Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-025-02804-0

ORIGINAL ARTICLE

Diabetes does not modify the renal-protective effect of intravenous amino acids infusion after cardiac surgery

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Received: 21 October 2025 / Accepted: 28 December 2025

Abstract

Purpose Acute kidney injury (AKI) is a common complication after cardiac surgery and is associated with increased morbidity and mortality. Intravenous amino acids (AA) infusion reduces postoperative AKI. Given the high prevalence of patients with diabetes and their increased susceptibility to renal injury, this study aimed to assess whether the renal-protective effect of AA infusion is maintained in this population.

Methods This post-hoc subgroup analysis examined patients with diabetes included in the multinational, double-blind, randomized, placebo-controlled PROTECTION trial. Participants were randomized to receive a continuous intravenous infusion of AA (2 g/kg of the ideal body weight per day; up to 72 h) or placebo during the perioperative period of cardiac surgery.

Results Among 644 patients with diabetes (AA $n=309$; placebo $n=335$), the incidence of any-stage AKI was 43.3% in the AA group versus 47.8% in the placebo group, with no significant interaction observed compared to patients without diabetes (interaction $p=0.82$). Similarly, stage 3 AKI occurred in 2.3% of patients in AA group versus 4.8% in the placebo group, with no interaction detected (interaction $p=0.65$).

Conclusion The beneficial effect of perioperative AA infusion has similar magnitude and direction among patients with or without diabetes. These findings support the use of AA infusion as a renal-protective strategy for all patients undergoing cardiac surgery.

Trial registration number ClinicalTrials.gov NCT03709264 – registered on October 17th, 2018.

Keywords Acute kidney injury · Amino acids · Anesthesia · Cardiac surgery · Cardiopulmonary bypass · Renal-replacement therapy

Introduction

Diabetes mellitus (DM) is a global epidemic affecting approximately 537 million adults as of 2021 [1]. Among surgical populations, up to 20% of individuals undergoing general surgery have DM,[1] and the prevalence is even higher in cardiac surgery cohorts, with studies reporting up to 43% of patients undergoing coronary artery bypass grafting (CABG) are affected [1, 2].

Acute kidney injury (AKI) is a frequent and serious complication after cardiac surgery, associated with substantial short- and long-term morbidity and mortality [3]. Among established risk factors, DM plays a central role as an independent determinant of AKI, complicating perioperative

A complete list of PROTECTION Study Group Collaborators is provided in the Supplementary Appendix

Extended author information available on the last page of the article

Published online: 09 January 2026

management of affected patients [4]. Furthermore, the relationship between AKI and DM is bidirectional: AKI is a potential contributor to the development of new-onset DM, creating a self-perpetuating cycle that accelerates progression towards chronic kidney disease (CKD) [5]. The coexistence of preexisting CKD further increases susceptibility to AKI [6]. In this complex clinical context, targeted preventive strategies are essential. A recent large randomized trial (the PROTECTION trial) demonstrated that intravenous amino acids (AA) infusion reduces the incidence of AKI in patients undergoing cardiac surgery [7]. By recruiting the renal functional reserve, AA may preserve kidney function from acute injury [8–12], even in high-risk subgroups [13, 14]. Given the high prevalence of DM in the cardiac surgical population and its strong association with the AKI risk [15], it is important to determine whether the efficacy of AA infusion differs between patients with or without DM.

Accordingly, we conducted a post-hoc analysis of the PROTECTION trial [7] to assess whether the perioperative AA infusion reduces the incidence of AKI after elective cardiac surgery in patients with DM.

Methods

Study design

This post-hoc analysis was conducted within the PROTECTION trial[7], a multinational, randomized, double-blind, placebo-controlled study performed across 22 institutions in different countries [7]. The PROTECTION trial enrolled patients scheduled for elective cardiac surgery with cardiopulmonary bypass (CPB) between October 28, 2019, and January 17, 2024. Details of the trial design and main results have been reported previously [7, 16]. Briefly, 3,511 adult patients meeting the eligibility criteria were randomized to receive a continuous intravenous infusion of either a balanced AA solution (Isopuramin 10%; Baxter, USA) at 2 g/kg of the ideal body weight per day (maximum 100 g/day), or a placebo (Ringer's solution; Baxter) at equivalent volume. The infusion was initiated in the operating room and continued for up to 72 h, until intensive care unit (ICU) discharge, or initiation of renal replacement therapy (RRT), whichever occurred first. The primary endpoint of the original trial was the occurrence of AKI, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [17]. Study protocols were approved by the ethics committees of all participating institutions, and all patients provided written informed consent. The trial was supported by the Italian Ministry of Health.

Inclusion and exclusion criteria

Eligible participants were adults (aged ≥ 18 years) undergoing elective cardiac surgery requiring CPB and a planned postoperative ICU stay of at least one night. Key exclusion criteria included ongoing or planned RRT and advanced CKD (estimated glomerular filtration rate [GFR] < 30 mL/min/1.73 m^2). For this post-hoc analysis, we included patients with pre-existing DM, defined as active treatment with insulin or glucose-lowering agents prior to surgery.

Outcomes

The primary endpoint was to compare AKI within 7 days after randomization (according to the KDIGO serum creatinine criteria [17]) in patients with or without DM. Baseline creatinine was defined as the most recent value obtained prior to randomization, either during hospital admission or within the previous 12 months. Secondary outcomes included the highest AKI stage, need for and duration of RRT, length of stay in ICU and hospital, duration of mechanical ventilation, and all-cause mortality at predefined time points. Interaction analyses were performed to evaluate the treatment effects (AA vs. placebo) stratified by DM status.

Statistical analysis

Categorical variables were reported as absolute frequencies and percentages and compared using chi-square or Fisher's exact tests, as appropriate. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and compared using t-test or Wilcoxon–Mann–Whitney test, as appropriate. Between-group differences in both primary and secondary outcomes were expressed as relative risks (RRs) for binary outcomes, and mean differences (MDs) for continuous variables, with corresponding 95% confidence intervals (CIs). A sensitivity analysis was performed among patients with DM receiving insulin therapy at baseline.

Subgroup analyses were performed according to sex, age, New York Heart Association (NYHA) heart failure class, and baseline eGFR. Interaction terms were reported as RRs with 95% CIs.Time-to-event analyses for any-stage AKI, and RRT initiation were performed using the Fine and Gray competing risk model, with death within the first 7 days treated as a competing event. Gray's test was used to compare cumulative incidence of functions, reporting subdistribution hazard ratios (SHRs) with 95% CIs.

Bayesian analysis of the primary outcome was also performed using a semi-informative prior derived from a recent meta-analysis [18] (excluding the PROTECTION trial to

prevent double counting), combined with a non-informative component on the log-RR scale. Event counts were modelled using binomial likelihoods, and 100,000 Monte Carlo simulations were used to generate the posterior RR distribution. We report the posterior probability of benefit (Pr[RR < 1]) and the corresponding 95% credible interval.

All analyses were two-sided, with $p<0.05$ considered statistically significant. Statistical analyses were performed using Stata version 18 (StataCorp, USA), R-software version 4.4.1 (R Foundation for Statistical Computing, Vienna), and SAS version 9.4 (SAS Institute, USA).

Results

Characteristics of the study population

Among the 3,511 patients enrolled in the PROTECTION trial, 644 (18.3%) had preexisting DM treated with medical therapy at the time of randomization. Of these, 309 were assigned to the AA group and 335 to the placebo group. Whitin this cohort with DM, 118 patients in the AA group and 122 in the placebo group were receiving insulin therapy at baseline (Fig. 1). Baseline demographic and intraoperative characteristics were well balanced between AA and placebo groups (Table 1 and Suppl. Table S1). Overall, 69% of patients with DM underwent CABG.

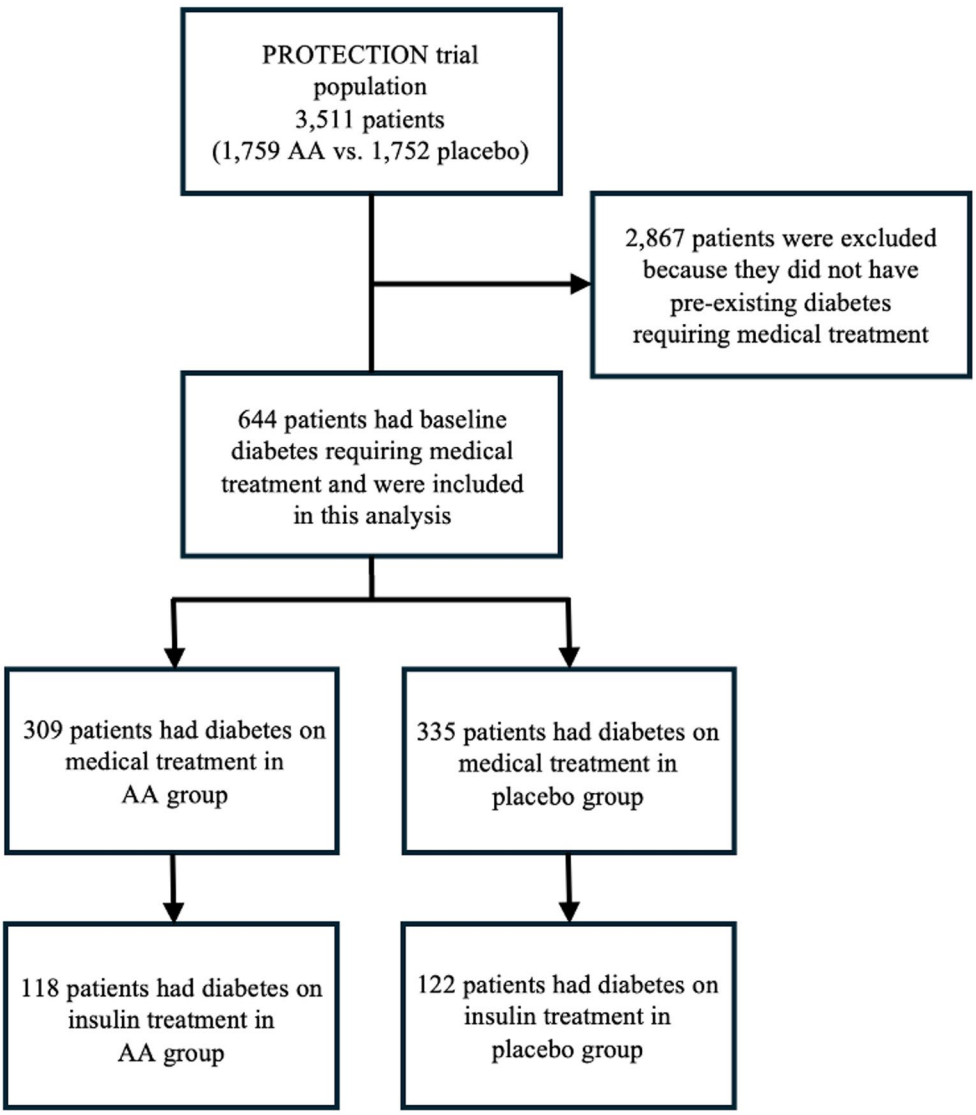

Fig. 1 Flow diagram of patient selection. AA denotes amino acids

Table 1 Baseline and intraoperative characteristics of patients with diabetes at randomization

	Amino Acids	Placebo
	N=309	*N*=335
Median age (IQR) — yr	68 (62–73)	69 (64–74)
Female sex — no. (%)	82 (26.5)	84 (25.1)
Median body-mass index (IQR)†	27.4 (24.5–30.1)	27.3 (24.6–30.8)
Median preoperative serum creatinine (IQR) — mg/dl	1.00 (0.83–1.20)	0.96 (0.81–1.18)
Median preoperative hemoglobin concentration (IQR) – g/dl	13.3 (11.8–14.3)	13.0 (11.8–14.3)
Median left ventricular ejection fraction (IQR) — %	55 (45–60)	55 (50–60)
New York Heart Association class — no. (%)		
I	47 (15.2)	59 (17.6)
II	149 (48.2)	164 (49.0)
III	96 (31.1)	104 (31.0)
IV	16 (5.2)	8 (2.4)
Current smoker — no. (%)	67 (21.7)	64 (19.1)
Race or ethnic group — no. (%)		
White	298 (96.4)	323 (96.4)
Asian	6 (1.9)	7 (2.1)
Other	5 (1.6)	5 (1.5)
Medical condition — no. (%)		
Arterial hypertension on medical treatment	262 (84.8)	289 (86.3)
Previous myocardial infarction	99 (32.0)	96 (28.7)
Atrial fibrillation	54 (17.5)	52 (15.5)
Previous stroke or transient ischemic attack	22 (7.1)	32 (9.6)
Cardiac catheterization in the past 48 h	39 (12.6)	42 (12.5)
Peripheral vascular disease	93 (30.1)	140 (41.8)
Previous cardiac surgery	14 (4.5)	13 (3.9)
Preoperative medical therapy — no. (%)		
Statin	214 (69.3)	239 (71.3)
Antiplatelet	205 (66.3)	216 (64.5)
Beta blockers	186 (60.2)	212 (63.3)
ACE inhibitor or ARB	193 (62.5)	203 (60.6)
Diuretics	143 (46.3)	150 (44.8)
Anticoagulant	66 (21.4)	91 (27.2)
Median duration of on-pump procedure (IQR) — min	92 (75–118)	97 (76–123)
Surgery type — no. (%)		
CABG	210 (68.0)	231 (69.0)
Aortic valve	100 (32.4)	118 (35.2)
Mitral valve	61 (19.7)	66 (19.7)
Other	11 (3.6)	8 (2.4)
Intraoperative loop diuretics — no. (%)	105 (34.0)	112 (33.4)
Use of hemofiltration during CPB — no. (%)	14 (4.5)	29 (8.7)
Intraoperative vasoactive and inotropic drugs — no. (%)	213 (68.9)	208 (62.1)
Norepinephrine	113 (36.6)	125 (37.3)
Epinephrine	77 (24.9)	67 (20.0)
Dobutamine	41 (13.3)	51 (15.2)
Other	14 (4.5)	13 (3.9)

*To convert serum creatinine to millimoles per liter, multiply by 88.4. Percentages may not total 100 because of rounding. ACE denotes angiotensin converting enzyme; ARB angiotensin receptor blocker; CABG coronary artery bypass graft; CPB cardiopulmonary bypass; 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). †The body-mass index is the weight in kilograms divided by the square of the height in meters.

Primary outcomes

The renal-protective effect of AA infusion on AKI was consistent across patients with and without DM, with no evidence of interaction (interaction $p=0.82$) (Fig. 2). Among patients with DM, the incidence of any-stage AKI was 43.3% in the AA group versus 47.8% in the placebo group (RR 0.91, 95% CI 0.77 to 1.08, $p=0.26$) (Table 2) (Suppl. Figure S1). In the Bayesian analysis, the posterior probability of any benefit (RR < 1) was 97.5%, indicating that, given prior evidence and the current data, there is a 97.5% probability that AA infusion truly reduces AKI incidence rather than increases it (Fig. 3).

Findings were confirmed in a sensitivity analysis limited to patients with DM receiving insulin therapy at baseline (Suppl. Figure S2) (Suppl. Table S2).

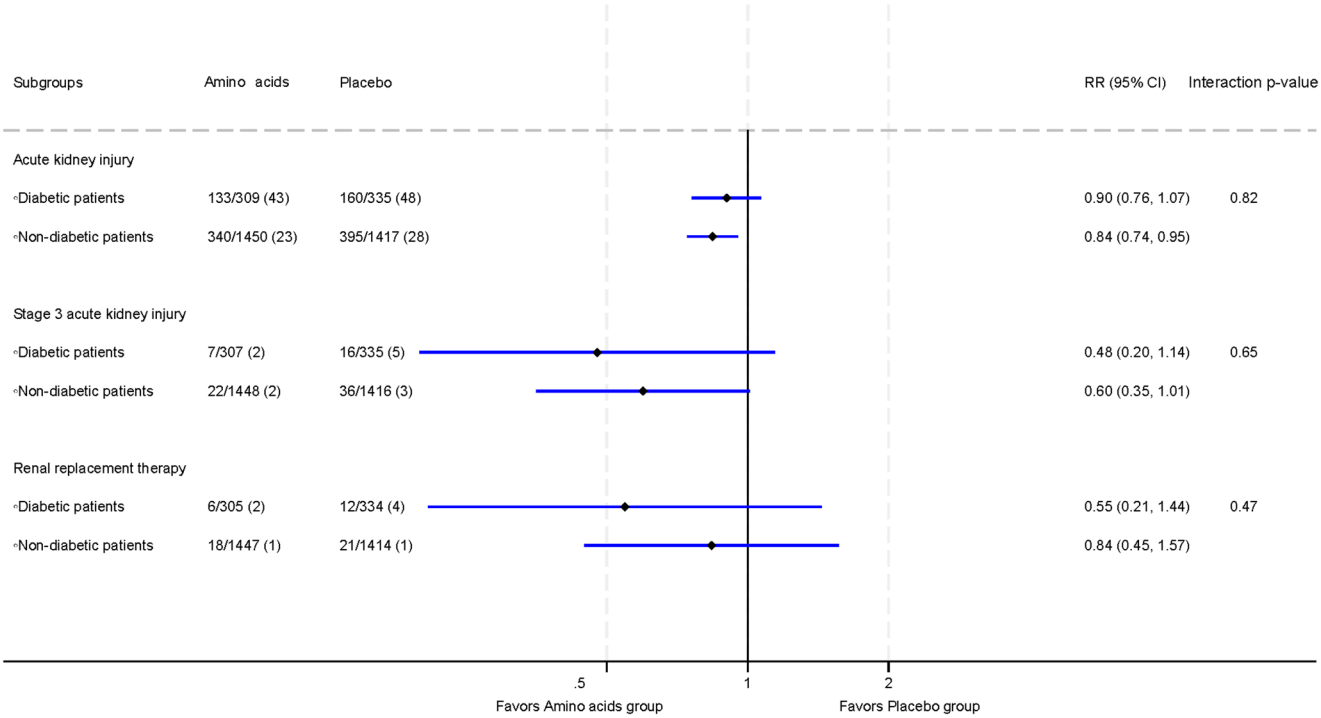

Fig. 2 Subgroup analyses for any stage acute kidney injury (AKI), stage 3 AKI, and need for renal replacement therapy according to diabetes status. RR denotes relative risk, CI confidence interval

Table 2 Primary and secondary outcomes in patients with baseline diabetes requiring medical treatment

	Amino acids ($n=309$)		Placebo ($n=335$)		Relative risk, absolute mean difference (95% CI)	p value
	Value	No. with missing data	Value	No. with missing data		
Primary outcome						
Incidence of in-hospital AKI † — no. (%)	133 (43.3)	2	160 (47.8)	0	0.91 (0.77 to 1.08)	0.26
Stage 1 AKI	120 (39.1)	2	138 (41.2)	0	0.95 (0.79 to 1.15)	0.59
Stage 2 AKI	6 (1.9)	2	6 (1.8)	0	1.09 (0.36 to 3.35)	0.88
Stage 3 AKI	7 (2.3)	2	16 (4.8)	0	0.48 (0.20 to 1.14)	0.089
Secondary outcomes						
Use of renal-replacement therapy — no. (%)	6 (2.0)	4	12 (3.6)	1	0.55 (0.21 to 1.44)	0.22
Renal-replacement therapy duration (IQR) — hours	35 (12 to 89)	0	45 (14 to 80)	1	-52.73 (-171.60 to 66.10)‡	0.35
Mechanical ventilation duration (IQR) — hours	12 (5 to 17)	14	10 (4 to 16)	14	2.52 (-7.02 to 12.07)‡	0.60
Length of stay in intensive care unit (IQR) – hours	43 (22 to 74)	10	44 (22 to 71)	5	-1.08 (-18.77 to 16.61)‡	0.90
Length of stay in hospital (IQR) — days	7 (6 to 11)	2	7 (6 to 11)	0	0.26 (-1.33 to 1.86)‡	0.74
Mortality in intensive care unit — no. (%)	12 (3.9)	1	13 (3.9)	0	1.00 (0.47 to 2.17)	0.99
Mortality at 30 days — no. (%)	17 (5.5)	1	17 (5.1)	0	1.09 (0.57 to 2.09)	0.80
Mortality at 90 days — no. (%)	18 (6.0)	7	18 (5.4)	3	1.10 (0.58 to 2.07)	0.77
Mortality at 180 days — no. (%)	21 (7.0)	10	20 (6.1)	5	1.16 (0.64 to 2.09)	0.63

*Data are presented as relative risks for dichotomous outcomes and as absolute mean differences for continuous outcomes. AKI denotes acute kidney injury; CI confidence interval; IQR interquartile range. †Acute kidney injury is defined according to KDIGO 2012 guidelines.‡Data presented as absolute mean difference

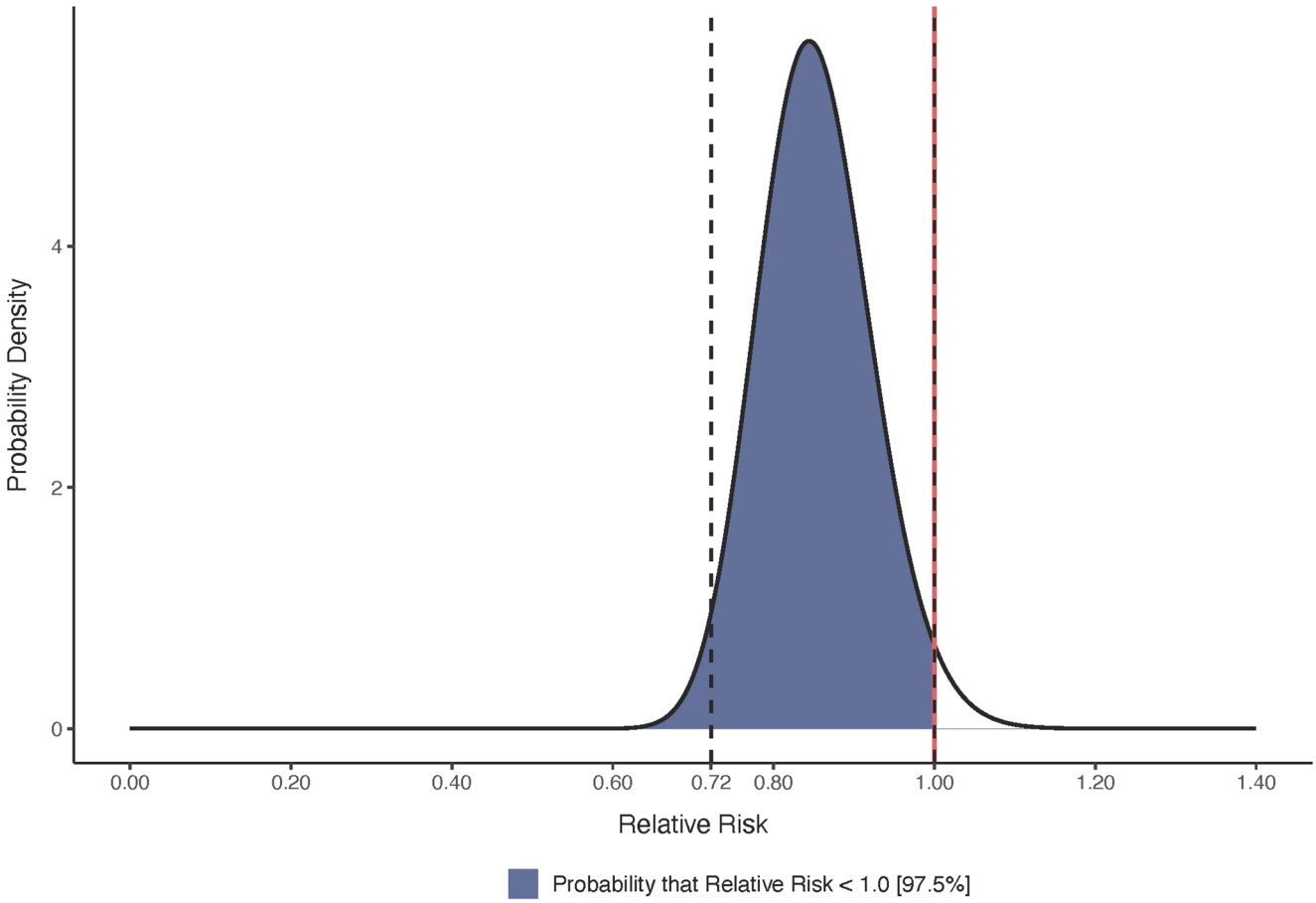

Fig. 3 Bayesian posterior probability distribution for acute kidney injury (AKI) comparing amino acid infusion with placebo. The shaded area represents the posterior probability of benefit (RR < 1)

Subgroup analyses showed no statistically significant differences across gender, age, baseline eGFR, or NYHA functional class (Suppl. Figure S3).

Secondary outcomes

The incidence of stage 3 AKI was 2.3% in the AA group vs. 4.8% in the placebo group (Suppl. Figure S4), with no evidence of interaction (interaction $p = 0.65$) (Fig. 2). Similarly, 6 patients (2.0%) in the AA group vs. 12 (3.6%) in the placebo group required RRT (interaction $p = 0.47$) (Fig. 2) (Suppl. Figures S5). No significant between-group differences were observed in other secondary outcomes, including duration of RRT, duration of mechanical ventilation, ICU stay, hospital stay, or all-cause mortality at any time point (Table 2). Sensitivity analyses limited to patients with DM receiving insulin therapy at baseline yielded consistent results across all secondary outcomes (Suppl. Table S2) (Suppl. Figures S6 and S7).

Discussion

Key findings

In this subgroup analysis of the PROTECTION trial, we evaluated the efficacy of perioperative intravenous AA infusion in 644 patients with DM undergoing cardiac surgery. The effect of AA on the prevention of postoperative AKI among patients with DM was consistent in both magnitude and direction with that observed in patients without DM, with no evidence of effect modification by DM status (interaction p-value = 0.82). Similar findings were obtained when stratifying by baseline insulin therapy, and results remained robust across multiple sensitivity analyses.

As expected, the incidence of AKI was significantly higher in patients with DM (> 40%) compared to the overall PROTECTION cohort (≈ 30%). The most severe outcome, stage 3 AKI, showed a marked numerical reduction in the diabetic subgroup: it was halved in the AA group (2.3%) compared to the placebo group (4.8%). The magnitude of the observed effect suggests consistency with the established renal-protective properties of AA, which were shown

to reduce the incidence of AKI in the overall PROTECTION trial population.

Relationship to previous studies

DM is a well-established risk factor for both microvascular and macrovascular disease, markedly increasing susceptibility to renal injury [19, 20]. Structural and functional changes in the diabetic kidney, such as glomerular hypertrophy, basement-membrane thickening, and interstitial fibrosis, contribute to impaired renal perfusion and filtration, predisposing patients to AKI during hemodynamic stress, such as cardiac surgery [19]. Importantly, intraoperative hemodynamic instability further amplifies this risk [21–23].

In our cohort, CABG was the most common procedure, consistent with the high prevalence of coronary artery disease in patients with DM [24]. Previous studies reported an increased incidence of AKI after CABG in this population [25–28] and similar findings have been described for other cardiovascular interventions, such as transcatheter aortic valve replacement [29].

Despite this recognized vulnerability, no prior studies have specifically evaluated the effect of AA infusion in patients with DM undergoing cardiac surgery. Experimental and clinical evidence, however, suggests that specific AA may confer renal protection through anti-inflammatory, antioxidant, and metabolic pathways. Histidine has been reported to reduce oxidative stress and inflammation [30, 31], tryptophan [30, 32, 33] and glutamine [30, 34] may modulate glucose metabolism and renal function through GLP-1–related pathways, while the role of branched-chain AA (BCAAs) remains debated [30]. Although heterogeneous, these data provide a plausible biological rationale for AA-mediated nephroprotection in DM. Our findings confirm that the clinical and economic [35] benefit observed in the overall PROTECTION population extends to patients with DM, independent of baseline antidiabetic therapy.

Implications of study findings

Understanding the role of DM in the context of AA-mediated renal protection may support the development of personalized preventive strategies for cardiac surgical patients at increased risk of AKI. In clinical practice, recognizing DM as a major risk factor and tailoring perioperative nephroprotection, including AA infusion, may help improve outcomes, optimize ICU resources use, and mitigate the long-term burden of AKI and CKD in this growing patient population. Mechanistic studies are warranted to clarify how renal functional reserve progressively declines as DM advances.

Strengths and limitations

Strengths of this analysis include its basis in a large, randomized, double-blind, placebo-controlled trial; the rigorous outcomes definition according to KDIGO criteria; and the availability of details subgroup data, including analyses stratified by insulin use and sensitivity testing. Nonetheless, several limitations should be acknowledged. First, this was a post-hoc exploratory analysis not powered for subgroup comparisons, which increases the risk of type II error. Second, the definition of DM was based on treatment status rather than metabolic parameters, with no data on disease duration, HbA1c, or the presence of micro- and macrovascular complications. Finally, these results may not be applied to patients undergoing off-pump or urgent cardiac surgery.

Future perspectives

Future studies should incorporate detailed metabolic and renal phenotyping. The integration of early renal biomarkers (e.g., NGAL, KIM-1, cystatin C) could enhance risk stratification and enable earlier detection of AKI in high-risk individuals. Long-term follow-up is needed to determine whether AA infusion influences CKD progression or cardiovascular outcomes in patients with DM. Ultimately, perioperative strategies that combine metabolic, nutritional, and pharmacological interventions could lead to more personalized and effective approaches for AKI prevention.

Conclusions

In this subgroup analysis of the PROTECTION trial, perioperative intravenous AA infusion was associated with a consistent reduction in postoperative AKI among patients with and without DM undergoing cardiac surgery. Despite their higher baseline risk of renal complications, patients with DM had similar benefits from AA infusion. These findings support the use of AA infusion as a preventive strategy in high-risk surgical populations and underscore the need for prospective trials specifically designed to confirm these results in cohorts with DM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40618-025-02804-0.

Acknowledgements None.

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Funding The PROTECTION trial was supported by a grant from the Italian Ministry of Health (RF-2016-02363260).

Declarations

Competing interests The authors declare that they have no conflict of interest.

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