ORIGINAL ARTICLE

A Randomized Trial of Intravenous Amino Acids for Kidney Protection

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ABSTRACT

BACKGROUND

Acute kidney injury (AKI) is a serious and common complication of cardiac surgery, for which reduced kidney perfusion is a key contributing factor. Intravenous amino acids increase kidney perfusion and recruit renal functional reserve. However, the efficacy of amino acids in reducing the occurrence of AKI after cardiac surgery is uncertain.

METHODS

In a multinational, double-blind trial, we randomly assigned adult patients who were scheduled to undergo cardiac surgery with cardiopulmonary bypass to receive an intravenous infusion of either a balanced mixture of amino acids, at a dose of 2 g per kilogram of ideal body weight per day, or placebo (Ringer's solution) for up to 3 days. The primary outcome was the occurrence of AKI, defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria. Secondary outcomes included the severity of AKI, the use and duration of kidney-replacement therapy, and all-cause 30-day mortality.

RESULTS

We recruited 3511 patients at 22 centers in three countries and assigned 1759 patients to the amino acid group and 1752 to the placebo group. AKI occurred in 474 patients (26.9%) in the amino acid group and in 555 (31.7%) in the placebo group (relative risk, 0.85; 95% confidence interval [CI], 0.77 to 0.94; P=0.002). Stage 3 AKI occurred in 29 patients (1.6%) and 52 patients (3.0%), respectively (relative risk, 0.56; 95% CI, 0.35 to 0.87). Kidney-replacement therapy was used in 24 patients (1.4%) in the amino acid group and in 33 patients (1.9%) in the placebo group. There were no substantial differences between the two groups in other secondary outcomes or in adverse events.

CONCLUSIONS

Among adult patients undergoing cardiac surgery, infusion of amino acids reduced the occurrence of AKI. (Funded by the Italian Ministry of Health; PROTECTION ClinicalTrials.gov number, NCT03709264.)

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Acute kidney injury (AKI) is a common complication of cardiac surgery.[1] Even mild or moderate AKI is independently associated with increased morbidity and mortality, including an increased risk of chronic kidney disease.[2] In patients with severe AKI, kidney-replacement therapy is common and is associated with doubling of hospitalization costs, decreased quality of life, and higher long-term mortality.[3-6] However, other than the implementation of supportive measures,[7] there is no single preventive intervention for cardiac surgery–associated AKI.

Renal hypoperfusion is a major contributor to decreased glomerular filtration rate (GFR) after cardiopulmonary bypass.[8-10] Studies in animals have shown that cardiopulmonary bypass decreases renal blood flow by more than 50%[11] and induces renal medullary tissue hypoxia,[12,13] which is followed by decreased GFR. These observations have now been confirmed in studies in humans.[14,15]

In the context of renal hypoperfusion, infusion of amino acids may exert protective effects in the kidneys by recruiting renal functional reserve. Previous studies have shown that infusion of amino acids increases nephron plasma flow by means of decreased afferent arteriolar resistance,[16,17] decreased tubuloglomerular feedback activation,[18,19] and increased cortical nitric oxide synthase activity.[20,21] Moreover, in studies in animals, amino acid infusion increased renal perfusion, renal oxygenation, and GFR.[22] Finally, pilot studies in humans have shown evidence that amino acid infusion is safe and has beneficial short-term[23] and long-term[24] effects on kidney function after cardiac surgery,[25] as well as potential survival benefits in critical illness in general.[24]

Accordingly, we performed the Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery (PROTECTION) trial, a multinational, double-blind, randomized, placebo-controlled trial involving adult patients who were scheduled to undergo cardiac surgery with cardiopulmonary bypass, to test the hypothesis that intravenous amino acid therapy would lead to a lower occurrence of postoperative AKI than placebo.

Methods

Trial Design

The PROTECTION trial was an investigator-initiated, double-blind, randomized trial that was conducted at 22 centers in three countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The ethics committee at each participating center approved the trial protocol, which is available at NEJM.org. All patients provided written informed consent. Details of the rationale and design of the study and the statistical analysis plan have been published previously.[26]

The PROTECTION trial was funded by the Italian Ministry of Health. The amino acid treatment (Isopuramin 10%, Baxter) and placebo (Ringer's solution, Baxter) were provided by the manufacturer and delivered in indistinguishable bottles (see the Supplementary Appendix). Neither the Italian Ministry of Health nor Baxter had a role in the conception or design of the trial, the collection or analysis of the data, or the writing of the manuscript. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

An independent data and safety monitoring committee reviewed the data and performed prespecified blinded interim analyses after the enrollment of 25%, 50%, and 75% of the planned number of participants. The steering committee designed and oversaw the trial. Data collection and outcome assessment were conducted by designated personnel at each site. Five of the authors analyzed the data, and the first author wrote the first draft of the manuscript. All the authors collaborated in the writing of the manuscript and agreed to submit the manuscript for publication. Further details about the trial design and trial sites are provided in the Supplementary Appendix.

Patients

All patients who were scheduled to undergo cardiac surgery were screened for eligibility. Patients were eligible if they were 18 years of age or older, were scheduled to undergo elective cardiac surgery requiring cardiopulmonary bypass, and were expected to stay in the intensive care unit (ICU) for at least one night after undergoing the surgery. Eligible patients had to have a baseline serum creatinine measurement before surgery — the most recently available measurement before randomization, obtained either during the current hospitalization or within 365 days before the current hospitalization. Table S1 in the Supplementary Appendix indicates the representativeness of pa-

tients included in the trial as compared with those worldwide.

The main exclusion criteria were preoperative treatment or planned treatment with intermittent or continuous kidney-replacement therapy and stage IV or greater chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) of less than 30 ml per minute per 1.73 m^2 of body-surface area calculated by the Cockcroft–Gault equation (see the complete description in the Supplementary Appendix).

RANDOMIZATION AND BLINDING

Before surgery, eligible patients were randomly assigned to receive amino acids or placebo. Randomization was performed by means of a Web-based system with the use of computer-generated, permuted-block sequences with stratification according to site. A Web-based central randomization service ensured concealment of trial-group assignment. Patients, physicians, investigators, data collectors, and outcome assessors were unaware of the group assignments. During the data analysis, statisticians and authors were also unaware of the group assignments. Pharmacists and trial nurses were aware of the assignments but were not involved in the data collection or data analysis.

TRIAL INTERVENTION

After randomization, each patient was assigned a unique trial number and a unique medication kit number. The medication kit number was matched to a blinded infusion of either amino acids or placebo, with a supply that was sufficient for at least a 72-hour infusion. Patients in the amino acid group received a blinded continuous infusion of a balanced mixture of amino acids at a dose of 2 g per kilogram of ideal body weight per day (up to a maximum of 100 g per day) from the time of operating-room admission until 72 hours after initiation of the infusion, discharge from the ICU, initiation of kidney-replacement therapy, or death (whichever occurred first). Patients in the placebo group received a blinded continuous infusion of Ringer's solution at the same rate and according to the same protocol.

If enteral or parenteral nutrition was initiated within the first 72 hours, the dose was adjusted to achieve a total amino acid intake of 2 g per kilogram of ideal body weight per day after accounting for nutritional amino acid intake. Details of the composition of the amino acid mixture and dose adjustments are available in the Supplementary Appendix.

We recommended the implementation of criteria to justify, but not necessarily trigger, initiation of kidney-replacement therapy (see the Supplementary Appendix). With the exception of measurements of serum creatinine, initiation of kidney-replacement therapy, and management of trial regimens, all aspects of perioperative management were left to the discretion of the attending physicians. Trial centers were asked to provide postoperative monitoring and kidney-protection management in accordance with Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines[27] and local protocols (see the Supplementary Appendix).

DATA COLLECTION AND FOLLOW-UP

We collected data on baseline characteristics and coexisting conditions, surgical procedure and intraoperative care, postoperative course in the ICU and in the hospital, major outcomes, adverse events, and protocol deviations. With respect to the occurrence of AKI (the primary outcome), measurement of serum creatinine levels for up to 7 days while the patients remained in the hospital was part of the protocol guidelines. Measurement of serum creatinine levels was also part of routine clinical practice while the patient was in the ICU. A trained investigator who was unaware of the group assignments performed telephone follow-up 30, 90, and 180 days after randomization. If a patient could not be contacted by telephone for follow-up, the investigator assessed vital status by contacting the patient's surgeons, the patient's general practitioner, or the city register office or by obtaining the patient's hospital electronic records.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome of the PROTECTION trial was the occurrence of AKI within the first week after surgery,[27] with AKI defined according to the KDIGO creatinine criteria for stage 1 or greater AKI.[28] Stage 1 AKI is defined as an increase in the serum creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) during a 48-hour period or a 50% increase from baseline during a 1-week period, stage 2 as a doubling of the baseline serum creatinine level, and stage 3 as a tripling of the baseline serum creatinine level or the

initiation of dialysis, with either occurring within 1 week after the insult (e.g., cardiac surgery). Prespecified secondary outcomes were the severity of AKI according to the KDIGO creatinine criteria, the use and duration of kidney-replacement therapy during the hospital stay, the duration of stay in the ICU and hospital, the duration of mechanical ventilation, and death from any cause documented at the time of ICU discharge, hospital discharge, or 30, 90, or 180 days after randomization. Prespecified subgroup analyses were performed according to age (≥75 vs. <75 years of age), New York Heart Association class (I or II vs. III or IV), and baseline eGFR (≤60 vs. >60 ml per minute per 1.73 m^2).

PRESPECIFIED ADVERSE EVENTS

Prespecified intraoperative and postoperative adverse events included cardiogenic shock, events requiring ICU readmission, arrhythmia, the need for reintubation, the need for noninvasive ventilation, adverse neurologic outcome, myocardial infarction, wound infection, sepsis, septic shock, and death (see the Supplementary Appendix for detailed criteria). We also obtained data on any possible adverse reactions to amino acids or placebo and protocol deviations. The cause of death was classified according to validated criteria[29] (see the Supplementary Appendix).

STATISTICAL ANALYSIS

On the basis of previous studies of cardiac surgery–associated AKI,[30] we hypothesized that AKI would develop in 25% of the patients in the placebo group. We estimated that a sample size of 1750 patients in each group (a total of 3500 patients) would give the trial 90% power to detect a 20% lower risk of AKI in the amino acid infusion group than in the placebo group at a two-sided alpha level of 0.05, accounting for the three interim analyses (for which the O'Brien–Fleming sequential tests were used),[31] withdrawals from the trial, and rounding (a sample size of 3066 patients would have provided 90% power with a significance level of 0.05 and was rounded to 3500 patients; see the Supplementary Appendix).

Planned interim analyses were performed after the enrollment of 25%, 50%, and 75% of the patients. The planned statistical analyses were published before completion of the trial.[26] Primary analyses were performed according to the intention-to-treat principle. Three analyses of the primary outcome with different methods of imputation of missing data were performed (details are provided in the Supplementary Appendix). Per-protocol and as-treated analyses were also performed.

Dichotomous data were compared with the use of the two-tailed chi-square test or Fisher's exact test when appropriate and are expressed as relative risks and 95% confidence intervals. Continuous variables with skewed distribution are expressed as medians and interquartile ranges. Variables with symmetric distribution are expressed as means and standard deviations. Between-group differences are reported as mean differences with 95% confidence intervals. We performed prespecified subgroup analyses according to heart failure class, age, and baseline eGFR, with values expressed as relative risks and 95% confidence intervals. We also performed a post hoc time-to-event analysis for AKI and for kidney-replacement therapy using the Kaplan–Meier estimator, with the corresponding 95% confidence interval, and four subgroup analyses of the primary outcome according to trial center, sex, height, and chronic kidney disease stage.

Data were stored in an electronic case-report form and analyzed with the use of Stata software, version 18 (StataCorp). A two-sided P value of less than 0.05 was considered to indicate statistical significance, with no adjustment for multiplicity.

RESULTS

PATIENTS

From October 2019 through January 2024, we screened 4415 patients for eligibility. Of these, 3652 provided informed consent and 3512 were enrolled. One patient in the placebo group withdrew consent before initiation of the trial regimen. Thus, 1759 patients were randomly assigned to the amino acid group and 1752 to the placebo group (Fig. S1). The demographic and clinical characteristics at baseline, surgical interventions, and management were similar in the two groups (Table 1 and Table S2).

STUDY INTERVENTION

The median dose of amino acids was 1260 ml (interquartile range, 1000 to 2592), corresponding to 126 g of amino acids (Table 2). The median duration of infusion was 30 hours (interquartile range, 25 to 56) in the amino acid group

and 31 hours (interquartile range, 25 to 68) in the placebo group. The median infusion rate was 40 ml per hour (interquartile range, 40 to 42) in both groups.

Most of the patients (2530 of 3511 patients [72.1%]) stopped receiving amino acids or placebo at ICU discharge; 795 patients (22.6%) completed the maximum 72-hour infusion. Twenty patients (0.6%) discontinued the regimen at initiation of kidney-replacement therapy. In 56 patients (1.6%) the regimen was discontinued in error. Fourteen patients (0.4%) died before the end of the 3-day infusion, and 1 patient (<0.1%) withdrew consent. Finally, crossover occurred in 4 patients (Fig. S1 and Table S3).

PRIMARY AND SECONDARY OUTCOMES

At the time of hospital discharge, AKI had developed in 474 patients in the amino acid group (26.9%) and in 555 patients in the placebo group (31.7%) (relative risk, 0.85; 95% confidence interval [CI], 0.77 to 0.94; P=0.002) (Table 3, Fig. 1, and Fig. S2). Most patients with AKI had stage 1 AKI — 430 patients in the amino acid group and 492 in the placebo group. However, stage 3 AKI was diagnosed in 29 patients in the amino acid group and in 52 patients in the placebo group. The results were similar in the per-protocol analysis, the as-treated analysis, and in all sensitivity analyses (Tables S4 through S8). The occurrence of AKI stratified according to trial center is shown in Figure S3, and additional postoperative data are provided in Tables S9, S10, and S11.

The use and median duration of kidney-replacement therapy, the median duration of mechanical ventilation, the median length of stay in the ICU and hospital, mortality in the ICU, and 30-day, 90-day, and 180-day mortality in the amino acid group and placebo group are presented in Table 3. The results of the subgroup analyses are presented in Figures S4 and S5. A Kaplan–Meier time-to-event plot for kidney-replacement therapy is shown in Figure S6, and the criteria for initiation of kidney-replacement therapy are listed in Table S12.

SAFETY EVENTS

We observed no significant differences between the two groups in the numbers of patients with prespecified adverse events (Table 4). Overall, 70 patients in the amino acid group and 62 in the placebo group underwent surgical revision for bleeding. The 30-day mortality was 2.8% (50 patients) in the amino acid group and 2.8% (49 patients) in the placebo group (Table S13). No adverse drug reactions were reported in either group.

DISCUSSION

In this multinational, double-blind, randomized, placebo-controlled trial, we compared the continuous infusion of amino acids with infusion of an equivalent amount of crystalloid solution with respect to the occurrence of AKI in adult patients scheduled for elective cardiac surgery with cardiopulmonary bypass. Continuous amino acid infusion resulted in a significantly lower occurrence of AKI than that with the crystalloid solution, without any effect on adverse events.

A short-term amino acid infusion increases eGFR by recruiting renal functional reserve and may confer kidney protection.[32] Previous studies in animals and pilot randomized clinical trials have consistently provided evidence of such beneficial effects.[16,18,19,22,33-35] The combination of improved renal medullary perfusion and improved glomerular blood flow may be a key factor in conferring such kidney protection.[36] However, in mice, a high-protein diet increased measured glomerular diameter through the action of endothelial growth factor.[37] Moreover, the specific beneficial diuretic and renal effects of amino acids have been confirmed in pilot studies involving patients undergoing surgery.[38] Finally, in patients undergoing cardiac surgery, renal functional reserve has been shown to be a crucial predictor of AKI and measure of kidney outcome,[25,39-42] and a preoperative protein load has been associated with improved long-term renal outcomes.[23] Our findings of a decreased percentage of patients with AKI overall and with stage 3 AKI are aligned with the above observations.

The infusion of amino acids appeared to be safe and effective for the prevention of AKI in patients undergoing cardiac surgery. Moreover, the lower percentage of patients with stage 3 AKI in the amino acid group than in the placebo group implied an effect on AKI severity. These findings appear to be clinically and epidemiologically important because they may apply to more than two million patients who undergo heart surgery worldwide every year and because AKI is an indepen-

Table 1. Demographic and Intraoperative Characteristics of Patients at Baseline.*

Characteristic	Amino Acid Group (N=1759)		Placebo Group (N=1752)	
	Value	No. with Missing Data	Value	No. with Missing Data
Median age (IQR) — yr	66 (57–73)	0	67 (58–73)	0
Female sex — no. (%)	530 (30.1)	0	527 (30.1)	0
Median body-mass index (IQR)†	26 (23–29)	0	26 (23–28)	0
Median preoperative serum creatinine level (IQR) — mg/dl‡	0.96 (0.81–1.11)	0	0.94 (0.81–1.10)	0
Median preoperative hemoglobin concentration (IQR) — g/dl	13.9 (12.8–15.0)	11	13.8 (12.6–14.9)	5
Median left ventricular ejection fraction (IQR) — %	59 (54–63)	15	60 (54–63)	11
New York Heart Association class — no. (%)§		1		1
I	403 (22.9)		404 (23.1)	
II	996 (56.6)		990 (56.5)	
III	327 (18.6)		335 (19.1)	
IV	32 (1.8)		22 (1.3)	
Current smoker — no. (%)	269 (15.3)	16	278 (15.9)	14
Race — no. (%)¶		0		0
White	1731 (98.4)		1718 (98.1)	
Asian	16 (0.9)		18 (1.0)	
Other	12 (0.7)		16 (0.9)	
Medical condition — no. (%)				
Arterial hypertension while receiving medical treatment	1090 (62.0)	1	1083 (61.8)	0
Previous myocardial infarction	268 (15.2)	2	256 (14.6)	3
Atrial fibrillation	300 (17.1)	3	287 (16.4)	2
Previous stroke or transient ischemic attack	78 (4.4)	16	87 (5.0)	13
Cardiac catheterization in the past 48 hours	304 (17.3)	6	331 (18.9)	7
Diabetes while receiving medical treatment	309 (17.6)	2	335 (19.1)	1
Peripheral vascular disease	307 (17.5)	7	340 (19.4)	1
Previous cardiac surgery	147 (8.4)	4	139 (7.9)	2
Preoperative medical therapy — no. (%)				
Beta-blockers	910 (51.7)	16	904 (51.6)	17
ARB or ACE inhibitor	903 (51.3)	15	885 (50.5)	18
Statin	793 (45.1)	16	748 (42.7)	18
Antiplatelet	676 (38.4)	17	678 (38.7)	18
Diuretics	632 (35.9)	15	628 (35.8)	18
Anticoagulant	370 (21.0)	17	355 (20.3)	18
Median duration of CPB (IQR) — min	93 (73–121)	35	94 (73–122)	36
Surgery type — no. (%)				
CABG	613 (34.8)	10	640 (36.5)	11
Mitral valve	669 (38.0)	9	634 (36.2)	4
Aortic valve	657 (37.4)	11	648 (37.0)	11
Other‖	137 (7.8)	4	138 (7.9)	3
Intraoperative loop diuretics — no. (%)	713 (40.5)	11	684 (39.0)	19

Table 1. (Continued.)

Characteristic	Amino Acid Group (N = 1759)		Placebo Group (N = 1752)	
	Value	No. with Missing Data	Value	No. with Missing Data
Median lowest temperature during CPB (IQR) — °C	31 (29–33)	40	31 (29–33)	40
Use of hemofiltration during CPB — no. (%)	175 (9.9)	13	161 (9.2)	17
Intraoperative vasoactive and inotropic drugs — no. (%)	1160 (65.9)	5	1105 (63.1)	11
Epinephrine	592 (33.7)	6	608 (34.7)	9
Norepinephrine	543 (30.9)	6	495 (28.3)	11
Dobutamine	165 (9.4)	12	142 (8.1)	9
Other‖	67 (3.8)	10	78 (4.5)	14

* Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, CPB cardiopulmonary bypass, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ To convert the values for serum creatinine to millimoles per liter, multiply by 88.4.
§ The New York Heart Association classification system for heart failure ranges from I to IV, with class I denoting a patient who is asymptomatic for heart failure and class IV denoting a patient with symptoms of heart failure while at rest.
¶ Race was reported by the patients.
‖ The other types of surgery and intraoperative vasoactive and inotropic drugs are listed in Table S2 in the Supplementary Appendix.

Table 2. Trial Interventions.*

Variable	Amino Acid Group (N = 1759)		Placebo Group (N = 1752)	
	Value	No. with Missing Data	Value	No. with Missing Data
Median infusion rate (IQR) — ml/hr	40 (40–42)	17	40 (40–42)	23
Median dose (IQR)				
In milliliters	1260 (1000–2592)	26	1272 (1000–2790)	25
In grams	126 (100–259)	26	127 (100–279)	25
Median duration of infusion (IQR) — hr	30 (25–56)	14	31 (25–68)	16
Reason for cessation of regimen — no. (%)		6		4
Discharge from intensive care unit	1284 (73.0)		1246 (71.1)	
Completion of 72-hr infusion	392 (22.3)		403 (23.0)	
Initiation of kidney-replacement therapy	6 (0.3)		14 (0.8)	
Death	9 (0.5)		5 (0.3)	
Withdrawal of consent	1 (0.1)		0 (0.0)	
Adverse reactions	0 (0.0)		0 (0.0)	
Error	31 (1.8)		25 (1.4)	
Physician decision	13 (0.7)		32 (1.8)	
Logistic reasons	2 (0.1)		5 (0.3)	

* Percentages may not total 100 because of rounding.

Table 3. Clinical Outcomes.*

Outcome	Amino Acid Group (N=1759)		Placebo Group (N=1752)		Relative Risk (95% CI)	P Value
	Value	No. with Missing Data	Value	No. with Missing Data		
Primary outcome						
In-hospital AKI — no. (%)†	474 (26.9)	2	555 (31.7)	0	0.85 (0.77 to 0.94)	0.002
Stage 1	430 (24.4)		492 (28.1)		0.87 (0.78 to 0.97)	
Stage 2	15 (0.9)		11 (0.6)		1.36 (0.63 to 2.95)	
Stage 3	29 (1.6)		52 (3.0)		0.56 (0.35 to 0.87)	
Secondary outcomes						
Use of kidney-replacement therapy — no. (%)	24 (1.4)	5	33 (1.9)	3	0.73 (0.43 to 1.22)	
Median duration of kidney-replacement therapy (IQR) — hr	64 (17–100)	1	64 (21–81)	2	9.79 (–62.13 to 81.70)‡	
Median duration of mechanical ventilation (IQR) — hr	11 (6–17)	48	11 (6–17)	47	–0.60 (–3.70 to 2.49)‡	
Median duration of stay in intensive care unit (IQR) — hr	30 (21–66)	24	34 (21–68)	21	1.39 (–4.78 to 7.57)‡	
Median duration of stay in hospital (IQR) — no. of nights	7 (5–9)	4	7 (6–9)	2	0.28 (–0.36 to 0.92)‡	
Mortality — no. (%)						
Before discharge from intensive care unit	34 (1.9)	1	38 (2.2)	1	0.89 (0.56 to 1.41)	
30-day	50 (2.8)	1	49 (2.8)	1	1.02 (0.69 to 1.50)	
90-day	56 (3.2)	19	53 (3.0)	23	1.05 (0.73 to 1.52)	
180-day	68 (3.9)	34	68 (3.9)	35	1.00 (0.72 to 1.38)	

* The 95% confidence intervals presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible.
† Acute kidney injury (AKI) is defined according to Kidney Disease: Improving Global Outcomes 2012 guidelines.
‡ Data are presented as the absolute mean difference.

dent risk factor for subsequent chronic kidney disease.[43]

This was a large trial that was based on broad and clear inclusion criteria and included a representative population of adult patients undergoing cardiac surgery. AKI occurred in approximately 30% of the patients, which is broadly consistent with findings in previous studies and with our sample-size calculations. Moreover, subgroup analyses were performed in populations that are theoretically at higher risk for AKI. Finally, the trial intervention is straightforward and would be readily translated into practice.

Our trial has several limitations. First, we used serum creatinine level alone to diagnose AKI because urinary catheters are typically removed within 48 to 72 hours after surgery. However, adding urinary output confirmed the robustness of our findings in a sensitivity analysis. Second, we did not measure newly identified biomarkers of kidney injury. However, detecting subclinical AKI was not the objective of this trial, and biomarkers of kidney injury, which are not included in the 2012 KDIGO AKI criteria, gained more relevance after the Acute Disease Quality Initiative consensus conference in 2020,[44] when our trial was already in progress. Third, we did not include a strict protocol for management or prevention of AKI in this trial. However, the use of KDIGO guidelines was recommended, and blinding of the intervention attenuated the effect of any selection, performance, or ascertainment bias. Fourth, although patients were representative of those undergoing elective cardiac surgery in Eu-

Table 4. Safety Events.*

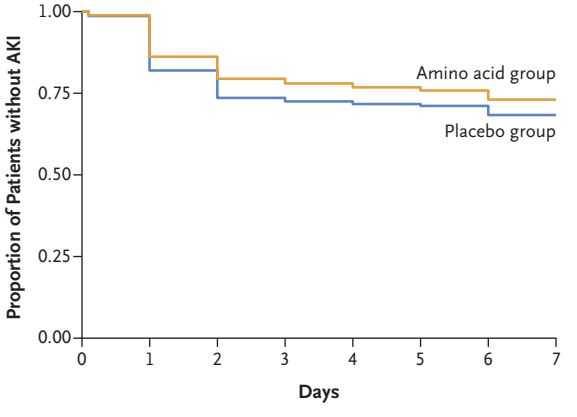
Safety Event	Amino Acid Group (N=1759)		Placebo Group (N=1752)		Relative Risk (95% CI)	P Value
	No. (%)	No. with Missing Data	No. (%)	No. with Missing Data		
Mechanical circulatory support†	112 (6.4)	14	120 (6.8)	11	0.93 (0.73 to 1.19)	0.57
Atrial fibrillation	581 (33.0)	3	540 (30.8)	3	1.07 (0.97 to 1.18)	0.16
Ventricular fibrillation	16 (0.9)	3	9 (0.5)	3	1.77 (0.78 to 4.00)	0.16
Surgical revision for bleeding	70 (4.0)	13	62 (3.5)	8	1.13 (0.81 to 1.58)	0.48
Sepsis	75 (4.3)	3	76 (4.3)	4	0.98 (0.72 to 1.34)	0.91
Septic shock	18 (1.0)	3	20 (1.1)	4	0.90 (0.48 to 1.69)	0.73
Stroke	16 (0.9)	3	11 (0.6)	3	1.45 (0.67 to 3.11)	0.34
Type 2 neurologic dysfunction	119 (6.8)	3	128 (7.3)	3	0.93 (0.73 to 1.18)	0.53
Need for noninvasive ventilation	518 (29.4)	3	615 (35.1)	4	0.94 (0.86 to 1.03)	0.19
Need for reintubation	67 (3.8)	3	53 (3.0)	3	1.26 (0.88 to 1.79)	0.20
Readmission to intensive care unit	54 (3.1)	18	52 (3.0)	19	1.03 (0.71 to 1.50)	0.86
Wound infection	28 (1.6)	3	34 (1.9)	3	0.82 (0.50 to 1.35)	0.43

* The 95% confidence intervals presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible.

† Mechanical circulatory support refers to intraaortic balloon pump, venoarterial extracorporeal membrane oxygenation, or left ventricular assist device, implemented either at the time of weaning from cardiopulmonary bypass or in the intensive care unit.

ropean and high-income countries, the trial population differed substantially from patients in low- and middle-income countries and from patients in geographic regions with an ethnic distribution that differed from that in our trial population (see the Supplementary Appendix). Fifth, we acknowledge the lack of data on tubular injury. However, no histologically validated markers of such hypothetical injury exist because renal biopsies are not performed during cardiac surgery and cannot be justified. Sixth, although serum creatinine values obtained before hospitalization would have been preferable, the majority of baseline serum creatinine levels were measured within a few days before surgery. Finally, some patients had protocol deviations (e.g., underwent off-pump surgery), but our findings in the per-protocol analyses were robust.

In this trial involving adult patients scheduled to undergo elective cardiac surgery with cardiopulmonary bypass, the infusion of amino acids significantly decreased the overall occurrence of AKI.



No. at Risk

Amino acid group	1759	1739	1516	1397	1372	1351	1334	1285
Placebo group	1752	1728	1436	1289	1270	1256	1246	1197

Figure 1. Freedom from Acute Kidney Injury.

A Kaplan–Meier time-to-event plot shows the proportion of patients in whom acute kidney injury (AKI) did not develop within 7 days after randomization.

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APPENDIX

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