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EFFECTS OF TWO TRANEXAMIC ACID DOSES ON CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY IN NON-ANAEMIC PATIENTS UNDERGOING ON-PUMP CARDIAC SURGERY

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Abstract

Objective: Cardiac surgery-associated acute kidney injury is a frequent and clinically significant complication, while the potential impact of tranexamic acid dosing on postoperative renal function remains uncertain. The study aims to compare the incidence of Cardiac surgery-associated acute kidney injury (CSA-AKI) and the stages of AKI between two different doses of Tranexamic acid (TXA) in non-anemic patients undergoing on-pump cardiac surgery; to determine whether the TXA dose is independently associated with CSA-AKI; and to identify predictors of postoperative renal function change and to compare short term renal outcomes in patients with and without CSA-AKI.

Materials and Methods: Prospective, randomized study that evaluated the renal safety of low-dose (20 mg/kg) and high-dose (50 mg/kg) TXA in 120 non-anemic patients undergoing on-pump cardiac surgery. Monitored variables were baseline serum creatinine, peak serum creatinine, discharge serum creatinine, creatinine ratio, 24-hour bleeding, and the incidence of transfusion.

Results: CSA-AKI occurred in 25% of patients in the low-dose TXA group, and 20% in the high-dose TXA group. Among patients who developed CSA-AKI, AKI stage 1 was the most common severity stage, 66.7% and 75% respectively. The TXA dose was not independently associated with CSA-AKI (OR 1.666, 95% CI 0.599–4.634, p=0.328). Transfusion was an independent predictor associated with higher peak-to-baseline serum creatinine ratio ($\beta = 0.191$, 95% CI 0.061–0.322, p=0.004). Patients who developed CSA-AKI had lower estimated glomerular filtration rate (eGFR) at discharge compared to patients without CSA-AKI (48 (40–59) vs 83 (68.5–107.5) mL/min/1.73 m^2; Mann–Whitney U test, $Z = -5.97$, $p < 0.001$).

Conclusion: Within the studied dosing range, the tranexamic acid dose was not independently associated with renal outcomes, suggesting that dosing decisions may prioritize bleeding and transfusion risk rather than renal safety concerns.

Keywords: *Acute kidney injury; Cardiac surgery; Cardiac surgery-associated acute kidney injury; Tranexamic acid.*

Introduction

Acute kidney injury (AKI) after cardiac surgery is ubiquitous. It occurs in a substantial proportion of patients depending on the differences in definitions and patient populations, where the incidence ranges from approximately 5% to over 40% (1), based on standardized criteria such as the Kidney Disease: Improving Global Outcomes (KDIGO) classification. It is a major factor for postoperative morbidity and mortality. Cardiac surgery-associated acute kidney injury (CSA-AKI) is defined as AKI occurs in the perioperative period after cardiac surgery, usually 48 to 72 hours after cardiac surgery, and it can be transient. The more severe forms of AKI according to the KDIGO classification (2) that may require renal replacement therapy (RRT) are less common, ranging from 1% to 4%; however they do carry a particularly high risk of postoperative morbidity and mortality. The development of CSA-AKI has profound implications for patient outcomes. AKI is independently associated with prolonged intensive care and hospital stay, increased incidence of RRT and higher short and long-term mortality in comparison with patients without AKI. Severe AKI substantially increases the perioperative mortality rates that can range from 20% to 60%, and indicates poorer long-term survival, worsening the preoperative kidney function, which may progress to chronic kidney disease (3).

The pathophysiology of CSA-AKI is multifactorial because of the unique conditions that arise during the perioperative cardiac surgery period, including surgical stress and cardiopulmonary bypass (CPB), which is associated with the hemodynamic and inflammatory response of the patient. Central mechanisms are renal hypoperfusion, ischemia and reperfusion exacerbated by inflammatory response, hemolysis, oxidative stress, endothelial disfunction and micro embolic events (4). At baseline, these insults compromise normal glomerular function and tubular integrity, resulting in declines in renal function and in fluid and electrolyte homeostasis. Tranexamic acid, a synthetic lysine analogue, is widely used in cardiac surgery to reduce perioperative bleeding and transfusion requirements by inhibiting fibrinolysis through blockade of plasminogen activation and suppression of plasmin activity. By stabilizing fibrin clot formation, TXA effectively reduces blood loss and allogeneic blood transfusion. Although higher doses may provide greater antifibrinolytic efficacy, they could also theoretically compromise renal safety. Excessive inhibition of fibrinolysis may promote a hypercoagulable state within the renal microcirculation, impairing fibrin degradation, leading to capillary thrombosis and microvascular obstruction. In addition to its role in fibrinolysis, plasmin participates in key inflammatory pathways and contributes to the maintenance of endothelial homeostasis. Its suppression may therefore alter the balance of inflammatory mediators and exacerbate acute kidney injury (5). Whether the enhanced hemostatic benefits of higher-dose TXA can be achieved without increasing the risk of postoperative acute kidney injury remains an important clinical question. The aim of the study was to compare the incidence of CSA-AKI and the stages of AKI between the studied doses of TXA in non-anemic patients undergoing on-pump cardiac surgery; to determine whether the TXA dose is independently associated with the incidence of CSA-AKI; to identify independent predictors of postoperative renal function change and to compare short term renal outcomes in the patients with and without CSA-AKI.

Materials and Methods

Type of study: This was a prospective, randomized, controlled study conducted at the department of Cardiac Surgery at Acibadem Sistina Hospital Skopje, between May 2024 and May 2025.

The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all of the participants before their enrollment.

Study Population: Adult non-anemic patients scheduled for elective or urgent isolated Aorto-coronary bypass surgery (CABG), aortic valve surgery and combined CABG, and aortic valve surgery requiring cardiopulmonary bypass (CPB) were eligible for inclusion. Anemia was defined according to the World Health Organization (WHO) criteria (6) as Hemoglobin concentration <130g/L in men and < 120g/L in women.

Exclusion criteria: Patients aged less than 18 years; known hypersensitivity or allergy to tranexamic acid; pregnancy; preoperative anemia; chronic kidney disease stage 4 and 5; planned surgery involving the Aorta or Mitral valve; Re-Do cardiac surgical procedures; off-pump cardiac surgery; treatment with vitamin K antagonists within 5 days before surgery or an International normalized ratio (INR) >1,5; treatment with direct oral anticoagulants 2 days before surgery; treatment with oral P2Y12 inhibitors without the recommended discontinuation period before surgery (Ticagrelor ≤2 days, Clopidogrel ≤4 days or Prasugrel ≤6 days); history of seizure disorder or current anticonvulsant therapy.

Randomization and Study Intervention: On the day of hospital admission, patients were randomly assigned in a 1:1 ratio to one of the two study groups using a computer-generated sequence of random numbers. Allocation concealment was ensured using sealed, opaque envelopes. Patients were assigned to receive either:

- Low-dose Tranexamic acid group (n=60): 20 mg/kg intravenous tranexamic acid or
- High-dose Tranexamic acid group (n=60): 50 mg/kg intravenous tranexamic acid.
- Tranexamic acid was administered as a single prophylactic intravenous dose 45 minutes before skin incision.

No additional doses were administered intraoperatively or during the first 24 postoperative hours. The selected dosing regimens were based on the recommendations of the International Society for Minimally Invasive Cardiothoracic Surgery (7), the Enhanced Recovery After Surgery Society (ERAS) perioperative guidelines for cardiac surgery (8), and published meta-analytic data regarding optimal tranexamic acid dosing in cardiac surgery by Zufferey et al. (9).

Perioperative Management: All patients underwent standardized perioperative care in line with institutional protocols, including anesthesia, cardiopulmonary bypass management, surgical techniques, and postoperative intensive care. Management was delivered by a multidisciplinary heart team.

Data Collection and Outcome Definitions: The following variables were collected for all participants: baseline serum creatinine, peak postoperative serum creatinine, serum creatinine level at hospital discharge, creatinine ratio (defined as peak serum creatinine divided by baseline serum creatinine), estimated Glomerular filtration rate (eGFR), incidence and stage of CSA-AKI, 24-hour bleeding (defined as thoracic drain output for 24 hours after surgery) and incidence of transfusion during hospitalization. CSA-AKI was defined according to the KDIGO criteria as an increase in serum creatinine to at least 1.5 times the baseline value or an absolute increase of ≥26.5 μmol/L during the postoperative period (2). The severity of CSA-AKI was classified according to KDIGO staging criteria (2). Stage 1: increase in serum creatinine to 1.5–1.9 times baseline or an absolute increase of ≥26.5 μmol/L; Stage 2: increase in serum creatinine to 2.0–2.9

times baseline; Stage 3: increase in serum creatinine to ≥3.0 times baseline, an absolute serum creatinine concentration ≥353.6 μmol/L or initiation of renal replacement therapy. Creatinine clearance was calculated using the Cockcroft–Gault equation and was used to estimate preoperative peak and eGFR discharge. Calculations were performed using the MDCalc online calculator (10). Short-term renal outcomes were assessed by comparing baseline eGFR and hospital discharge eGFR between patients with and without CSA-AKI.

Statistical Analysis: Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data and as median (interquartile range (IQR)) for non-normally distributed data. Categorical variables are expressed as absolute counts and percentages. Baseline characteristics between the two randomized groups were compared using one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The primary outcome, the incidence of CSA-AKI, is presented as the number and percentage of affected patients in each study group. The association between tranexamic acid dose and the occurrence of CSA-AKI was evaluated using multivariable logistic regression analysis and is reported as odds ratios (ORs) with 95% confidence intervals (CIs).

To identify independent predictors of postoperative renal function, postoperative creatinine change was analyzed using a generalized linear model with gamma distribution and log-link function. The dependent variable was the creatinine ratio, defined as peak postoperative serum creatinine divided by baseline serum creatinine. All statistical analyses were performed using IBM SPSS Statistics version 26. A p value <0.05 was considered statistically significant.

Results

In this study 120 non-anemic patients undergoing on-pump cardiac surgery were enrolled and randomized in two TXA groups. The anthropometric measurements and medical history are shown in Table 1.

Table 1. Preoperative data, low-dose TXA (20mg/kg) and high-dose TXA (50mg/kg)

	low-dose TXA (n=60)	high-dose TXA (n=60)	p value
Gender (male)	32 (53,3%)	39 (65%)	0.194
Weight (kg)	80,54±16,18	82,59±16,85	0.498
Height (m)	1,66±0,98	1,69±0,87	0.118
Age (year)	66 (62-73)	66,5 (62,2-73,7)	0.735
Hypertension	57 (95%)	60 (100%)	0.244
Diabetes Mellitus	21 (35%)	23 (38,3%)	0.705
Peripheral artery disease	10 (16,7%)	13 (21,7%)	0.487
ASA			0.810

	low-dose TXA (n=60)	high-dose TXA (n=60)	p value
2	10 (16,7%)	11 (18,3%)	
3	49 (81,7%)	47 (79,5%)	
4	1 (1,6%)	2 (2,2%)	
STS risk score	1,11 (0,73-1,72)	1,06 (0,54-2)	0.562
Hemoglobin (g/L)	140 (133-149)	141 (133-154)	0.544
Serum Creatinine (μmol/l)	75 (66-97)	83 (69-94,75)	0.337
eGFR ml/min/1,73²	69 (52,25-88,5)	72,5 (58,25-93)	0.553
ACE inhibitors	45 (75%)	45 (75%)	1
Diuretics	23 (38,3%)	27 (45%)	0.459

There were no statistical differences between the randomized groups. In both groups, the male gender was predominant with 53,3% vs 65%. The studied patients were at similar age and with similar comorbidities. The preoperative hemoglobin level was similar between the groups, p=0.544 for comparison. The high-dose TXA group had higher preoperative serum creatinine and preoperative eGFR levels, though statistically insignificant, in comparison to the low-dose TXA group, p=0.337 and p=0.553. There was no significant statistical difference in the preoperative therapy in the two study groups.

Elective surgical procedures predominated in both study groups (88,3% vs 93,3%, p=0.529). Coronary bypass surgery was the most common procedure in both study groups, 61,7% in the low-dose and 51,6% in the high-dose TXA group. In the low-dose TXA group, the aortic cross-clamp time was insignificantly shorter, 46 min, than in the high-dose TXA group, 50 minutes, p=0.226.

There was no statistical difference in the catecholamine support across the studied groups, 71,7% and 75% respectively. There were no significant statistical differences in the postoperative data across the studied groups. The volume of 24-hour bleeding between the groups was 355ml and 340ml, low- and high-dose groups respectively (p=0.944). There was borderline significance in the incidence of transfusion across the low-dose and high-dose TXA groups (p=0.060), as shown in Table 2.

Table 2. Intra and postoperative data, low-dose TXA (20mg/kg) and high-dose TXA (50mg/kg)

	low-dose TXA (n=60)	high-dose TXA (n=60)	p value
Status of procedure			0.529
Elective	53 (88,3%)	56 (93,3%)	
Urgent	7 (11,7%)	4 (6,7%)	
Procedure type			0.269

	low-dose TXA (n=60)	high-dose TXA (n=60)	p value
Aortocoronary bypass	37 (61,7%)	31 (51,6%)	
Open chamber surgery	23 (38,3%)	29 (48,4%)	
Aortic cross-clamp time (min)	46 (31-60,75)	50 (39,25-64,75)	0.226
Catecholamine support	43 (71,7%)	45 (75%)	0.679
Peak Serum Creatinine (μmol/l)	81 (59,75-112,5)	79 (67-103,5)	0.753
Acute Kidney Injury	15 (25%)	12 (20%)	0.512
24-hour bleeding (ml)	355 (292,5-447,5)	340 (270-475)	0.944
Transfusion	42 (70%)	32 (53%)	0.060
Discharge Serum Creatinine (μmol/l)	75 (57-97,75)	76 (65,25-95,25)	0.378
Discharge eGFR ml/min/1,73²	72,5 (53,25-98,5)	76 (58,25-99,5)	0.444

There was similar renal safety for both dosing groups of TXA. No significant statistical difference between the incidence of CSA-AKI was observed between the studied groups, (p=0.512), although the incidence was higher in the low-dose than the high dose TXA group, (25% vs 20%), as shown in Figure 1.

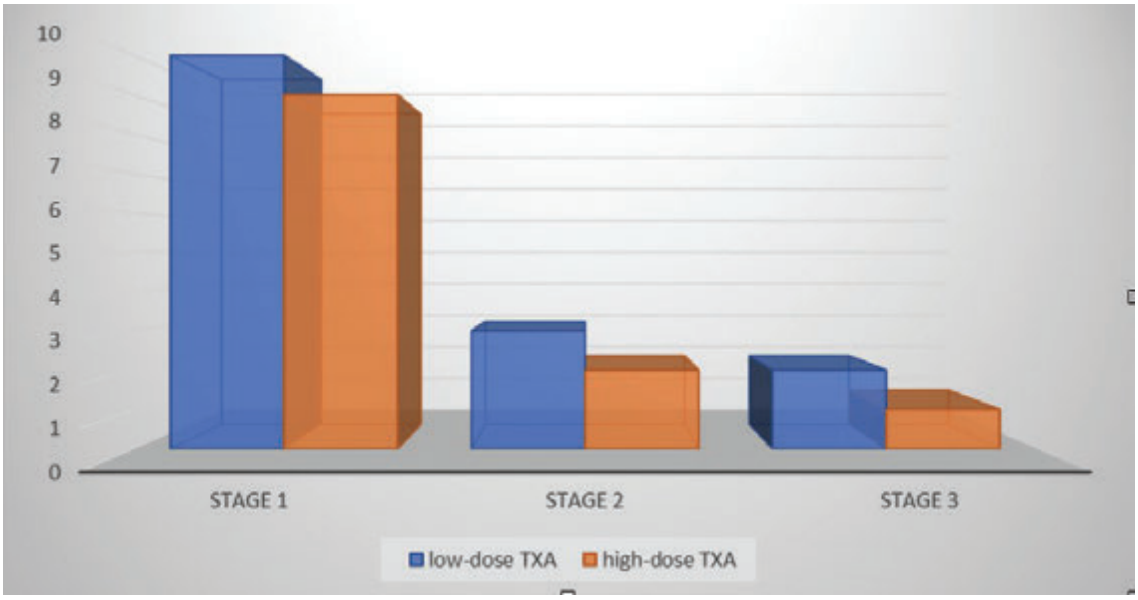

Figure 1. Graphical presentation of the incidence of CSA-AKI across the studied groups

As shown in Figure 2, Acute Kidney Injury Stage 1 was the most frequently observed category of CSA-AKI in both study groups, occurring in 10 patients in the low-dose group and in 9 patients in the high-dose Tranexamic acid group. There was no statistically significant difference in the distribution of CSA-AKI stages between the two groups (p = 0.877). Renal replacement therapy was required in only one patient in the low-dose tranexamic acid group.

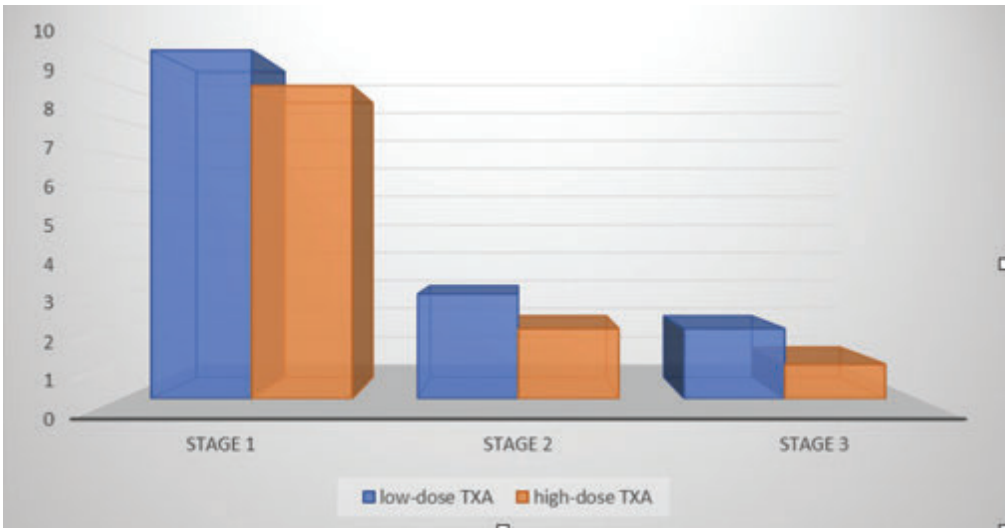

Figure 2. Graphical presentation of stages of CSA-AKI across the studied groups

In a multivariate logistic regression analysis, after adjustment for age, baseline serum creatinine, type of cardiac surgery, aortic cross-clamp time and transfusion incidence there was no independent association between the dose of TXA and the incidence of CSA-AKI (OR 1.666, 95% CI 0.599–4.634, p=0.328). Also, a Gamma log-link generalized linear model was used with creatinine ratio (peak creatinine divided by baseline creatinine) as a dependent variable to estimate the subtle changes of the two doses of TXA on postoperative serum creatinine change. After adjusting for BMI, type of surgical procedure, aortic cross-clamp time and incidence of transfusion, the studied doses of TXA were not independently associated with postoperative creatinine change (β = -0.015, 95% CI 0.137-0.108, p = 0.813). However, the incidence of transfusion was an independent predictor associated with increased postoperative serum creatinine change (β = 0.191, 95% CI 0.061–0.322, p =0.004). Patients with CSA-AKI had a significantly lower eGFR at discharge compared to the patients without CSA-AKI (48 (40-59) vs 83 (68,5-107,5) ml/min/1,73^2; Mann-Whitney U test, Z=-5,97, p<0,001), with a large effect size (r=0,55), shown in Figure 3.

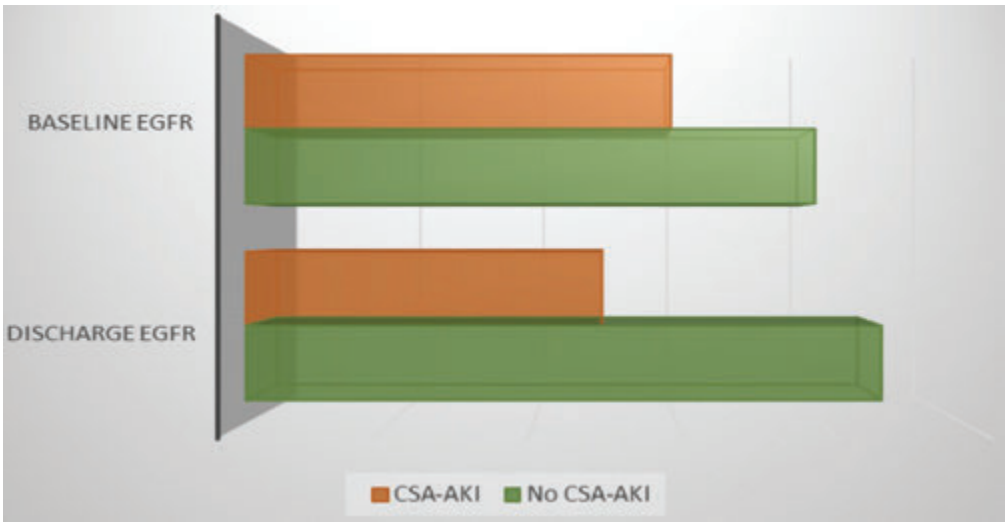

Figure 3. Graphical presentation of baseline eGFR and discharge eGFR across the patients with CSA-AKI and without CSA-AKI

Discussion

This randomized prospective study evaluated the effects of different prophylactic doses of TXA on the incidence and severity of CSA-AKI in non-anemic patients undergoing on-pump cardiac surgery and identified predictors of postoperative renal function changes and short-term renal outcomes.

The findings suggest that there was no statistically significant difference in the incidence of CSA-AKI and the severity of AKI between the low-dose and high-dose TXA groups. The incidence of CSA-AKI was slightly higher in the low-dose than in the high-dose TXA group, (25% vs 20%). Although the incidence was statistically insignificant, it does suggest that the studied higher dose of TXA does not produce additional nephrotoxic burden in the perioperative cardiac surgical setting. Multivariate logistic regression analysis further confirmed the absence of independent association between the TXA dose and the incidence of CSA-AKI (OR 1.666, 95% CI 0.599–4.634, p=0.328), indicating the renal safety of TXA and a possibility that other perioperative factors have a more substantial role in the development of CSA-AKI. These findings align with the findings from the ATACAS trail (11) where TXA significantly reduced perioperative bleeding without increasing the risk of AKI in comparison to placebo in a large randomized trial of patients undergoing coronary bypass surgery. Meta-analyses by Henry et al. (12) and Zhang et al. (13) evaluating antifibrinolytic use in cardiac surgery have also shown no consistent increase in renal complication that can be attributed to TXA. The results of our study simply extend these observations by specifically comparing different doses of TXA and suggest that dose escalation within clinically acceptable ranges does not produce higher renal risk. The lack of dose-response relationship in our study is a strong point against clinically relevant renal burden in the studied dosing range.

Stage 1 AKI was the most common severity category, occurring in 10 patients in the low-dose TXA group and 9 patients in the high-dose TXA group. Stage 2 AKI was observed in 3 and 2 patients, respectively, while Stage 3 AKI occurred in 2 and 1 patients, respectively. Only 1 patient required renal replacement therapy in the low-dose TXA group. This distribution is consistent with the studies from Hobson et al. (14) and Rosner et al. (15), where mild AKI severity cases dominate, while more severe AKI cases occur less frequently but have substantial risk of morbidity and mortality. These findings further imply that higher TXA dosing group does not influence the CSA-AKI incidence, but also does not influence the clinical progression of AKI severity.

To assess whether TXA dosing exerted an independent effect on subtle postoperative renal dysfunction not captured by KDIGO-defined AKI (2), renal function was analyzed using a gamma log-link generalized linear model, with creatinine ratio (peak serum creatinine divided by baseline serum creatinine) being the dependent variable. There was no statistically significant association between the TXA dosing group and the creatinine ratio (β =-0.015, 95% CI 0.137-0.108, p=0.813), supporting the renal safety of the investigated TXA doses.

These results are consistent with the findings of Myles et al. (11) that demonstrate no excess risk of renal injury related to the administration of tranexamic acid in cardiac surgery patients. High-dose TXA was associated with a non-significant 1.5% reduction in the creatinine ratio, suggesting a potential but unproven renal protective effect. In contrast, perioperative blood transfusion emerged as an independent predictor of increased creatinine ratio (β=0.191, 95% CI 0.061–0.322, p=0.004), corresponding to an approximately 21% higher peak-to-baseline creati-

nine ratio in transfused patients compared with non-transfused patients. This finding is consistent with prior evidence by Rosner et al. (15) linking red blood cell transfusion to an increased risk of postoperative acute kidney injury and adverse renal outcomes in cardiac surgery.

Importantly, the patients who developed CSA-AKI had significantly lower discharge eGFR compared with patients without AKI, (Mann-Whitney U test, Z=-5,97, p<0,001).

This finding highlights the clinical relevance that even predominantly mild CSA-AKI has impact on renal recovery and long-term renal function, supporting evidence that postoperative AKI is associated with persistent renal dysfunction, increased risk of chronic kidney disease and adverse long-term outcomes (16). Thus, while TXA dosing appears not to influence renal risk, prevention of CSA-AKI remains a critical perioperative objective.

Several limitations should be considered. The sample size may limit detection of rare outcomes such as severe CSA-AKI and RRT. Renal function was assessed using serum creatinine measurements, which may not fully capture early and subclinical kidney injury. The findings apply to the studied dosing groups of TXA and cannot be generalized to the extremely high dosing regimens.

Conclusion

Tranexamic acid is widely used to reduce bleeding and transfusion requirements, and clinicians often balance hemostatic efficacy against potential adverse effects, including renal complications. Our results suggest that within the studied dosing range, TXA dose selection may be guided primarily by bleeding and transfusion risk factors rather than concerns about differential renal toxicity. Furthermore, the strong association between CSA-AKI and reduced discharge renal function emphasizes the need for continued focus on established renal protective strategies.

The absence of TXA dose–related renal burden supports its continued use as part of a comprehensive blood conservation protocol in cardiac surgery.

Declarations

Ethics approval and consent to participate: The study was approved by the institutional ethics committee of Acibadem Sistina Hospital, prior to patient enrollment, Approval reference: 02-15663/02, Date of approval: 04/12/2023, Chair of the Ethical Committee: Prof. Andrej Petrov, MD, PhD. All participants received detailed information regarding the study objectives and procedures, and provided written informed consent prior to inclusion.

Informed consent: Written informed consent was obtained from all participants included in the study.

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Availability of data and materials: Data are available from the corresponding author upon reasonable request.

Author's contributions: Conceptualization R.A.; methodology, R.A. and S.M.; investigation, R.A., K.J.B., N.A., S.J., S.D.; data curation, R.A. and K.J.B.; writing – original draft, R.A. and S.M.; writing – review and editing, S.M. and K.J.B.; project administration N.A. All authors have read and agreed to the published version of the manuscript.

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