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Original Article

Perioperative Bleeding Is Not an Independent Risk Factor for Acute Kidney Injury in On-pump Cardiac Surgery—A Post-hoc Analysis of a Randomized Clinical Trial

Hanna E. Vlasov, MD*[,1], Liisa M. Petäjä, MD, PhD*, Erika M. Wilkman, MD, PhD*, Akseli T. Talvasto*, Minna K. Ilmakunnas, MD, PhD*[,†], Peter M. Raivio, MD, PhD[‡], Seppo T. Hiippala, MD, PhD*, Raili T. Suojaranta, MD, PhD*, Tatu S. Juvonen, MD, PhD[‡], Eero J. Pesonen, MD, PhD*

[*]*Department of Anesthesiology and Intensive Care Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

[†]*Finnish Red Cross Blood Service, Finland*

[‡]*Department of Cardiac Surgery, Heart and Lung Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

Objectives: To study the association between bleeding and acute kidney injury (AKI).

Design: Post-hoc study of a randomized trial of 4% albumin versus Ringer's acetate for cardiopulmonary bypass priming and perioperative volume replacement.

Setting: Single-center study.

Patients: 1,386 on-pump cardiac surgical patients.

Measurements and Results: AKI was defined by the Kidney Disease: Improving Global Outcomes creatinine criteria, and bleeding by the Universal Definition of Perioperative Bleeding (UDPB) classification. With univariably independent factors, two logistic regression analyses (Model 1: AKI Risk Score, EuroSCORE II, and UDPB class; Model 2: risk scores, components of the UDPB classification, and factor VIII/von Willebrand factor concentrate) and a mediation analysis (Model 3: risk scores, UDPB class, and perioperative factors) were performed.

A total of 139 (10%) patients developed AKI. In Model 1, UDPB class "severe" (odds ratio: 2.16, 95% confidence interval: 1.19-3.89), "massive" bleeding (6.78, 1.8-25.33), and AKI Risk Score (1.51, 1.29-1.78) were associated with AKI. In Model 2, AKI Risk Score (1.55, 1.33-1.82) and fresh frozen plasma transfusion (1.29, 1.06-1.58) were associated with AKI. In Model 3, the combined UDPB classes "severe" and "massive" bleeding did not have a direct effect (regression coefficient: 0.32, 95% confidence interval: −0.26 to 0.91), while mean arterial pressure (0.08, 0.003-0.21) and fluid balance (0.12, 0.17-0.27) had indirect effects on AKI.

Conclusions: In on-pump cardiac surgery, perioperative bleeding was not an independent risk factor for AKI but manifested as AKI via hypotension and higher fluid balance. Prevention of bleeding may reduce AKI in cardiac surgery.

Key Words: perioperative bleeding; acute kidney injury; on-pump cardiac surgery

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[1]*Address correspondence to:* Hanna Vlasov, MD, Perioperative and Intensive Care Medicine, Meilahti Hospital, P.O. Box 340, 00029 HUS, Helsinki, Finland; Tel.: +358-50-4270156.

E-mail address: hanna.vlasov@hus.fi (H.E. Vlasov).

ACUTE KIDNEY INJURY (AKI) is common after cardiac surgery.[1,2] The incidence of cardiac surgery–associated AKI (CSA-AKI), defined by the Kidney Disease: Improving Global

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Outcomes (KDIGO) criteria, varies between 20% and 30%.[1,3] Multiple preoperative and perioperative factors have been found to contribute to the development of CSA-AKI, but it is still not completely understood.[4-7] Cardiopulmonary bypass (CPB)–induced systemic inflammation, reduced renal perfusion, renal medullary hypoxia, central venous congestion, ischemia-reperfusion injury, oxidative stress, embolism, hemolysis, and nephrotoxic agents are considered the main pathophysiological mechanisms causing CSA-AKI.[3,5-9]

In previous studies, management of bleeding with blood products and coagulation factor concentrates, as well as higher classes in the Universal Definition of Perioperative Bleeding (UDPB) classification, were associated with an increased risk of AKI.[10-16] The UDPB classification was developed and validated in adult cardiac surgery patients to quantify perioperative bleeding;[17] it is based on chest tube blood loss, need for re-exploration, or delayed sternal closure for bleeding, as well as administration of blood products and coagulation factor concentrates.[17] The UDPB classification as an explanatory variable for CSA-AKI is problematic since it includes factors related to both bleeding itself and its management. Differentiation between these two aspects as potential risk factors for CSA-AKI has clinical implications for patient care.

In the ALBumin In Cardiac Surgery (ALBICS) trial, 1,386 adult cardiac surgical patients were randomized to perioperative administration of either 4% albumin or Ringer's acetate during surgery and in the first 24 postoperative hours.[18] Compared with Ringer's acetate, albumin administration was accompanied by significantly increased bleeding as defined by the UDPB classification.[19] During the 90-day follow-up period, there was no significant difference between the study groups in CSA-AKI incidence, with 2.6% in the albumin group and 3.3% in the Ringer's group developing KDIGO stage 2 to 3 AKI.[18]

The aim of this post-hoc analysis of the ALBICS trial was to investigate the significance of bleeding and its treatment in the development of CSA-AKI.

Methods

Patients

This post-hoc analysis is based on the ALBICS trial patient cohort of 1,386 adult cardiac surgical patients.[18,20] The trial was approved by the local Ethics Committee (HUS/2291/2016, February 8, 2017, revision January 18, 2019) and by the Finnish Medicines Agency (136/2015 25.11.2016 and 30.01.2017, EudraCT 2015-002556-27); it was registered in the ClinicalTrials.gov database (NCT02560519). All patients provided written informed consent before participation. Patients were enrolled in the trial from March 21, 2017, to January 14, 2020 (the last follow-up ended on April 13, 2020) (Supplementary Fig 1).

The included patients were aged 18 to 90 years and underwent primary or repeat cardiac surgery with CPB, either independently or in combination as follows: coronary artery bypass grafting (CABG); replacement or repair of aortic, mitral, or tricuspid valves; MAZE procedure or its modifications; and aortic root or ascending aorta surgery without hypothermic circulatory arrest. Exclusion criteria were described in detail previously.[18]

Trial Intervention

The hospital pharmacy independently performed computer-generated randomization 1:1 into two trial groups, applying block sizes of 12 to 30.[18,20] Blinding procedure for study solutions and detailed methodology of the ALBICS trial were published previously.[20] The intervention period included the intraoperative period and the first 24 postoperative hours in the intensive care unit (ICU) or until discharge from the ICU (whichever occurred first).[20] During the intervention period, patients received, blindly, study solutions comprising either pure Ringer's acetate (Baxter Viaflo, Helsinki, Finland) or albumin in a final concentration of 4%. Study solutions were used for CPB priming (total volume 1,500 mL) and up to 3,200 mL as volume replacement, covering both the intraoperative period and the first 24 hours in the ICU. In the albumin group, 300 mL of Albuman 200 g/L (Prothya Biosolutions Netherlands B.V., Amsterdam, Netherlands) was added to the initial prime of 1,200 mL of Ringer's acetate to yield the final albumin concentration of 4%. For volume replacement, Albuman 40 g/L (Prothya Biosolutions Netherlands B.V., Amsterdam, Netherlands) was used in the albumin group. If more than 3,200 mL of volume replacement was required, Ringer's acetate was administered thereafter in both groups. Volume replacement was based on clinical evaluation. The mean study fluid volume for volume replacement during the intervention period was 2,285 ± 809 mL.

Perioperative Management

Anesthesia included induction with propofol or etomidate, opioid, and rocuronium; maintenance with sevoflurane and an opioid infusion; and postoperative sedation with propofol. CPB was performed under mild hypothermia (34°C-35°C), using a nonpulsatile roller pump and a membrane oxygenator. Norepinephrine was the first-line vasopressor, and vasopressin the second. Boluses of phenylephrine, ephedrine, or norepinephrine were administered as needed. For inotropic treatment, epinephrine, milrinone (typically with an initial bolus of 1-2 mg), and/or levosimendan were used. Furosemide was administered as needed, based on clinical judgment. Mannitol was not used. During the intervention period, three doses of 1,500 mg of cefuroxime were administered for all patients and two doses of 1,000 mg of vancomycin were administered for valve surgery patients and for patients who were admitted to the hospital more than 3 days prior to surgery. Antibiotic doses were reduced based on the estimated glomerular filtration rate, as recommended in the Summary of Product Characteristics delivered by the manufacturers of the antibiotics.

For bleeding prophylaxis, tranexamic acid was used, and for re-do surgery patients presenting with normal or only slightly reduced creatinine values, aprotinin was administered as two boluses (2,000,000 IU intravenously and 2,000,000 IU in CPB priming) with an intraoperative infusion (2,000,0000 IU). Intraoperatively, blood products and coagulation factor concentrates were administered based on clinical evaluation, including rotational thromboelastometry and conventional coagulation tests. Postoperatively, management of excessive bleeding was based on the institutional standard operating procedure as follows: red blood cell (RBC) transfusion if hematocrit was below 30%; administration of platelets if platelet count was below 100×10^9/L; and administration of fibrinogen concentrate if plasma fibrinogen was below 1.5 g/L.

Outcome Measure and Risk Factors

The outcome measure was AKI (as defined by the KDIGO creatinine criteria) within the first 4 postoperative days.[4] Preoperative risk factors and type of surgery were defined using AKI Risk Score and EuroSCORE II.[3,21] Bleeding was defined using the UDPB classification.[17] In the UDPB classification, bleeding is categorized into five classes: insignificant (class 0), mild (class 1), moderate (class 2), severe (class 3), and massive (class 4). In mediation analysis, the UDPB class was included as a dichotomic variable by combining the two highest UDPB classes (classes 3 and 4) as "UDPB-high" and the other classes as "UDPB-low." For statistical purposes, risk factors were categorized as either "preoperative" or "perioperative." Perioperative factors included intra- and postoperative but not preoperative factors. The following perioperative factors were included: albumin study group; CPB time; time-weighted average mean arterial pressure (MAP); vasopressor dose; inotropic dose; fluid balance; UDPB class or its components (chest tube drainage; transfusions of RBC, fresh frozen plasma [FFP] and platelets; administrations of fibrinogen and prothrombin complex concentrate [PCC]; and resternotomy); administration of coagulation factor VIII/von Willebrand factor (FVIII/VWF) concentrate; hematocrit, plasma chloride concentration; chloride dose; pH; and administrations of tranexamic acid and aprotinin (Supplementary Table 1). Excluding chest tube drainage, UDPB components were analyzed in the operating room after CPB and within the first 24 hours in the ICU. Chest tube drainage was analyzed within the first 12 postoperative hours.[17] Plasma chloride concentration was assessed only during the postoperative phase, while intraoperative data were not available. All other perioperative risk factors were assessed during the intervention period (ie, intraoperative phase and the first 24 postoperative hours in the ICU or until discharge from the ICU, whichever occurred first).[20]

Data Collection

Apart from data on smoking history (retrospectively collected), preoperative demographic and medical data were prospectively collected during the preoperative anesthetic assessment; clinical data in the operating room and ICU from clinical software (Picis Clinical Solutions, version 8.2.13, Wakefield, MA), using an IT application tailored for the ALBICS trial;[20] and laboratory values manually on the ward.

Plasma Samples

Plasma creatinine concentrations were measured in the hospital laboratory with a photometric enzymatic method within the week before surgery and daily postoperatively. Using a photometric bromocresol purple method, plasma albumin concentrations were measured in the hospital laboratory from plasma samples in ethylenediaminetetraacetic acid, collected before anesthesia induction. Plasma samples were not available for 22 patients in the albumin group and 30 patients in the Ringer's group.

Statistical Analysis

Univariable analyses were performed to study the associations between preoperative and perioperative factors and AKI by applying independent samples *t*-test, Fisher's exact test, and Mann-Whitney U-test, as appropriate (variables shown in Supplementary Table 1). Multicollinearity between the independent variables was tested with variation inflation factor (VIF) analysis and variables with a VIF value under 4 were accepted. Based on the results of the univariable analyses with $p < 0.05$, two logistic regression analyses (Models 1 and 2) and a mediation analysis applying logistic regression analysis (Model 3) for AKI development were performed. In Model 1, risk scores (AKI Risk Score and EuroSCORE II) and the UDPB class were included. In Model 2, risk scores, the components of the UDPB classification, and administration of FVIII/VWF concentrate were included. In Model 3, bleeding (defined as UDPB-high *v* UDPB-low) was included as an exposure variable; MAP, fluid balance, vasopressor dose, inotropic dose, and hematocrit were included as mediator variables; and risk scores and CPB time were included as covariates, as shown in the directed acyclic graph (Supplementary Fig 2). Direct and indirect effects of the mediation analysis are presented as regression coefficients. The number of bootstrap samples was set to 5,000 to provide accurate bootstrap confidence intervals (CIs) in the mediation analysis. In Models 2 and 3, all other UDPB components were analyzed according to the UDPB classification, but RBC and FFP were analyzed as continuous variables as a modification of the UDPB classification. Variables in the multivariable analyses were restricted to less than one per eight AKI patients.[22] The capability of Models 1 and 2 to predict AKI was assessed by applying area under the curve of receiver operating characteristics (AUC-ROC) analysis.

Data are presented as numbers with percentages, means with standard deviations (SDs), odds ratios (ORs) with 95% CIs, or regression coefficients with 95% CIs, as appropriate. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were conducted with IBM SPSS 28

software (IBM, Armonk, NY) and the PROCESS Procedure for SPSS version 4.2 (written by Andrew F. Hayes, Ph.D., www.afhayes.com).

Results

Patient Characteristics

Of the 1,386 patients, 139 (10.0%) developed AKI: 112 (8.1%) KDIGO stage 1; 21 (1.5%) stage 2; and 6 (0.4%) stage 3.

Preoperative characteristics and type of surgery for patients with and without AKI according to AKI Risk Score and EuroSCORE II are presented in Table 1. Compared with patients without AKI, AKI patients were older; had higher body mass index, lower preoperative hemoglobin, lower preoperative glomerular filtration rate; more often had hypertension, insulin-dependent diabetes mellitus, and reduced left ventricular ejection fraction; and had more often undergone thoracic aortic surgery or multiple (three or more) procedures (Table 1).

According to the UDPB classification, perioperative bleeding was insignificant (class 0) in 786 patients (56.7%), mild (class 1) in 167 patients (12.0%), moderate (class 2) in 321 patients (23.2%), severe (class 3) in 102 patients (7.4%), and massive (class 4) in 10 patients (0.7%). The UDPB class was significantly higher in patients with than without AKI (Table 2). AKI incidences in the UDPB classes were 8.1% (class 0), 8.4% (class 1), 12.1% (class 2), 17.6% (class 3), and 40.0% (class 4).

Table 1
Preoperative and Operative Demographics of Patients With (n = 139) and Without (n = 1,247) AKI, According to AKI Risk Score and EuroSCORE II

	Components of AKI Risk Score, AKI *v* Non-AKI Patients	p Value	Components of EuroSCORE II, AKI *v* Non-AKI Patients	p Value
Preoperative factors				
Age, y	67.9 ± 9.0 *v* 65.1 ± 10.0			<0.001
Female sex, %	18.0 *v* 21.7			0.38
Body mass index, kg/m^2	29.6 ± 5.6 *v* 27.7 ± 4.7	<0.001		
Smoking,* %	56.8/28.1/15.1 *v* 61.1/24.7/14.2	0.60		
NYHA class (1/2/3/4), %	7.2/44.2/37.0/11.6 *v* 8.7/41.9/37.5 /11.8			0.94
PVD, %	17.3 *v* 11.5			0.06
Diabetes mellitus,† %	22.3 *v* 22.6	1.00	17.3 *v* 7.9†	0.001
Hypertension, %	77.7 *v* 67.0	0.01		
Hemoglobin, g/L	136.6 ± 13.8 *v* 141.1 ± 13.1	<0.001		
Time category from angiography to surgery‡, %	82.7/17.3/0.0 *v* 80.4/19.2/0.4	0.79		
Three-vessel CAD, %	38.8 *v* 33.8	0.26		
LVEF ≤50%, %	28.8 *v* 18.4			0.01
GFR, mL/min/1.73 m^2	74.4 ± 18.8 *v* 80.7 ± 16.3	<0.001		
Creatinine clearance, mL/min§, %			51.1/42.4/6.5 *v* 59.8/36.5/3.6	0.11
Pulmonary disease, %			10.8 *v* 7.4	0.26
Poor mobility, %			5.0 *v* 2.6	0.19
CCS angina class IV, %			12.2 *v* 9.0	0.22
Recent MI, %			28.1 *v* 21.7	0.20
Previous cardiac surgery, %			3.6 *v* 2.6	0.47
PAH‖, %			66.2/27.3/6.5 *v* 75.9/19.8/4.2	0.06
Type of surgery				
Urgent, %	28.1 *v* 27.3			0.84
Isolated CABG, %	38.8 *v* 45.9			0.13
Isolated valve, %	15.1 *v* 24.1	0.02		
CABG + one valve, %	7.9 *v* 7.9	1.00		
Other/multiple procedure, %	38.1 *v* 22.2	<0.001		
Surgery of aortic root/thoracic aorta¶, %			18.7 *v* 9.9	0.006
Isolated non-CABG, %			20.9 *v* 27.5	0.06
2 procedures, %			22.3 *v* 16.7	1.0
≥3 procedures, %			18.0 *v* 9.9	0.01

Data are presented as means with standard deviations, or percentages.

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association Functional Classification; PAH, pulmonary artery hypertension; PVD, peripheral vascular disease.

* In categories: never smoked/ex-smoker/current smoker.

† In EuroSCORE II, diabetes is defined as diabetes on insulin treatment.

‡ Proportion of patients in categories: angiography performed over 14 days before surgery and/or during the index admission but over 24 hours before surgery and/or within 24 hours before surgery.

§ Proportion of patients in categories: normal >85 mL/min/moderate 50-85 mL/min/severe <50 mL/min.

‖ Proportion of patients in categories: systolic pulmonary artery pressure <31 mmHg/31-55 mmHg/>55 mmHg.

¶ Hypothermic circulatory arrest not needed.

Table 2
Results of Univariable Analyses

	No AKI (n = 1,247)	AKI (n = 139)	p Value
Preoperative factors			
AKI Risk Score	19.0 ± 12.1	26.2 ± 13.5	<0.001
EuroSCORE II	2.5 ± 3.1	3.6± 3.9	<0.001
Albumin, g/L	38.6 ± 4.7	37.8 ± 5.4	0.08
Indices of bleeding			
Patient distribution in UDPB classes*, %	57.9/12.3/22.6/6.7/0.5	46.0/10.1/28.1/12.9/2.9	<0.001
Chest tube drainage, mL†	525 ± 318	490 ± 262	0.21
RBC transfusion‡, mL	119 ± 375	249 ± 581	<0.001
FFP transfusion‡, mL	75 ± 254	204 ± 445	<0.001
Platelet transfusion‡, %	20.0	30.9	0.004
Fibrinogen administration‡, %	3.6	8.6	0.011
Prothrombin complex concentrate administration‡, n %	5.2	7.9	0.24
FVIII/VWF administration‡, %	3.3	8.6	0.005
Resternotomy for bleeding, %	3.3	6.5	0.09
Intraoperative and postoperative factors			
Albumin study group, %	50.4	46.0	0.37
Cardiopulmonary bypass time, min	107.5 ± 39.3	125.8 ± 57.9	<0.001
Mean arterial pressure, mmHg§,‖	77.3 ± 6.1	74.0 ± 7.0	<0.001
Vasopressor dose, μg/kg/min§,¶	0.04 ± 0.05	0.08 ± 0.09	<0.001
Inotropic dose, μg/kg/min§,¶	0.73 ± 1.25	1.10 ± 1.47	0.001
Fluid balance, mL§	4,550 ± 1,529	5,442 ± 2,105	<0.001
Hematocrit, %§,‖	32.9 ± 3.3	32.0 ± 3.0	0.002
Chloride dose of fluids, mmol§	810 ± 157	825 ± 167	0.29
Plasma chloride during the first 24 hours in the ICU, mmol/L‖	109.2 ± 2.4	109.5 ± 2.4	0.28
pH§,‖	7.38 ± 0.02	7.38 ± 0.02	0.07
Tranexamic acid dose, mg§	35,492.8 ± 1,158.7	3,680.1 ± 1,922.3	0.10
Aprotinin administration, %§	0.9	1.4	0.38

Abbreviations: AKI, acute kidney injury; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FFP, fresh frozen plasma; FVIII/VWF, factor VIII/von Willebrand factor concentrate; ICU, intensive care unit; MAP, mean arterial pressure; RBC, red blood cell; UDPB, Universal Definition of Perioperative Bleeding.

* UDPB classes: insignificant/mild/moderate/severe/massive.

† Within first 12 postoperative hours.

‡ After CPB and within first 24 postoperative hours.

§ During the intervention period.

‖ Based on area under the curve of all measurements.

¶ Time-weighted average dose.

Univariable Analyses

Both EuroSCORE II and AKI Risk Score were higher in patients with AKI than those without (Table 2). Regarding bleeding, AKI patients had higher UDPB class and lower hematocrit during the intervention period, received higher amounts of RBCs and FFP, and more often received fibrinogen and FVIII/VWF concentrates and platelets (Table 2). As for other perioperative (ie, intra- and postoperative, see Methods) factors, AKI patients had longer CPB times, lower MAPs, higher vasopressor and inotropic doses, and more positive fluid balances (Table 2).

Multivariable Analyses

In the logistic regression analysis, including the risk scores (ie, AKI Risk Score and EuroSCORE II) and the UDPB class (Model 1), the following factors were statistically significantly associated with AKI: the highest UDPB classes 3 and 4 (indicating severe and massive bleeding) and the AKI Risk Score (Fig 1 and Supplementary Table 2). The AUC-ROC of Model 1 to predict AKI was 0.69 (95% CI: 0.65-0.74).

In the logistic regression analysis, including the risk scores, the components of the UDPB classification, and FVIII/VWF concentrate administration (Model 2), the following factors were statistically significantly associated with AKI: AKI Risk Score and FFP transfusion (Fig 1 and Supplementary Table 2). The AUC-ROC of Model 2 to predict AKI was 0.71 (95% CI: 0.66-0.75).

In the mediation analysis (Model 3), UDPB-high did not have a direct effect on AKI, while MAP and fluid balance as mediators had indirect effects on AKI (Table 3). The incidences of AKI and UDPB-high and other perioperative factors are presented in the different MAP and fluid balance ranges in Figs 2 and 3.

Discussion

The main finding of this post-hoc analysis of 1,386 on-pump cardiac surgical patients from the ALBICS trial was that perioperative bleeding assessed by the UDPB classification was

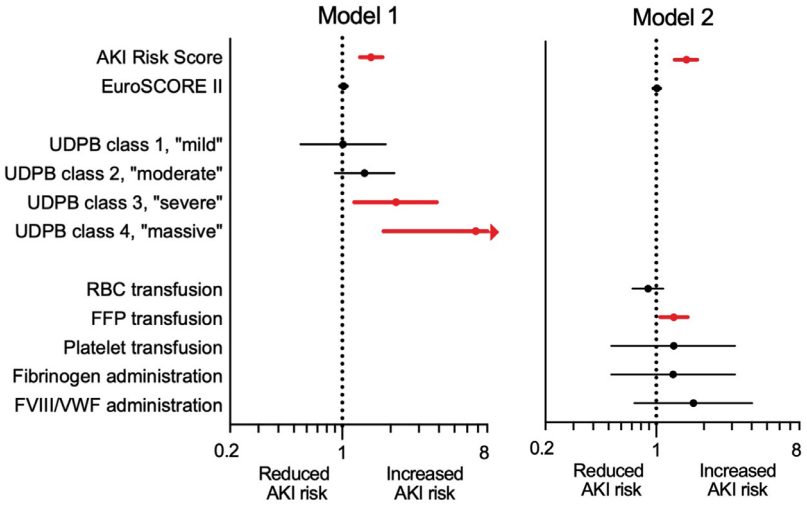

Fig 1. Logistic regression models predicting acute kidney injury. Model 1: risk scores and UDPB class; Model 2: risk scores, components of the UDPB classification, and FVIII/VWF administration. AKI, acute kidney injury; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FFP, fresh frozen plasma; FVIII/VWF, coagulation factor VIII/von Willebrand factor concentrate; RBC, red blood cell; UDPB, Universal Definition of Perioperative Bleeding.

not an independent risk factor for AKI when adjusted for other perioperative risk factors (Model 3). Instead, based on the mediation analysis (Model 3), hemodynamic instability as a consequence of bleeding plausibly manifested as lower MAP and higher fluid balance, thereby possibly leading to the development of CSA-AKI in bleeding patients. Furthermore, of administered blood products and coagulation factor concentrates, only FFP transfusion was independently associated with CSA-AKI (Model 2).

Perioperative bleeding was assessed by the Universal Definition of Perioperative Bleeding classification. Corroborating previous studies,[14-16] UDPB classes 3 and 4 independently predicted CSA-AKI (Model 1) when adjusted only for preoperative risk scores (AKI Risk Score and EuroSCORE II). When mediation analysis was performed including UDPB-high (ie, the combination of the UDPB classes 3 and 4) as exposure and perioperative factors as mediators or covariates, UDPB-high did not directly associate with CSA-AKI. Instead, decreasing MAP and increasing fluid balance mediated the indirect effects of bleeding on the evolution of CSA-AKI. In earlier studies, perioperative hypotension has been associated with an increased risk of CSA-AKI.[23-27] Management of perioperative blood loss with both crystalloids and blood products often leads to a more positive fluid balance, which is a risk factor for CSA-AKI.[28,29] As a well-known consequence of bleeding, hemodynamic instability likely exposed bleeding patients to developing CSA-AKI.

Table 3
Results of Mediation Analysis Predicting CSA-AKI Development

Variable	Regression Coefficient	95% CI
UDPB-high (classes 3 and 4)	0.32	−0.26 to 0.91
MAP*,†	0.08	0.003 to 0.21
Fluid balance*	0.12	0.17 to 0.27
Hematocrit*,†	0.08	−0.05 to 0.22
Vasopressor dose*	0.05	−0.11 to 0.20
Inotropic dose*	−0.03	−0.11 to 0.02

Abbreviations: CI, confidence interval; CSA-AKI, cardiac surgery−associated acute kidney injury; MAP, mean arterial pressure; UDPB, Universal definition of perioperative bleeding.

* During the intervention period of intraoperative phase and the first 24 hours in the intensive care unit.

† Based on area under the curve of all measurements.

Previous studies have reached conflicting conclusions on the role of blood product and coagulation factor concentrate administrations in CSA-AKI development. In a study by Kindzelski et al., RBC, FFP, or platelet administrations were independently associated with any stage of CSA-AKI when adjusted for preoperative and procedure-related factors.[10] Similarly, when adjusted with intraoperative and postoperative factors, intraoperative RBC administration is associated with moderate-to-severe AKI.[30] In a retrospective study of 4,217 CABG patients, RBC, FFP, and platelet transfusions were associated with CSA-AKI in univariate analyses, but only RBC transfusion was an independent predictor of CSA-AKI in multivariable analysis.[31] While in some studies, there was no independent association of CSA-AKI with FFP or PCC administrations,[32-34] in others, both FFP[13] and PCC[12] administrations were found to contribute independently to CSA-AKI development. In a meta-analysis, compared with placebo, fibrinogen administration did not increase CSA-AKI development.[35]

In the present study, although AKI patients received higher amounts of RBC and FFP transfusions and more frequently platelet transfusions as well as fibrinogen and FVIII/VWF concentrates, only FFP transfusion was an independent risk factor for CSA-AKI in a multivariable analysis (Model 2). Rather than a direct effect of FFP on CSA-AKI development, the current authors speculate that the association between FFP administration and CSA-AKI reflects volume replacement of hypovolemic bleeding patients with FFP transfusions. The performance of Model 2 to predict CSA-AKI was intermediate (AUC-ROC: 0.71, 95% CI: 0.66-0.75) and of similar magnitude as in Model 1 (0.69, 0.65-0.74).

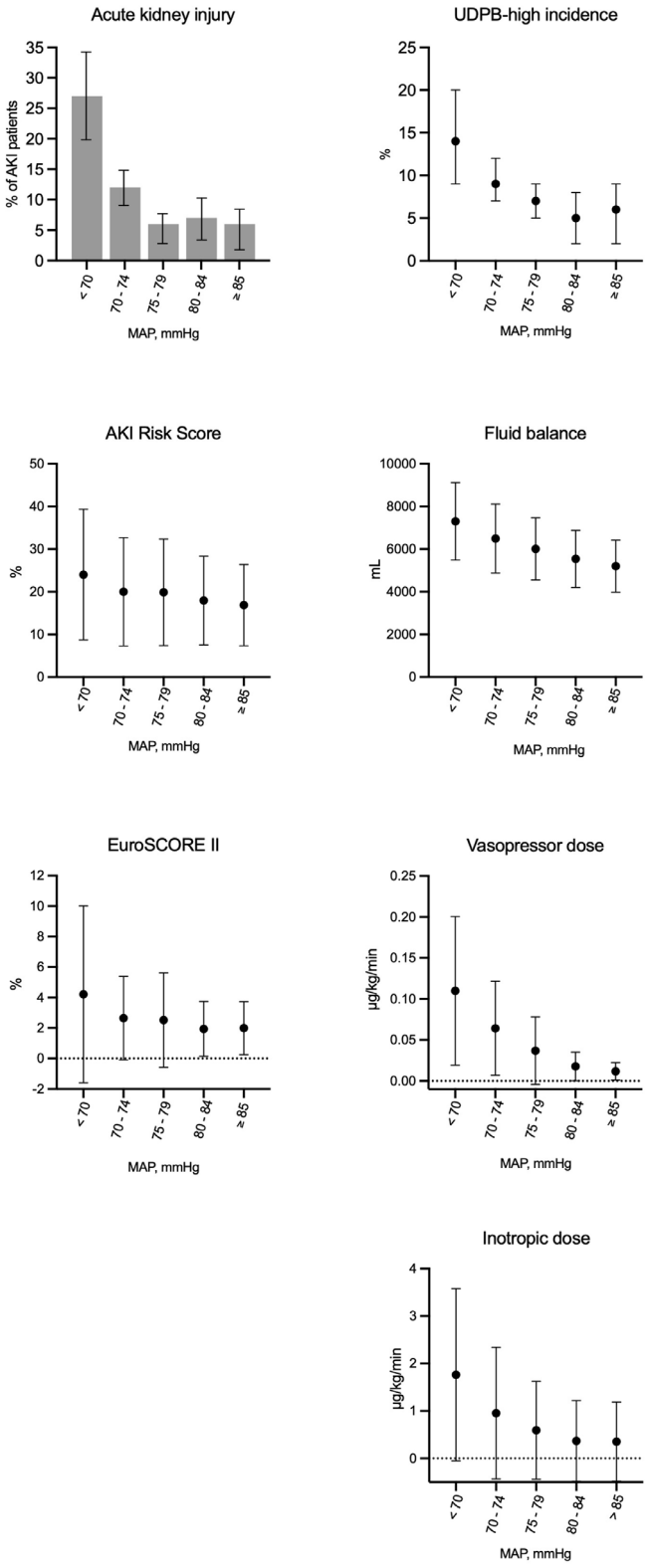

Fig 2. Risk scores, UDPB-high, acute kidney injury, and hemodynamics in different mean arterial pressure ranges. Patient numbers in MAP ranges are as follows: <70 mmHg (n = 153), 70-74 mmHg (n = 412), 75-79 mmHg (n = 455), 80-84 mmHg (n = 223), and ≥85 mmHg (n = 143). The data for acute kidney injury are shown as a percentage of all AKI patients and UDPB-high incidence as percentage and 95% CI. Otherwise, the data are presented with means and standard deviations. Continuous data and UDPB class were measured during surgery and the first 24 hours postoperatively, and AKI within the first f4 postoperative days. AKI, acute kidney injury; CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MAP, mean arterial pressure; UDPB, universal definition of perioperative bleeding.

So far, research has focused mainly on preoperative factors predisposing to CSA-AKI. Consequently, research has offered few treatment strategies to prevent CSA-AKI. In essence, the findings of the present study suggest that bleeding itself was not directly associated with AKI, but by predisposing to perioperative hypotension and higher fluid balance, it increases the risk of AKI. This suggests that the prevention of hypotension and high fluid balance in a bleeding patient probably provides a means of preventing CSA-AKI.

In the present study, MAP was assessed as a time-weighted average of all measurements in the intervention period. MAP correlated inversely with fluid balance as well as vasopressor and inotrope doses. In other words, the patients with the lowest MAP received the most intense treatment, suggesting refractory hypotension. Potentially, the refractory nature of hypotension underlines the importance of prevention of hypotension. Based on the present results, prevention of bleeding may be one way to prevent perioperative hypotension. Although the mean difference of time-weighted MAP between the AKI and non-AKI patients was only 3 mmHg, a MAP threshold of 75 mmHg was found, below which AKI incidence increased steeply. Importantly, a similar finding of increasing risk for AKI in MAP values below 75 mmHg has been found in cardiac surgical and septic patients.[30,36]

Two further details of the present findings merit comment. First, increased perioperative fluid balance has been associated with increased AKI incidence in observational studies[28,29] In the present study, a U-shaped association between postoperative fluid balance and AKI incidence was observed, so that its incidence in patients with a fluid balance less than 2,500 mL was double that of patients with a fluid balance of 2,500 to 3,499 mL. This suggests that a too-restrictive fluid treatment in hemodynamically stable patients may increase the risk of AKI. Second, preoperative and perioperative hyperchloremia have previously been associated with CSA-AKI.[37,38] In the present study, however, neither postoperative mean plasma chloride concentration nor chloride load were associated with AKI.

The present study has some limitations. First, AKI was assessed within the first 4 postoperative days instead of the first week, as defined in the KDIGO criteria.[4] A significant proportion of patients was discharged to the referral hospitals by the 5th postoperative day, limiting the availability of creatinine data. Second, the AKI incidence in the ALBICS patient cohort was lower (10.0%) than the incidence expected according to the AKI Risk Score (19.7%). Likewise, the 90-day mortality was 0.4% and lower than the predicted median mortality of 1.7%, according to EuroSCORE II.[18] Therefore, the current findings cannot be generalized to cohorts with higher mortality and AKI incidence. Third, the ALBICS trial was a single-center study, which limits the generalizability of the present post-

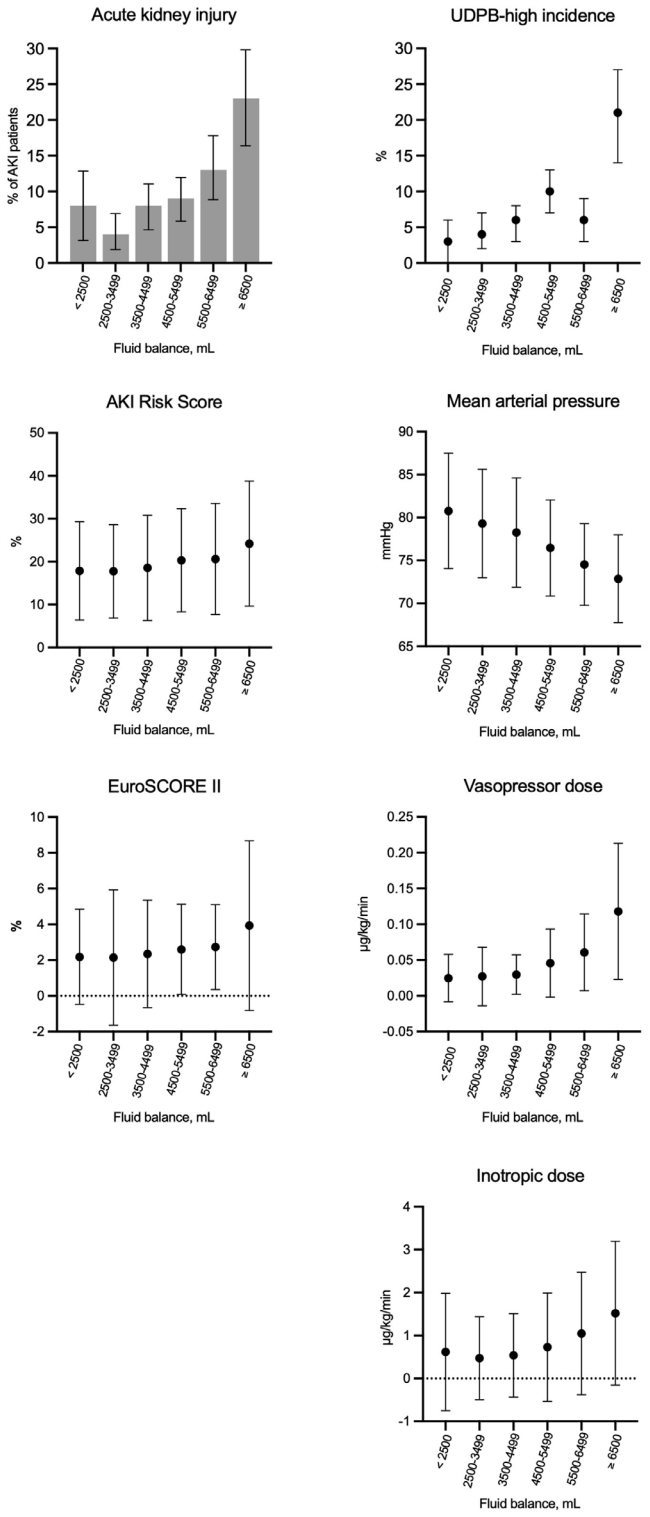

Fig 3. Risk scores, UDPB-high, acute kidney injury, and hemodynamics in different fluid balance ranges. Patient numbers in fluid balance ranges are as follows: <2,500 mL (n = 101), 2,500-3,499 mL (n = 237), 3,500-4,499 mL (n = 331), 4,500-5,499 mL (n = 349), 5,500-6,499 mL (n = 214), and ≥6,500 mL (n = 154). The data for acute kidney injury are shown as a percentage of all AKI patients and UDPB-high incidence as percentage and 95% CI. Otherwise, the data are presented with means and standard deviations. Continuous data and UDPB class were measured during surgery and the first 24 hours postoperatively, and AKI within the first 4 postoperative days. AKI, acute kidney injury; CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; UDPB, universal definition of perioperative bleeding.

hoc results. This study also has strengths. First, bleeding was defined by the UDPB classification, which is validated in cardiac surgery.[14-17] Second, a wide spectrum of accurate intra- and postoperative data relevant to AKI development was prospectively retrieved and analyzed. In the previous corresponding studies applying the UDPB classification, only preoperative factors and type of surgery were included.[14-16]

In conclusion, perioperative bleeding was not an independent risk factor for CSA-AKI. Based on the mediation analysis, hypotension and higher fluid balance, as possible consequences of bleeding, led to the development of CSA-AKI in bleeding patients. The present results suggest that prevention of bleeding might reduce AKI incidence in on-pump cardiac surgery.

Declaration of competing interest

The authors declare the following financial interestsand/or personal relationships that may be considered potential competing interests: The ALBICS trial was supported financially by Prothya Biosolutions Ltd (former Sanquin Plasma Products), Amsterdam, The Netherlands.

CRediT authorship contribution statement

Hanna E. Vlasov: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Liisa M. Petäjä:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Erika M. Wilkman:** Writing – review & editing, Investigation, Conceptualization. **Akseli T. Talvasto:** Writing – review & editing, Formal analysis. **Minna K. Ilmakunnas:** Writing – review & editing, Formal analysis. **Peter M. Raivio:** Writing – review & editing, Investigation, Formal analysis. **Seppo T. Hiippala:** Writing – review & editing, Investigation, Conceptualization. **Raili T. Suojaranta:** Writing – review & editing, Investigation, Conceptualization. **Tatu S. Juvonen:** Writing – review & editing, Investigation, Conceptualization. **Eero J. Pesonen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Informed Patient Consent

The ALBICS trial was conducted according to the Declaration of Helsinki. Informed consent was obtained from the patients before surgery.

ERB Approval

The Ethics Committee of the Hospital District of Helsinki and Uusimaa, Helsinki, Finland (HUS/2291/2016, 14.12.2016/6.2.2017/14.6.2017) approved this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2025.03.006.

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