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Intravenous amino acids for renal protection in patients receiving temporary mechanical circulatory support: a secondary subgroup analysis of the PROTECTION study

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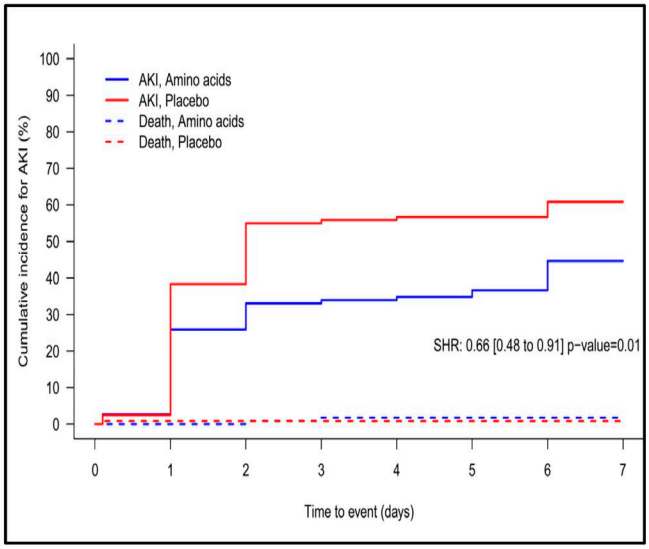
Intravenous amino acids for renal protection in patients receiving temporary mechanical circulatory support: a secondary subgroup analysis of the PROTECTION study

Summary

In this post-hoc analysis of a multicenter, randomized, double-blind study, we found that perioperative administration of intravenous amino-acids, as compared with placebo, reduces rate of AKI in patients requiring tMCS following cardiac surgery (44.6% vs. 60.8%; relative risk 0.73; 95% confidence interval [0.57 to 0.94]; p=0.01; NNT=6)



Legend: AKI = acute kidney injury; NNT = number needed to treat; tMCS = temporary mechanical circulatory support; SHR = Sub-distribution hazard ratio

Abstract

OBJECTIVES: In cardiac surgery patients, acute kidney injury (AKI) frequently occurs in the setting of haemodynamic instability and treatment with temporary mechanical circulatory support (tMCS). Recent evidence suggests amino acids (AA) infusion may reduce AKI rate. However, the effect of AA infusion in patients requiring tMCS may be less effective.

METHODS: We performed a secondary analysis of the PROTECTION multicentre randomized controlled trial including all patients treated with tMCS. Patients undergoing elective cardiac surgery with cardiopulmonary bypass were randomized to receive 2 g/kg ideal body weight/day of intravenous AA to a maximum of 100 g/day or matching placebo from operating room admission until up to 3 days, receipt of renal-replacement therapy, discharge from ICU or death. The primary outcome of the PROTECTION study was the rate of AKI, as in this secondary analysis. A total of 3511 patients were randomized in the study.

RESULTS: We studied 232 patients who received tMCS, 112 randomized to AA infusion and 120 to placebo. The median preoperative serum creatinine value was significantly higher among AA group patients (AA: 1.08, interquartile range 0.90–1.26; placebo: 0.98, interquartile range 0.85–1.15; $P = 0.02$). The rate of AKI, however, was lower in patients randomized to AA (44.6% vs 60.8%; relative risk 0.73; 95% confidence interval (0.57–0.94); $P = 0.01$; number needed to treat = 6). We found no significant differences in secondary outcomes.

CONCLUSIONS: Short-term AA infusion appears to reduce rate of AKI among patients requiring tMCS. Use of AA in this population at high-risk for renal failure appears justified.

Clinical trial registration number: ClinicalTrials.gov NCT03709264.

Keywords: Cardiogenic shock • Acute kidney injury • Renal-replacement therapy • Acute heart failure • Extracorporeal membrane oxygenation • Micro-axial flow pump

ABBREVIATIONS

AA	Amino acids
AKI	Acute kidney injury
CI	Confidence interval
ECMO	Extracorporeal membrane oxygenation
EQ-5D	European quality of life-five dimensions
IABP	Intra-aortic balloon pump
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
RR	Relative risk
RRT	Renal-replacement therapy
SHR	Sub-distribution hazard ratio
tMCS	Temporary mechanical circulatory support

INTRODUCTION

In cardiac surgery patients, acute kidney injury (AKI) is particularly common in the presence of haemodynamic instability and

is associated with increased short- and long-term morbidity and mortality [1–6]. The rate and severity of AKI increase with shock severity [3, 7]. They are particularly high among patients receiving temporary mechanical circulatory support (tMCS) [7]. Moreover, AKI requiring renal-replacement therapy (RRT) is also a major complication of severe cardiogenic shock requiring tMCS [8] and may jeopardize the outcomes of these devices [9].

Renal hypoperfusion is a believed to be a major contributor to development of AKI in patients with cardiogenic shock [10]. Several pre-clinical studies and small randomized controlled trials have suggested that intravenous amino acids (AA) infusion may recruit renal functional reserve [11, 12] and, thereby, improve renal function in humans [12–16].

We recently completed the Intravenous Amino Acids Therapy for Kidney Protection in Cardiac Surgery (PROTECTION) trial, a multicentre randomized controlled trial comparing perioperative intravenous AA infusion versus placebo in patients undergoing cardiac surgery with cardiopulmonary bypass [17–19]. The study showed that perioperative, short-term AA infusion reduced the rate of AKI, including severe AKI [18].

Thus, we hypothesized that, in these patients, considering the degree of haemodynamic instability and renal hypoperfusion, the efficacy of AA infusion would be insufficient to prevent AKI. To test this hypothesis, we performed a *post-hoc* analysis of the PROTECTION study to investigate the effect on AKI of intravenous AA in patients who received perioperative tMCS.

PATIENTS AND METHODS

Study design

We performed a *post-hoc* subgroup analysis of a multinational, randomized, double-blind, placebo-controlled trial (the PROTECTION trial), including 3511 adult patients undergoing elective cardiac surgery with cardiopulmonary bypass between October 2019 and January 2024.

After providing written informed consent, eligible patients were randomized to receive a continuous infusion of a mixture of AA (Isopuramin 10%, Baxter) at a dose of 2 g/kg of ideal body weight/day (up to a maximum of 100 g per day) or an equivalent dose of placebo (Ringer's solution, Baxter), from operating room admission and for a maximum of 72 h. The details of the protocol and of the study have been previously published [17, 18].

Ethics Committee at each participating centre approved the trial protocol.

Population

In this subgroup analysis, we included all the patients randomized into the PROTECTION trial who received any type of perioperative tMCS. Our population was divided into 2 groups according to randomization-based treatment assignment (AA and placebo groups).

Outcomes

The primary outcome was the incidence of AKI, defined by the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria [20, 21].

To assess possible subgroups in the overall PROTECTION population, we performed an interaction analysis of the incidence of AKI in the AA and placebo groups, according to the application of tMCS and, more specifically, the application of intra-aortic balloon pump (IABP) and of extracorporeal membrane oxygenation (ECMO).

Secondary outcomes included severity of AKI as defined by the KDIGO AKI guidelines [20, 21], the need for RRT during hospital stay, duration of ICU and hospital stay, duration of mechanical ventilation, all-cause mortality at different time points (ICU discharge, 30-day, 90-day and 180-day mortality) and quality of life at 180 days, evaluated by European quality of life-five dimensions (EQ-5D). The EQ-5D estimates quality of life by considering 5 domains, and then using a subjective rating scale from 0 to 100. A higher score indicates better quality of life.

Statistical analysis

Dichotomous variables were compared using the two-tailed chi-square test or Fisher's exact test, as appropriate. Normality of data distribution was tested with the Shapiro–Wilk test. Continuous variables with skewed distribution were expressed as medians and interquartile ranges (IQRs) and compared using the Wilcoxon Mann–Whitney test. For continuous variables with normal distribution, we employed means and standard deviations, compared using the *t*-test. For the primary outcome, we applied the chi-square test and reported the difference between groups as a relative risk (RR) with its 95% confidence intervals (CIs). Between-group differences for secondary outcomes were reported as RRs or mean differences with their 95% CIs for dichotomous and continuous variables. Dichotomous outcomes, analysed using the chi-square test, included severity of AKI, need for renal replacement therapy, ICU mortality, 30-day mortality, 90-day mortality and 180-day mortality. Continuous outcomes, analysed using the *t*-test, included length of ICU stay, length of hospital stay, duration of mechanical ventilation and quality of life at 180 days. In the interaction model, values were expressed as RRs and their 95% CIs. For the time-to-event analyses of AKI, AKI stage 3 and RRT, we employed a Fine and Gray model, considering death as a competing risk within the first 7 days. Sub-distribution hazard ratios (SHR) with their 95% CIs were calculated to compare the risk between the 2 treatment groups, and the curves were represented using a cumulative incidence function. For the time-to-event analysis of death, we used a Cox proportional hazards model, compared the survival curves with the log-rank test, and displayed them using a Kaplan–Meier plot; the results were reported as hazard ratios with their 95% CIs. We performed a sensitivity analysis based only on the patients who received IABP as the tMCS device. No imputation for missing data was applied.

A two-sided P-value < 0.05 was considered statistically significant. Data were analysed using SAS (Statistical Analysis System Inc, Cary, NC, release 9.4.), Stata software, version 18 (StataCorp, Texas) and R-software version 4.4.1 (R-project, Vienna).

RESULTS

Among the PROTECTION trial population, a total of 232 patients received perioperative tMCS (at least 1 type) and were included in this secondary study (112 in the AA group vs 120 in the

placebo group) (Supplementary Material, Fig. S1). Among these patients, IABP was used in 90/112 (80.4%) AA patients vs 107/120 (89.2%) placebo patients. Moreover, 17 vs 14 patients received ECMO, and 13 vs 9 patients required other types of tMCS [e.g. left ventricular assist device, Impella® (Abiomed, Danvers, MA, USA)]. The median preoperative serum creatinine value was significantly higher among AA group patients (AA: 1.08, IQR, 0.90–1.26; placebo: 0.98, IQR, 0.85–1.15; $P = 0.02$). There was balance between the AA and placebo groups in terms of all other baseline demographic and clinical characteristics, surgical interventions, intraoperative management (Table 1) (Supplementary Material, Table S1) and haemodynamic status on ICU admission (Supplementary Material, Table S2).

Study intervention

The median study product infusion rate was 40 ml/h (IQR, 40–40) in both groups. Patients received a median dose of 3000 ml of study drug, corresponding to 300 g of AA (Supplementary Material, Table S3). Most of them (58.0% vs 53.3%, in AA and control group, respectively) completed the maximum 72-h treatment period, while 29.5% vs 25.8% stopped the infusion due to ICU discharge.

Primary and secondary outcomes

Among patients receiving perioperative tMCS, AKI was common with a rate >60% in the placebo group, rising to >90% in patients

Table 1: Baseline and intraoperative characteristics of study patients requiring perioperative temporary mechanical circulatory support

Variable	Amino acids group *N* = 112	Placebo group *N* = 120	*P*-value
Age (year), median (IQR)	66.0 (58.8; 73.0)	69.0 (61.0; 74.0)	0.108
Female sex, *n* (%)	30 (26.8)	35 (29.2)	0.797
Body-mass index, median (IQR)[a]	25.4 (23.5; 28.5)	25.9 (23.1; 28.2)	0.917
Preoperative serum creatinine (mg/dl), median (IQR)[b]	1.08 (0.90; 1.26)	0.98 (0.85; 1.15)	0.020
Left ventricular ejection fraction (%), median (IQR)	49.5 (39.0; 60.0)	52.5 (40.0; 60.0)	0.327
New York Heart Association class, *n* (%)			
I	19 (17.0)	8 (6.67)	0.025
II	63 (56.2)	78 (65.0)	0.219
III	27 (24.1)	29 (24.2)	1.000
IV	3 (2.7)	5 (4.2)	0.723
Current smoker, *n* (%)	26 (23.2)	22 (18.3)	0.605
Race or ethnic group, *n* (%)			0.498
White	112 (100)	117 (97.5)	
Other	0 (0.0)	3 (2.5)	
Medical condition, *n* (%)			
Arterial hypertension on medical treatment	69 (61.6)	75 (62.5)	0.996
Previous myocardial infarction	30 (26.8)	27 (22.5)	0.403
Atrial fibrillation	35 (31.2)	43 (35.8)	0.549
Previous stroke or transient ischemic attack	6 (5.4)	6 (5.0)	1.000
Cardiac catheterization in the past 48 h	19 (17.0)	13 (10.8)	0.253
Diabetes on medical treatment	27 (24.1)	27 (22.5)	0.698
Peripheral vascular disease	17 (15.2)	29 (24.2)	0.074
Previous cardiac surgery	17 (15.2)	21 (17.5)	0.764
Preoperative medical therapy, *n* (%)			
Beta blockers	71 (63.4)	82 (68.3)	0.513
ARB or ACE inhibitor	56 (50.0)	72 (60.0)	0.162
Statin	52 (46.4)	56 (46.7)	1.000
Antiplatelet	50 (44.6)	51 (42.5)	0.844
Diuretics	61 (54.5)	70 (58.3)	0.644
Anticoagulant	36 (32.1)	44 (36.7)	0.558
Duration of cardiopulmonary bypass (min), median (IQR)	106 (81.5; 129)	114 (90.0; 158)	0.077
Surgery type, *n* (%)			
CABG	53 (47.3)	55 (45.8)	0.946
Mitral valve	45 (40.2)	57 (47.5)	0.322
Aortic valve	39 (34.8)	46 (38.3)	0.424
Other	6 (5.4)	7 (5.8)	0.627
Intraoperative loop diuretics, *n* (%)	61 (54.5)	59 (49.2)	0.631
Use of haemofiltration during CPB, *n* (%)	17 (15.2)	14 (11.7)	0.584
Intraoperative vasoactive and inotropic drugs, *n* (%)	102 (91.1)	112 (93.3)	0.453
Epinephrine	89 (79.5)	96 (80.0)	1.000
Norepinephrine	42 (37.5)	49 (40.8)	0.591
Dobutamine	8 (7.1)	8 (6.7)	0.494
Other	3 (2.7)	6 (5.0)	0.409

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; Hb: haemoglobin; IQR: interquartile range; NYHA: New York Heart Association class for heart failure (range I–IV, class I is a patient asymptomatic for heart failure, class IV is a patient with symptoms of heart failure at rest).

[a]The body-mass index is the weight in kilograms divided by the square of the height in meters.

[b]To convert the values for serum creatinine to millimoles per liter, multiply by 88.4.

Table 2: Outcomes in patients with temporary mechanical circulatory support

Primary outcome	Amino acid group ($n = 112$)		Placebo group ($n = 120$)		Relative risk, absolute Mean Difference (95% CI)[a]	*P*-value
	Value	No. with missing data	Value	No. with missing data		
In-hospital AKI, *n* (%)[b]	50 (44.6)	0	73 (60.8)	0	0.73 (0.57 to 0.94)	0.01
Stage 1	40 (35.7)		57 (47.5)		0.75 (0.55 to 1.03)	0.07
Stage 2	0 (0.0)		0 (0.0)		N/A	N/A
Stage 3	10 (8.9)		16 (13.3)		0.67 (0.32 to 1.41)	0.29
Secondary outcomes						
Renal-replacement therapy during hospital stay, *n* (%)	9 (8.0)	0	12 (10.0)	0	0.80 (0.35 to 1.83)	0.60
Duration of mechanical ventilation (hours), median (IQR)	24 (16 to 74)	6	21 (15 to 46)	6	−18.22 (−40.96 to 4.51)[c]	0.12
Duration of stay in intensive care unit (hours), median (IQR)	89 (48 to 144)	1	90 (51 to 159)	1	12.77 (−36.20 to 61.74)[c]	0.61
Duration of stay in hospital (nights), median (IQR)	10 (6 to 15)	0	8 (6 to 15)	0	0.27 (−3.37 to 3.91)[c]	0.88
ICU mortality, *n* (%)	14 (12.5)	0	15 (12.5)	0	1.00 (0.51 to 1.98)	1.00
30-day mortality, *n* (%)	16 (14.3)	0	18 (15.0)	0	0.95 (0.51 to 1.77)	0.88
90-day mortality, *n* (%)	17 (15.2)	0	17 (14.2)	1	1.06 (0.57 to 1.98)	0.85
180-day mortality, *n* (%)	18 (16.1)	0	19 (15.8)	1	1.01 (0.56 to 1.81)	0.98
Quality of life at 180 days (EQ-5D), median (IQR)[d]	80 (70 to 90)	54	80 (70 to 90)	63	1.23 (−6.19 to 8.65)[c]	0.74

AKI: acute kidney injury; CI: confidence interval; IQR: interquartile range; EQ-5D: European quality of life-five dimensions.

[a]Data are presented as relative risks for dichotomous outcomes and as absolute mean differences for continuous outcomes.

[b]Acute kidney injury is defined according to KDIGO 2012 guidelines.

[c]Data are presented as absolute mean difference.

[d]The EQ-5D estimates quality of life by considering five domains, and then using a subjective rating scale from 0 to 100. A higher score indicates better quality of life.

receiving ECMO. We found a statistically significant reduction of AKI in the AA group compared to placebo [44.6% vs 60.8%; RR, 0.73; 95% CI, 0.57–0.94; $P = 0.01$; number needed to treat = 6] (Table 2) (Graphical abstract). When we considered death as a competing risk, Fine and Gray competing risks analysis showed a SHR of 0.66 (95% CI, 0.48–0.91) for AKI in the AA group compared to placebo, with a 34% reduction in the cumulative risk (Grey's test $P = 0.01$) (Fig. 1).

Stage 1 AKI was diagnosed in the majority of patients ($n = 40$, 35.7% vs $n = 57$, 47.5%; RR, 0.75; 95% CI, 0.55–1.03; $P = 0.07$). No patients had stage 2 AKI; however, there was a >30% RR reduction in stage 3 AKI ($n = 10$, 8.9% vs $n = 16$, 13.3%; RR, 0.67; 95% CI, 0.32–1.41; $P = 0.29$) (Table 2). Six patients in the AA group and 12 patients in the placebo group received RRT during the first 7 days after surgery, but only 1 in each group was diagnosed as stage 3 AKI because of this RRT initiation. Eight patients died within the first 7 days in each of the 2 randomization groups. There were no significant differences in other secondary outcomes. Cumulative incidence figures for AKI stage 3 and RRT are shown in Supplementary Figs S2 and S3 (SHR, 0.66; 95% CI, 0.30–1.43, $P = 0.29$; and SHR, 0.50; 95% CI, 0.20–1.40; $P = 0.20$, respectively). Criteria for RRT initiation are listed in Supplementary Material, Table S4.

Survival analysis for all-cause mortality at 180 days post-randomization revealed no significant difference between the 2 groups (hazard ratio, 1.02; 95% CI, 0.54–1.94; log rank *P*-value = 0.95), further supporting the safety profile of AA treatment with respect to long-term mortality (Supplementary Material, Fig. S4).

We found no significant subgroup effect of tMCS in the interaction analysis including all PROTECTION patients (interaction *P*-value = 0.09) (Fig. 2). Sensitivity analysis including only patients who received IABP confirmed the beneficial effect of AA on AKI (43.3% vs 61.7%; RR, 0.70; 95% CI, 0.53–0.93; $P = 0.01$; number needed to treat = 5) (Supplementary Material, Table S5). Among patients who received ECMO, AKI occurred in 82.4% (AA group) vs 92.9% (placebo group) (RR, 0.89; 95% CI, 0.68–1.15; $P = 0.39$) (Supplementary Material, Table S6).

DISCUSSION

Key findings

Among the PROTECTION study population, we found that in patients receiving IABP, the rate of AKI was >60%, and such rate increased to >90% in patients treated with ECMO. In these patients receiving tMCS, however, contrary to our expectations, we found that perioperative, short-term AA infusion significantly reduced the rate of AKI by 30%. Finally, this reduction was similar in magnitude for stages 1 and 3 AKI and for the use of RRT.

Relationship to previous studies and pathophysiological background

The overall rate of AKI in our study is consistent with previous data from studies of patients requiring tMCS for circulatory failure [1–3, 9, 22, 23], including patient with post-cardiotomy shock [24]. However, we observed a slightly lower rate of AKI requiring RRT, suggesting a possible different baseline risk of AKI between patients with low cardiac output syndromes in the setting of cardiac surgery compared with patients with other causes of cardiogenic shock and/or a more conservative approach to the start of RRT.

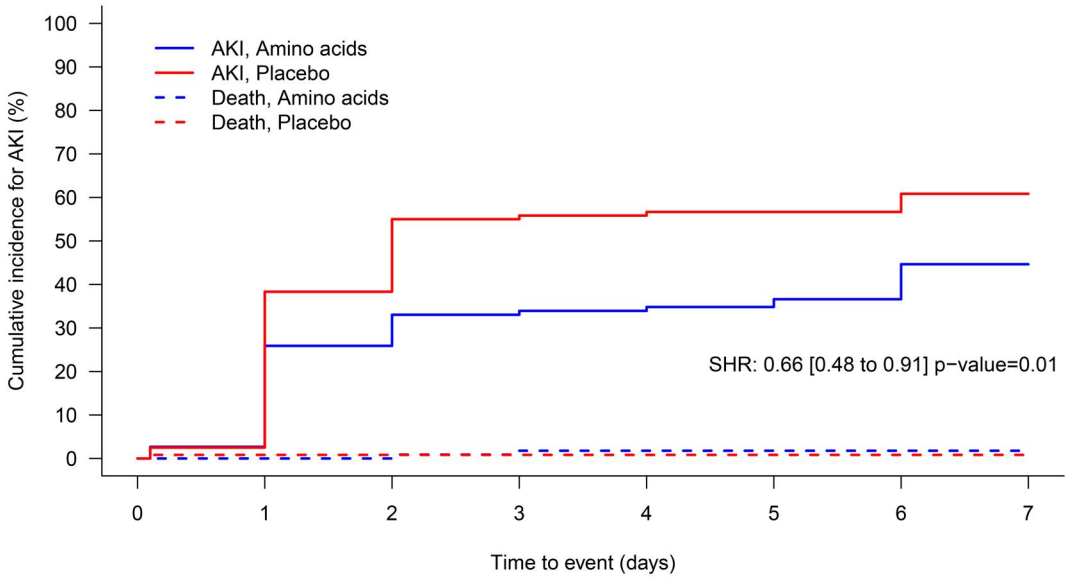


Figure 1: Cumulative incidence of acute kidney injury (primary outcome). AKI: acute kidney injury; CI: confidence interval; SHR: sub-distribution hazard ratio.

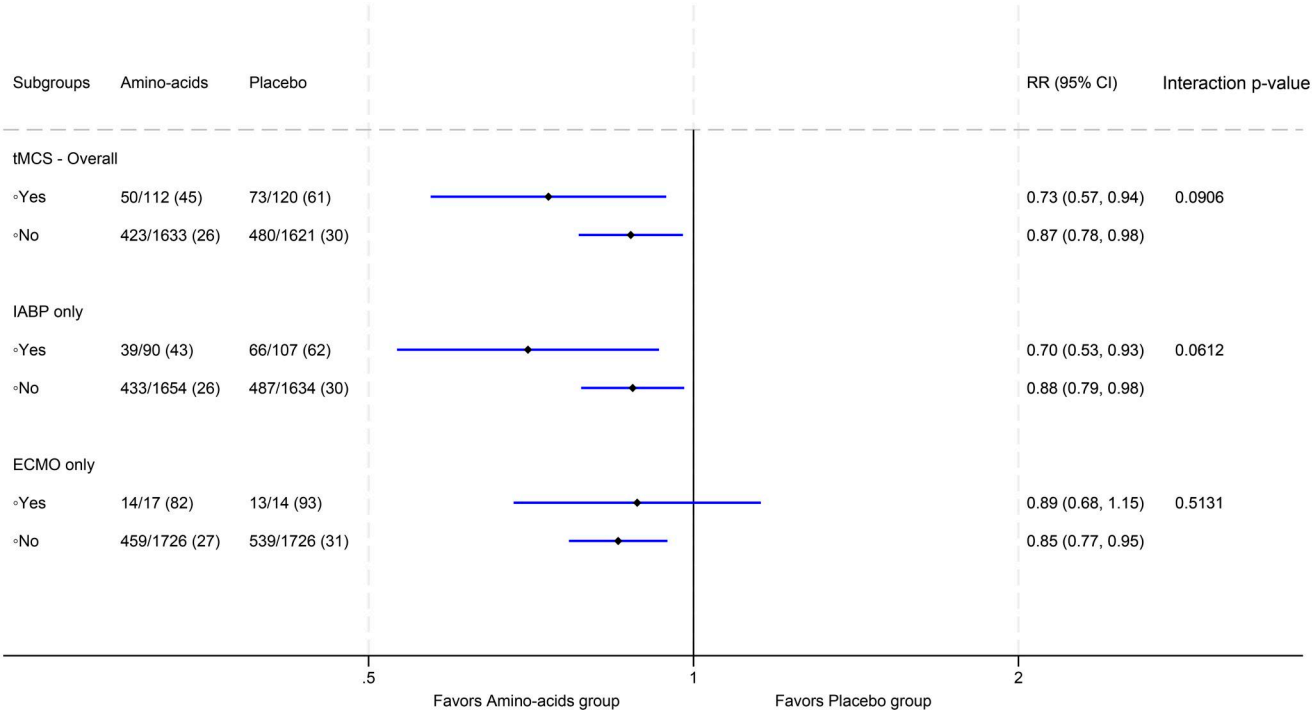


Figure 2: Subgroup analyses for the occurrence of acute kidney injury stratified by the use of temporary mechanical circulatory support. CI: confidence interval; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; RR: relative risk; tMCS: temporary mechanical circulatory support.

AKI in patients on tMCS is particularly complex, since multiple, interacting and sometimes synergistic pathophysiological elements may contribute to AKI [25], including haemolysis [26–28]. Furthermore, ischaemia-reperfusion injury might be expected at the time of tMCS initiation, which is associated with AKI development [29, 30]. Moreover, during tMCS, the interface between circulating blood and the artificial surfaces of the devices may precipitate a degree of haemolysis, bleeding and formation of microthrombi and inflammation [31]. Because of all the above-mentioned mechanisms, there has been great interest in the prevention and treatment of AKI in patients on tMCS. Despite several approaches that may mitigate such risk (e.g. avoidance of nephrotoxins, adequate optimization of haemodynamics, antithrombotic treatment, avoidance of haemolysis), no single therapeutic interventions had yet been found to reduce the incidence of AKI in this setting.

Implication of study findings

Our findings suggest that the effects of AA infusion on the occurrence of AKI seen in the primary trial apply to patients receiving tMCS. Moreover, they suggest that such an effect was mostly dependent on the largest group of such tMCS patients, those receiving IABP. They also suggest the need of further investigations of AA infusion in patients receiving advanced support such as ECMO after cardiac surgery. Finally, they suggest that the magnitude of effect was similar for AKI stage 1, AKI stage 3 and the need for RRT. Considering the overall findings of the PROTECTION study, we suggest AA infusion using the PROTECTION protocol to all patients undergoing cardiac surgery meeting inclusion/exclusion criteria of the study. Furthermore, we believe that the effect of AA infusion in patients receiving tMCS should be investigated in dedicated studies. Considering the overall results of the PROTECTION study, the absence of significant adverse events and the high rate of AKI in patients receiving tMCS, we believe that administration of AAs according to the PROTECTION protocol in patients receiving tMCS is justified.

Strengths and limitations of the study

To the best of our knowledge, this is the 1st study investigating the effect of short-term intravenous AA infusion on AKI in patients receiving tMCS [12]. Our study is also the 1st to provide data from a double-blinded randomized controlled trial on a strategy for potential protection from AKI in this specific population [12]. Our overall study was multicentre, randomized and double-blinded in design, thus presenting a high internal and external validity. Our data are consistent with previous pre-clinical and clinical studies and have a strong biological rationale. The intervention is cheap, simple and safe, and may be easily applied to the majority of patients.

We acknowledge several limitations. Our observations showed a statistically significant decrease in AKI only for patients receiving the IABP. As only a minority received other support devices, the study was not sufficiently powered to detect an effect in such patients. However, we cannot exclude a differential effect of AA in pulsatile versus continuous flow tMCS [32–36]. As IABP is generally reserved for patients with less-severe shock, we also cannot exclude that patients in the early stage of low cardiac output syndromes may benefit more or less from AKI-preventing strategies. Despite randomization, the poorer baseline kidney function in the treatment group may have underestimated the therapeutic potential of AA. On the other hand, a non-significant trend towards longer cardiopulmonary bypass time (a risk factor for AKI) was recorded in the placebo patients. All these issues may have influenced results and warrant exploration in future studies. Furthermore, since the PROTECTION trial was designed as a pragmatic study, we did not collect certain scores and parameters that could have provided a more comprehensive understanding of patients' disease severity and haemodynamic status at ICU admission, such as the APACHE2 and SOFA scores, as well as cardiac output and $ScvO_2$. Our results were primarily driven by a reduction in stage 1 AKI, although the magnitude and direction of results were consistent for different AKI severity stages. A similar reduction in severe (stage 3) AKI was observed in the overall PROTECTION population. This is a secondary post-hoc subgroup analysis; therefore, we are underpowered to investigate specific outcomes and, in this *post-hoc* study, we are not assessing the primary objective of the PROTECTION trial. Nevertheless, this is the 1st hypothesis-generating study in this unique high-risk population. Our data derive from patients who received tMCS following cardiac surgery and were mostly supported with IABP. Therefore, our data may not apply to patients with other causes of low cardiac output syndromes or receiving different types of tMCS, in particular those receiving micro-axial flow pump. We did not collect data on haemolysis rate, which may have a significant impact on rate of AKI in patients receiving tMCS [9, 26–28]. In such cases, our findings may not apply.

CONCLUSIONS

In patients requiring tMCS following cardiac surgery, intravenous AA infusion reduced the rate and severity of AKI. Further clinical studies focused on patients receiving tMCS in surgical and non-surgical settings appear justified.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

FUNDING

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Conflict of interest: none declared.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

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