting that the observed benefits of amino acids infusion may apply to this subgroup. In an amino acids before-and-after study by Brusasco *et al.*,[21] no data were shown on the presence of CKD. In a randomized study by Doig *et al.*,[22] less than 10% of patients had CKD. However, in the secondary analyses of this study by Zhu *et al.*,[23] patients without abnormal renal function at randomization had similar clinical outcomes when given amino acids compared to placebo as patients with abnormal renal function at randomization. These studies suggest that amino acids infusion could be beneficial regardless of baseline renal function, are aligned with our findings, and support the potential advantage of amino acids infusion in CKD patients.[24]

Finally, in a study by Husain-Syed *et al.*,[25] patients with CKD were excluded. However, even among cardiac surgery patients without CKD, there was significant variability in preoperative renal functional reserve, which, if low, predicted an increased risk of postoperative AKI. This evidence is consistent with our observations in CKD patients, which had high incidence of AKI with likely lower renal functional reserve. A major putative mechanism of action of amino acids is recruitment of renal functional reserve, and patients with CKD have

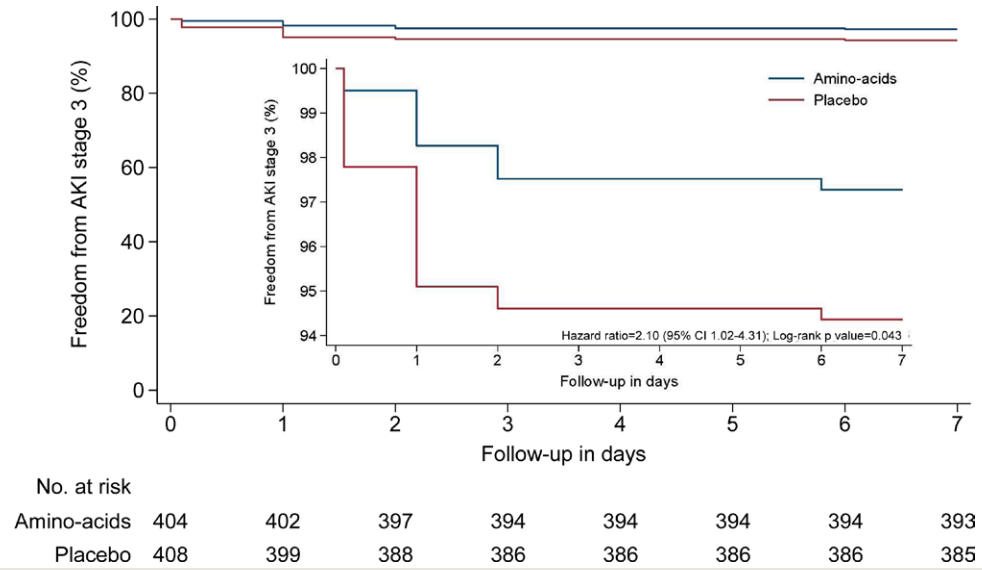

Fig. 3. Kaplan–Meier time-to-event plot for stage 3 acute kidney injury (AKI) in patients with baseline estimated glomerular filtration rate of less than 60 ml · min^{-1} · 1.73 m^{-2}. CI, confidence interval.

a decreased ability to recruit renal functional reserve. Thus, it is logical to hypothesize that the protective effect of amino acids on the postoperative estimated glomerular filtration rate would be decreased in patients with CKD. Our study, however, demonstrates that even in such patients, amino acids therapy increased the postoperative estimated glomerular filtration rate and reduced postoperative AKI when compared with placebo. This suggests that other protective mechanisms may also be present.

Implications of Study Findings

Our study confirms the beneficial effect of amino acids in preventing AKI and improving the estimated glomerular filtration rate by showing its effects also in CKD patients. These findings imply that because CKD patients have a higher incidence of AKI compared to patients without CKD, the use of amino acids in this population is even more efficient, with a number needed to treat of 14 compared to 26 in non-CKD patients. Finally, the halving of AKI stage 3 rates in the CKD treatment group with a 40% reduction in the use of renal-replacement therapy highlights the effectiveness of the treatment in the prevention of the most severe grades of AKI.

Strengths and Limitations

This analysis has several strengths. It is based on a large multicenter randomized double-blind international trial dataset with a large group of CKD patients within it. Thus, it carries no appreciable risk of selection bias, ascertainment bias, and performance bias. The CKD cohort is clinically important because of its high risk of postoperative AKI, as confirmed in this study, and because of its relatively high prevalence among patients undergoing cardiac surgery with CPB. This study is physiologically and pharmacologically significant as it enhances our understanding of amino acids, which appear to improve estimated glomerular filtration rate by recruiting available renal functional reserve. Our findings demonstrate that amino acids may also be effective in CKD patients, in which reduced renal functional reserve would be expected to affect their ability to maintain or improve postoperative estimated glomerular filtration rate. This aspect is further supported by the fact that the rate of stage 3 AKI was halved, the need for renal-replacement therapy decreased by 40%, and the number needed to treat to prevent an episode of AKI was 14. All these observations are clinically relevant.

We acknowledge several limitations. This is a preplanned secondary study of a cohort embedded with a large double-blind randomized controlled trial that was not designed to specifically test the hypothesis assessed here. Thus, our findings are only hypothesis-generating. However, they appear consistent and robust to sensitivity analyses, and they are aligned with the findings of the main trial. We did not assess the impact of urinary output on the occurrence of AKI. However, in patients after cardiac surgery, the urinary catheter is typically removed on day two making such assessment problematic. We used serum creatinine to monitor changes in estimated glomerular filtration rate. Additional assessment with other markers such as albuminuria and cystatin C would have added robustness to our findings. However, given the double-blinded nature of the study, the difference between groups would not have been subject to bias. Lastly, we do

not have long-term follow-up data to provide information on the longer-term sequalae of AKI in these patients. However, previous literature suggests a strong association between AKI and subsequent loss of renal functional reserve[25] and between AKI on CKD and subsequent worsening of CKD. Thus, long term follow-up of CKD patients treated with amino acids is important and the subject of a current investigation.

Conclusions

In CKD patients receiving cardiac surgery with CPB, the administration of a continuous infusion of amino acids was effective in preventing AKI. The reduction of AKI in the amino acids group was similar in patients with or without CKD. In addition, in this subgroup at higher risk of AKI, amino acids more than halved the rate of stage 3 AKI and reduced the use of renal-replacement therapy by 40%. These findings were robust to multiple sensitivity analyses and imply that amino acids infusion improves postoperative estimated glomerular filtration rate and decreases the occurrence of AKI in CKD patients. They also imply a number needed to treat of 14, suggesting that amino acids therapy is particularly efficient in CKD patients making them a key target population for amino acids infusion in the setting of cardiac surgery.

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Competing Interests

Dr. Guarracino has received consulting fees from Abbott (Abbot Park, Illinois), AOP Orphan (Pisa, Italy), Chiesi Farmaceutici (Parma, Italy), Edwards (Irivine, California), Masimo (Irivine, California), Orion pharma (Espoo, Finland), Vygon (Ecouen, France), and Viatris (Canonsburg, Pennsylvania). Dr. Brazzi has received consulting fees from SIARE (Bologna, Italy) and 3M (St. Paul, Minnesota). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: landoni.giovanni@hsr.it. Raw data available at: landoni.giovanni@hsr.it.

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Supplemental Digital Content

Supplemental file. https://links.lww.com/ALN/D785
Supplemental Table S1. Baseline and intraoperative characteristics.
Supplemental Table S2. Outcomes for patients with a baseline CKD.
Supplemental Table S3. Outcomes for CKD patients (CKD-EPI 2021 equation).
Supplemental Fig. S1. Flow diagram illustrating patient selection.
Supplemental Fig. S2. Occurrence of AKI stratified by baseline estimated glomerular filtration rate.
Supplemental Fig. S3. Estimated glomerular filtration rate in patients with normal kidney function.
Supplemental Fig. S4. Renal-replacement therapy free probability in patients with baseline CKD.
Supplemental Fig. S5. AKI stratified by baseline estimated glomerular filtration rate (CKD-EPI 2021).
Supplemental Fig. S6. Estimated glomerular filtration rate in CKD patients (CKD-EPI 2021 equation).

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