ESC European Society of Cardiology

European Heart Journal (2025) **46**, 38–54
https://doi.org/10.1093/eurheartj/ehae602

FASTTRACK – CLINICAL RESEARCH
Acute cardiovascular care

Proenkephalin improves cardio-renal risk prediction in acute coronary syndromes: the KID-ACS score

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Received 2 May 2024; revised 7 August 2024; accepted 22 August 2024; online publish-ahead-of-print 31 August 2024

See the editorial comment for this article 'Cardio-renal risk stratification and acute kidney injury in acute coronary syndromes', by L. Crisanti and C. Mueller, https://doi.org/10.1093/eurheartj/ehae717.

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Abstract

Background and Aims Circulating proenkephalin (PENK) is a stable endogenous polypeptide with fast response to glomerular dysfunction and tubular damage. This study examined the predictive value of PENK for renal outcomes and mortality in patients with acute coronary syndrome (ACS).

Methods Proenkephalin was measured in plasma in a prospective multicentre ACS cohort from Switzerland ($n = 4787$) and in validation cohorts from the UK ($n = 1141$), Czechia ($n = 927$), and Germany ($n = 220$). A biomarker-enhanced risk score (KID-ACS score) for simultaneous prediction of in-hospital acute kidney injury (AKI) and 30-day mortality was derived and externally validated.

Results On multivariable adjustment for established risk factors, circulating PENK remained associated with in-hospital AKI [per $\log_2$ increase: adjusted odds ratio 1.53, 95% confidence interval (CI) 1.13–2.09, $P = .007$] and 30-day mortality (adjusted hazard ratio 2.73, 95% CI 1.85–4.02, $P < .001$). The KID-ACS score integrates PENK and showed an area under the receiver operating characteristic curve (AUC) of .72 (95% CI .68–.76) for in-hospital AKI and .91 (95% CI .87–.95) for 30-day mortality in the derivation cohort. Upon external validation, KID-ACS achieved similarly high performance for in-hospital AKI (Zurich: AUC .73, 95% CI .70–.77; Czechia: AUC .75, 95% CI .68–.81; Germany: AUC .71, 95% CI .55–.87) and 30-day mortality (UK: AUC .87, 95% CI .83–.91; Czechia: AUC .91, 95% CI .87–.94; Germany: AUC .96, 95% CI .92–1.00), outperforming the contrast-associated AKI score and the Global Registry of Acute Coronary Events 2.0 score, respectively.

Conclusions Circulating PENK offers incremental value for predicting in-hospital AKI and mortality in ACS. The simple six-item KID-ACS risk score integrates PENK and provides a novel tool for simultaneous assessment of renal and mortality risk in patients with ACS.

Structured Graphical Abstract

Key Question

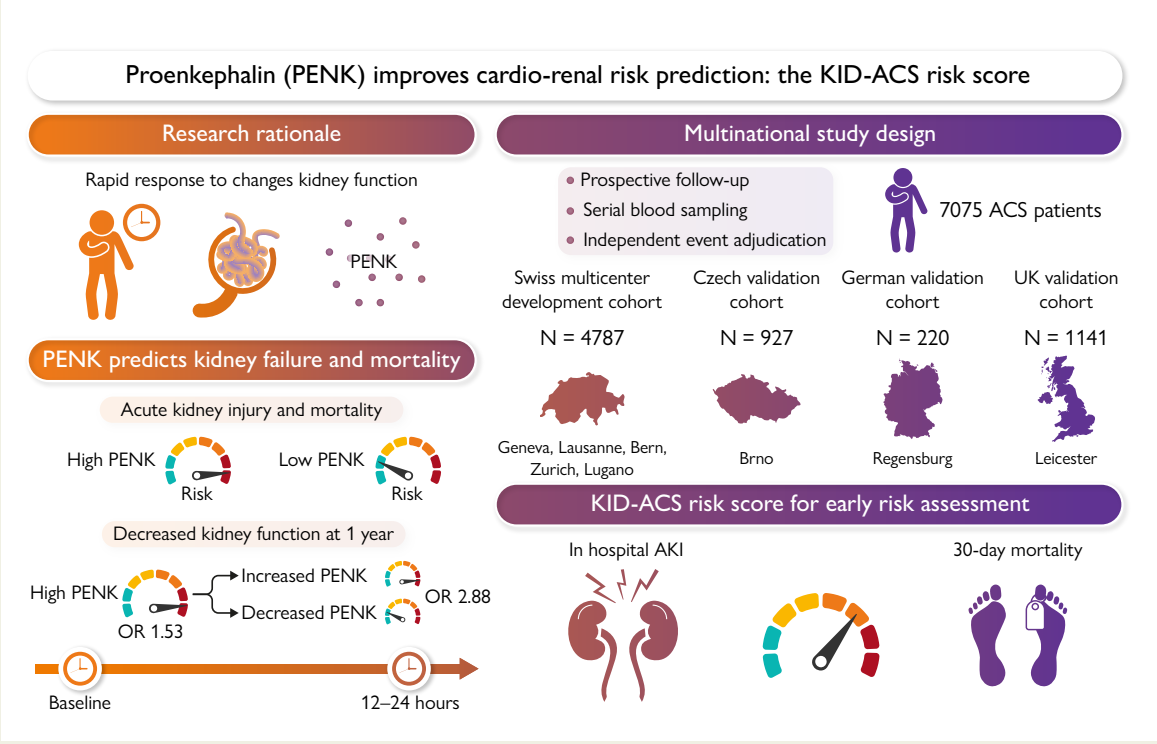
Does circulating proenkephalin (PENK) improve early assessment of renal and mortality risk in patients with acute coronary syndrome (ACS)?

Key Finding

Circulating PENK ranked among the strongest predictors of renal outcomes and mortality. The newly developed 6-item KID-ACS risk score for in-hospital AKI and 30-day mortality integrated PENK levels and outperformed established risk models. KID-ACS showed excellent predictive performance in external validation cohorts and required fewer patient variables than established risk scores.

Take Home Message

Circulating PENK is a strong predictor of in-hospital AKI and 30-day mortality informing early risk assessment using the KID-ACS score.



Circulating proenkephalin (PENK) was identified as a novel marker of in-hospital acute kidney injury (AKI) and increased mortality risk in patients with acute coronary syndrome (ACS). Circulating PENK levels were measured at presentation in three independent prospective ACS cohorts from Switzerland, the UK, Czechia, and Germany. In the multicentre Swiss cohort (SPUM-ACS Biomarker Study), PENK levels were additionally measured after 12–24 h. High levels of PENK were independently associated with increased risk of in-hospital AKI (per $\log_2$ increase, adjusted odds ratio 1.53) and 30-day mortality (per $\log_2$ increase, adjusted odds ratio 2.73) beyond established risk factors. Patients with dynamic increase in PENK levels at 12–24 h displayed 2.88-fold higher in-hospital AKI risk when adjusting for established risk factors. The newly developed six-item KID-ACS risk score for in-hospital AKI and 30-day mortality integrates PENK levels outperforms established risk models. KID-ACS showed excellent predictive performance upon external validation and requires fewer patient variables.

Keywords Acute coronary syndromes • Acute kidney injury • Mortality risk • Proenkephalin • Risk prediction

Introduction

The early assessment of renal and mortality risk is essential to guide treatment decisions in patients with acute coronary syndrome (ACS).[1,2] In particular, the combination of low cardiac output, renal congestion, and high comorbidity burden predispose the ACS patient population to increased risk of poor renal outcomes. Acute kidney injury (AKI) is a frequent complication of ischaemia-related haemodynamic impairment and coronary revascularization, which is linked to excess mortality.[3] However, established risk scores for AKI and mortality in this population show limited predictive performance,[1,3,4] involve different risk calculators for each outcome, and require a myriad of patient variables.

Moreover, currently available risk models[1,3,4] in patients with ACS, who undergo percutaneous coronary intervention (PCI) in most cases, rely on serum creatinine, a notoriously unreliable marker with delayed response to acute kidney damage.[5,6] While changes in creatinine are not detectable until nearly 50% of kidney function in healthy individuals is lost,[7–9] new functional biomarkers with an earlier response to changes in kidney function allow for improved prediction of renal and cardiovascular outcomes.[7,10]

Proenkephalin (PENK) is a stable endogenous polypeptide, which reflects glomerular dysfunction and tubular damage.[7,11–13] Given its fast response to kidney dysfunction,[14] PENK has emerged as a real-time biomarker of AKI[7,11,15,16] in critically ill patients and holds promise to guide timely preventive management strategies in ACS.[17]

Harnessing four prospective ACS cohorts from Switzerland, the UK, Czechia, and Germany, we herein aimed to study the predictive value of PENK and to develop and externally validate a simple biomarker-enhanced risk score for early assessment of both AKI and mortality risk in patients with ACS.

Methods

Study design

We used prospective ACS cohorts from Switzerland ($n = 4787$), the UK ($n = 1141$), Czechia ($n = 927$), and Germany ($n = 220$) (Supplementary data online, *Figure S1*). The multicentre prospective Swiss cohort (SPUM-ACS Biomarker Study, ClinicalTrials.gov Identifier: NCT01000701) was used to study the predictive value of PENK and to derive a biomarker-enhanced risk score for AKI and mortality (KID-ACS score).[18,19] The UK cohort (Leicester Acute Myocardial Infarction Peptide study)[17] was used for external validation of the mortality prediction model. The Czech (Global Research on Acute Conditions Team study)[20,21] and German cohorts[22] were used for external validation of the AKI and mortality prediction models.

In the investigator-initiated, multicentre prospective SPUM-ACS Biomarker Study, a total of 4787 patients with ACS were recruited from December 2009 to December 2017.[18,19,23–30] Acute coronary syndrome diagnoses were independently confirmed by experienced cardiologists at local study facilities.[19,24] Guideline-directed therapy regimens were applied, as reported previously.[24] Characteristics of the UK cohort,[17] the Czech cohort,[17,20,21] and the German cohort[22] are summarized in the Supplementary data.

All study participants gave written informed consent.[17,19,21,22] The present study was carried out in accordance with the Declaration of Helsinki and approved by local Ethics Committees (reference number: EK-1688/2019-01809).[17,19,21,22]

Biomarker measurements

Ethylenediaminetetraacetic acid (EDTA) blood samples were obtained at time of presentation (Timepoint 1, all cohorts) and after 12–24 h (Timepoint 2, Swiss cohort).[19,24] Plasma samples were immediately frozen and stored at −80°C. Proenkephalin levels were centrally measured using a sandwich immunoassay targeting PENK amino acids 119–159 (sphingotest penKid, SphingoTec GmbH, Hennigsdorf, Germany) with a lower limit of detection equivalent to 5.5 pmol/L.[17,31,32] A Centro LB 960 microtitre plate luminometer (Berthold Technologies GmbH & Co. KG) was used to measure luminescence. Intra- and inter-assay coefficients of variation amounted to 6.4% and 9.5% at 50 pmol/L and 4.0% and 6.5% at 150 pmol/L, respectively. Laboratory personnel blinded to sample allocation and patient data conducted the measurements. Biomarkers analysed and assays used are summarized in the Supplementary data.

Study endpoints, follow-up, and outcome adjudication

Primary endpoints were in-hospital AKI and 30-day mortality. Additional endpoints were chronic kidney disease (CKD) and mortality at 1 year. Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which require an absolute (≥.3 mg/dL) or a relative (≥1.5 times) increase of serum creatinine assessed at hospital discharge compared with baseline values, as reported previously.[3,6,15,33–38] Chronic kidney disease was defined as decrease of estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2 calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation,[39] as reported previously.[40–45] Patients on dialysis were excluded from analyses involving the prediction of renal outcomes. Patients with eGFR <60 mL/min/1.73 m^2 were excluded from analyses involving the 1-year CKD endpoint.

In Switzerland, patients with ACS were followed up at hospital discharge, at 30 days (phone call), and 1 year (clinical visit). Trained study personnel at the respective study centres collected baseline and event data using a centralized web-based data entry system (CARDIOBASE, Clinical Trial Unit and Department of Cardiology, University Hospital Bern, Bern, Switzerland, and Webspirit Systems GmbH, Ulm, Germany).[19] An independent clinical endpoint committee involving three certified expert cardiologists blinded to patients' baseline characteristics assessed fatal events using pre-specified adjudication forms.[19] Data collection was overseen by a committee including expert cardiologists from each study site. The adjudication of outcomes in the UK cohort, the Czech cohort, and the German cohort is summarized in the Supplementary data.

Predictive value of proenkephalin

To study the association of PENK with renal outcomes and mortality, continuous levels of PENK were $\log_2$-transformed, i.e. relative effect estimates correspond to a doubling in PENK levels.[19] In addition, patients were divided according to PENK quartiles (Q) and biomarker levels analysed on a categorical scale. Dynamic changes in PENK levels within the first 12–24 h after presentation were studied on a continuous scale (per 10 pmol/L increase) and on a categorical scale (increase vs. decrease). To study the predictive value of peri-procedural changes in PENK for in-hospital AKI, we conducted a subgroup analysis in patients who underwent PCI before the second measurement. Cox proportional hazards regression models were used to examine the association of PENK at presentation with fatal events at 30 days and 1 year (365 days). Logistic regression models were used to study the association of PENK with in-hospital AKI and CKD at 1 year. In addition, we used logistic regression to explore the relationship of in-hospital AKI with CKD at 1 year and with mortality at 1 year.[46] Multivariable analyses were conducted using a stepwise approach adjusting for predefined covariables. Based on previous observations and biological plausibility, covariables for the prediction of fatal events included sex, age, ACS type, history of diabetes, high-sensitivity C-reactive protein, high-sensitivity troponin T (hs-TnT), revascularization, history of smoking, and the Global Registry of Acute Coronary Events (GRACE) 2.0 risk at baseline using predefined thresholds for mortality risk.[19,24,47] Predictions of in-hospital AKI using PENK levels at presentation were adjusted for sex, body mass index (BMI),

systolic blood pressure, and the contrast-associated AKI (CA-AKI) risk score (Model 1), which integrates ACS type, eGFR, left ventricular ejection fraction, diabetes, haemoglobin, glucose, heart failure on admission, and age.[3] Predictions of in-hospital AKI using dynamic changes in PENK levels were adjusted for sex, BMI, systolic blood pressure, procedure duration, and the CA-AKI risk score (Model 2), which integrates ACS type, eGFR, left ventricular ejection fraction, diabetes, haemoglobin, glucose, heart failure on admission, age, contrast volume, procedural bleed, slow flow or no flow post procedure, and complex anatomy.[3] Predictions of CKD at 1 year using PENK levels at presentation were adjusted for sex, BMI, history of smoking, and variables included in the Framingham Risk Score for the Development of Chronic Kidney Disease (Model 2),[43] which lacks a score nomogram: age, history of diabetes, history of hypertension, and eGFR category. Predictions of CKD at 1 year using dynamic changes in PENK levels were adjusted for sex, BMI, history of smoking, procedure duration, contrast volume, and variables included in the Framingham Risk Score for the Development of Chronic Kidney Disease (Model 2)[43]: age, history of diabetes, history of hypertension, and eGFR category. Analyses exploring the association between in-hospital AKI and CKD at 1 year were adjusted for sex, BMI, history of smoking, procedure duration, contrast volume, and variables included in the Framingham Risk Score for the Development of Chronic Kidney Disease (Model 2)[43]: age, history of diabetes, history of hypertension, and eGFR. Additional exploratory analyses included multivariable adjustments for established and emerging biomarkers, alternative adjustment strategies, and an alternative definition of 1-year renal outcome, defined as 30% relative decline in eGFR (see Supplementary data).

Score development

The KID-ACS risk score was developed in the Swiss multicentre cohort of prospectively recruited patients with ACS. Separate prediction models were derived for the prediction of in-hospital AKI and 30-day mortality (see Supplementary data). In the development of the in-hospital AKI model, patients from study centre Zurich were reserved for external validation.

Recursive feature elimination was applied to identify the most relevant predictors for in-hospital AKI and 30-day mortality.[48–53] We found substantial overlap in the top-ranking predictors of both endpoints, including circulating PENK, and chose the number of features at the inflection point of performance.[48,53] Among the top 10 predictors for both outcomes, 6 variables were included in the final multivariable models: age, cardiac arrest, PENK, N-terminal pro-B-type natriuretic peptide (NT-proBNP), leucocyte count, and glucose. In addition, we developed an extended seven-item post-procedural prediction model for in-hospital AKI, which incorporates peri-procedural changes in PENK levels and achieves slightly improved performance (see Supplementary data). Final models were transformed into a risk score available from a nomogram, which assigns integer points to each factor based on the magnitude of association with in-hospital AKI and 30-mortality.

Performance analysis and external validation

Discrimination was assessed by the area under the receiver operating characteristic (ROC) curve (AUC).[54] Calibration was assessed graphically using smoothed calibration curves.[55] Clinical utility was evaluated using decision curve analyses.[56] Based on statistical power considerations, model performance was compared to established risk models for in-hospital AKI (i.e. the CA-AKI risk score[3]) and mortality (i.e. the GRACE 2.0 score[4]) in the Zurich validation cohort and the UK validation cohort, respectively. We tested non-inferiority of KID-ACS compared to established risk scores at −.05 delta AUC using a one-sided hypothesis test (see Supplementary data). Incremental discrimination was evaluated by comparing the AUC using DeLong's test for paired ROC curves.[57] Incremental reclassification over existing models was evaluated using the continuous net reclassification improvement (NRI).[58]

Statistical analyses

Density plots and quantile–quantile plots were applied to assess the distribution of continuous variables. Normal variables are presented as mean ± standard deviation (SD) and non-normal variables as median and interquartile range (IQR).[19] Categorical data are reported as counts and valid percentages.[19] Continuous variables were compared with unpaired Student's *t*-test and Mann–Whitney *U* test, and categorical variables with the χ^2 test and Fisher's exact test.[59] The association of circulating PENK with clinical outcomes was studied in complete case regression models, as appropriate.[24,46,58] Risk score development was based on power calculations[48,60] and conducted using multiply imputed data (see Supplementary data, *Table S25*).[18,56,61] To analyse a potential impact of the imputation on the results, sensitivity analyses were conducted using complete cases.[18] Resampling techniques (i.e. bootstrapping with 1000 replicates)[19,59] were used for internal validation of the independent association of PENK with in-hospital AKI and 30-day mortality. *P*-values and confidence intervals (CIs) are two sided unless specified otherwise. The study followed the framework for development, validation, and transparent reporting of prediction models summarized by Steyerberg and Vergouwe[55] and the TRIPOD statement[62] and was conducted according to the principles of the STROBE statement.[54] Statistical analyses were performed with R software version 4.2.2. A detailed description of the statistical analyses is provided in the Supplementary data.

Results

Circulating proenkephalin is elevated in the acute phase of acute coronary syndrome

A total of 7075 patients with ACS were enrolled in Switzerland ($n = 4787$), the UK ($n = 1141$), Czechia ($n = 927$), and Germany ($n = 220$) (see Supplementary data online, *Figure S1*). Circulating PENK levels at presentation were significantly elevated in patients with ACS compared to sex- and age- matched control subjects [62.7 IQR (50.1–80.2) pmol/L vs. 50.2 IQR (43.5–58.5) pmol/L, $P < .001$] and decreased within the first 12–24 h [53.4 (41.9–71.2) pmol/L, $P < .001$]. Dynamic increases in the first 12–24 h occurred in 964 (31.3%) patients. A total of 443 (10.3%) and 421 (15.2%) patients developed in-hospital AKI and 1-year CKD, respectively (*Tables 1* and *2*, Supplementary data online, *Tables S1–S3*).

Proenkephalin levels predict renal outcomes and mortality beyond established risk scores

Circulating PENK was identified as a useful predictor of in-hospital AKI above and beyond established risk factors and the CA-AKI risk score [per $\log_2$ increase: adjusted odds ratio (OR) 1.53, 95% CI 1.13–2.09, $P = .007$; Q4 vs. Q1–Q3: adjusted OR 1.64, 95% CI 1.15–2.32, $P = .006$; *Figure 1A*, Supplementary data online, *Tables S4* and *S5*]. Moreover, high PENK levels translated into increased rates of CKD at 1-year follow-up adjusting for established risk factors and the Framingham Risk Score for the Development of Chronic Kidney Disease[43] (per $\log_2$ increase: adjusted OR 2.23, 95% CI 1.52–3.27, $P < .001$; Q4 vs. Q1–Q3: OR 1.62, 95% CI 1.13–2.28, $P = .007$; *Figure 1B*, Supplementary data online, *Tables S4*, *S5*, *S22* and *S23*). Exploratory analyses on the association of PENK levels and renal outcomes, considering established and emerging biomarkers including cystatin C, alternative adjustment strategies, and relative eGFR changes as outcome, yielded similar results (see Supplementary data online,

Table 1 Baseline characteristics of patients with acute coronary syndrome in the Swiss cohort (SPUM-ACS Biomarker Study) according to proenkephalin quartiles

	All patients ($n = 4311$)	PENK quartile 1 <50.1 pmol/L ($n = 1074$)	PENK quartile 2 >50.1–62.7 pmol/L ($n = 1072$)	PENK quartile 3 >62.7–79.9 pmol/L ($n = 1073$)	PENK quartile 4 >79.9 pmol/L ($n = 1092$)	*P*-value
Age (years)	63.3 ± 12.4	58.5 ± 10.1	61.4 ± 11.6	63.3 ± 12.2	70.0 ± 12.5	<.001
Female	879/4311 (20.4%)	124/1074 (11.5%)	169/1072 (15.8%)	218/1073 (20.3%)	368/1092 (33.7%)	<.001
BMI (kg/m^2)	27.1 ± 4.4	28.3 ± 4.6	27.2 ± 4.2	26.9 ± 4.2	26.0 ± 4.1	<.001
Body surface area (m^2)	1.9 ± .2	2.0 ± .2	2.0 ± .2	1.9 ± .2	1.8 ± .2	<.001
STEMI	2252/4311 (52.2%)	484/1074 (45.1%)	519/1072 (48.4%)	604/1073 (56.3%)	645/1092 (59.1%)	<.001
Heart rate (b.p.m.)	76.7 ± 15.7	78.2 ± 15.6	76.4 ± 15.1	76.0 ± 15.3	76.3 ± 16.6	.006
Systolic blood pressure (mmHg)	129.1 ± 23.5	129.0 ± 23.2	130.8 ± 22.7	128.9 ± 22.9	127.7 ± 25.0	.022
Left ventricular ejection fraction (%)	51.7 ± 11.2	52.5 ± 10.6	52.3 ± 11.1	51.9 ± 10.7	49.7 ± 12.3	<.001
Killip class						<.001
I	3675/4197 (87.6%)	977/1051 (93.0%)	933/1048 (89.0%)	917/1046 (87.7%)	848/1052 (80.6%)	
II	344/4197 (8.2%)	51/1051 (4.9%)	78/1048 (7.4%)	89/1046 (8.5%)	126/1052 (12.0%)	
III	84/4197 (2.0%)	13/1051 (1.2%)	21/1048 (2.0%)	22/1046 (2.1%)	28/1052 (2.7%)	
IV	94/4197 (2.2%)	10/1051 (1.0%)	16/1048 (1.5%)	18/1046 (1.7%)	50/1052 (4.8%)	
Smoking						<.001
Current smoker	1649/4247 (38.8%)	485/1062 (45.7%)	450/1058 (42.5%)	389/1061 (36.7%)	325/1066 (30.5%)	
Former smoker	1189/4247 (28.0%)	278/1062 (26.2%)	290/1058 (27.4%)	320/1061 (30.2%)	301/1066 (28.2%)	
Non-smoker	1409/4247 (33.2%)	299/1062 (28.2%)	318/1058 (30.1%)	352/1061 (33.2%)	440/1066 (41.3%)	
Medical history						
Myocardial infarction	522/4303 (12.1%)	102/1074 (9.5%)	111/1069 (10.4%)	131/1071 (12.2%)	178/1089 (16.3%)	<.001
Diabetes						<.001
No diabetes	3560/4241 (83.9%)	875/1047 (83.6%)	908/1057 (85.9%)	913/1058 (86.3%)	864/1079 (80.1%)	
Non-insulin treated	471/4241 (11.1%)	129/1047 (12.3%)	101/1057 (9.6%)	111/1058 (10.5%)	130/1079 (12.0%)	
Insulin treated	210/4241 (5.0%)	43/1047 (4.1%)	48/1057 (4.5%)	34/1058 (3.2%)	85/1079 (7.9%)	
Hypertension	2409/4309 (55.9%)	556/1074 (51.8%)	566/1072 (52.8%)	579/1073 (54.0%)	708/1090 (65.0%)	<.001
Dyslipidaemia	2754/4310 (63.9%)	712/1074 (66.3%)	675/1072 (63.0%)	678/1073 (63.2%)	689/1091 (63.2%)	.311
Family history of CAD	1056/4252 (24.8%)	272/1061 (25.6%)	269/1062 (25.3%)	283/1057 (26.8%)	232/1072 (21.6%)	.037
Cerebrovascular disease	160/4311 (3.7%)	28/1074 (2.6%)	23/1072 (2.1%)	44/1073 (4.1%)	65/1092 (6.0%)	<.001

Continued

Table 1 *Continued*

	All patients ($n = 4311$)	PENK quartile 1 <50.1 pmol/L ($n = 1074$)	PENK quartile 2 >50.1–62.7 pmol/L ($n = 1072$)	PENK quartile 3 >62.7–79.9 pmol/L ($n = 1073$)	PENK quartile 4 >79.9 pmol/L ($n = 1092$)	*P*-value
Heart failure	54/4309 (1.3%)	4/1074 (.4%)	14/1072 (1.3%)	4/1073 (.4%)	32/1090 (2.9%)	<.001
Dialysis	21/4311 (.5%)	1/1074 (.1%)	0/1072 (.0%)	1/1073 (.1%)	19/1092 (1.7%)	<.001
Clinical chemistry and haematology						
Haemoglobin (g/dL)	13.8 (12.7–14.9)	14.2 (13.2–15.2)	14.1 (13.0–15.0)	13.8 (12.9–14.9)	13.1 (11.8–14.3)	<.001
WBC (G/L)	9.6 (7.5–12.2)	9.8 (7.5–12.2)	9.6 (7.4–12.0)	9.6 (7.6–12.0)	9.4 (7.3–12.3)	.783
Neutrophils (G/L)	7.0 (5.0–9.4)	6.9 (4.9–9.4)	7.0 (4.9–9.4)	7.1 (5.0–9.3)	7.0 (5.1–9.7)	.472
Lymphocytes (G/L)	1.8 (1.2–2.8)	2.1 (1.4–4.2)	1.8 (1.3–2.7)	1.7 (1.2–2.5)	1.6 (1.1–2.4)	<.001
NL ratio	4.5 (2.7–7.4)	4.0 (2.5–6.5)	4.2 (2.6–7.1)	4.8 (3.1–7.6)	4.9 (2.9–8.3)	<.001
High-sensitivity C-reactive protein (mg/L)	2.7 (1.1–7.3)	3.2 (1.2–9.3)	2.5 (1.1–6.2)	2.2 (1.0–5.5)	2.9 (1.1–8.6)	<.001
LDL-C (mmol/L)	3.1 (2.4–3.8)	3.2 (2.5–3.9)	3.2 (2.5–3.9)	3.1 (2.4–3.9)	2.9 (2.1–3.7)	<.001
HbA1c (%)	5.8 (5.5–6.3)	5.7 (5.5–6.3)	5.7 (5.5–6.2)	5.8 (5.5–6.1)	5.8 (5.5–6.5)	.073
Glucose (mg/dL)	115 (101–142)	117 (103–144)	114 (99–137)	115 (101–142)	119 (101–146)	.004
PENK (pmol/L)	62.7 (50.1–80.2)	42.8 (37.4–46.8)	56.4 (53.4–59.5)	70.1 (66.2–74.4)	95.8 (86.2–115.2)	<.001
Creatinine (mg/dL)	.9 (.7–1.0)	.8 (.7–.9)	.8 (.7–1.0)	.9 (.8–1.0)	1.0 (.8–1.3)	<.001
eGFR[a] (mL/min/1.73 m^2)	88.2 (72.2–99.2)	96.8 (87.8–104.3)	92.4 (82.1–101.4)	85.9 (72.9–97.3)	68.4 (50.2–85.2)	<.001
NT-proBNP (ng/L)	334 (108–1158)	283 (85–838)	267 (95–881)	275 (99–990)	625 (167–2380)	<.001
hs-TnT (ng/L)	197 (59–642)	233 (54–755)	189 (61–684)	177 (55–586)	195 (65–579)	.214
Baseline medication						
Aspirin	1229/2777 (44.3%)	243/629 (38.6%)	280/643 (43.5%)	302/689 (43.8%)	404/816 (49.5%)	.001
P2Y12 inhibitors	320/1912 (16.7%)	63/452 (13.9%)	70/429 (16.3%)	75/469 (16.0%)	112/562 (19.9%)	.075
Beta-blocker	978/2760 (35.4%)	190/626 (30.4%)	202/636 (31.8%)	240/687 (34.9%)	346/811 (42.7%)	<.001
ACE-inhibitor/ARB	1474/2757 (53.5%)	302/624 (48.4%)	308/635 (48.5%)	341/687 (49.6%)	523/811 (64.5%)	<.001
Vitamin K antagonist/DOAC	170/2775 (6.1%)	24/628 (3.8%)	26/642 (4.0%)	43/689 (6.2%)	77/816 (9.4%)	<.001
Diuretic	674/2771 (24.3%)	118/627 (18.8%)	132/639 (20.7%)	139/689 (20.2%)	285/816 (34.9%)	<.001
Immunosuppressive drugs	118/2775 (4.3%)	22/628 (3.5%)	17/642 (2.6%)	19/689 (2.8%)	60/816 (7.4%)	<.001
NSAID	165/2775 (5.9%)	39/628 (6.2%)	38/642 (5.9%)	38/689 (5.5%)	50/816 (6.1%)	.949
Oral antidiabetics	502/2775 (18.1%)	131/628 (20.9%)	116/642 (18.1%)	117/689 (17.0%)	138/816 (16.9%)	.205

Continued

Table 1 *Continued*

	All patients ($n = 4311$)	PENK quartile 1 <50.1 pmol/L ($n = 1074$)	PENK quartile 2 >50.1–62.7 pmol/L ($n = 1072$)	PENK quartile 3 >62.7–79.9 pmol/L ($n = 1073$)	PENK quartile 4 >79.9 pmol/L ($n = 1092$)	*P*-value
Outcomes						
30-day death	59/4311 (1.4%)	6/1074 (.6%)	6/1072 (.6%)	8/1073 (.7%)	39/1092 (3.6%)	<.001
1-year death	148/4311 (3.4%)	21/1074 (2.0%)	24/1072 (2.2%)	22/1073 (2.1%)	81/1092 (7.4%)	<.001
In-hospital AKI	443/4157 (10.7%)	80/1033 (7.7%)	78/1019 (7.7%)	94/1036 (9.1%)	191/1069 (17.9%)	<.001
1-year CKD[b]	421/2763 (15.2%)	28/714 (3.9%)	51/730 (7.0%)	112/722 (15.5%)	230/597 (38.5%)	<.001

Categorical data are shown as numbers and percentages (%). Continuous data are presented as median and IQR or as mean ± SD. Groups were compared using analysis of variance, the Kruskal–Wallis test, the χ^2 test, or Fisher's exact test, as appropriate.

ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-TnT, high-sensitivity troponin T; LDL-C, low-density lipoprotein cholesterol; NL, neutrophil–lymphocyte; NSAID, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PENK, proenkephalin; STEMI, ST-segment elevation myocardial infarction; WBC, white blood count.

[a]The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation.

[b]Chronic kidney disease is defined as decrease in eGFR to <60 mL/min/1.73 m^2 at 1-year follow-up.[40,45]

Tables S6–S10). Of note, the development of AKI during index hospitalization was strongly related to 1-year CKD (adjusted OR 5.00, 95% CI 3.17–7.86, $P < .001$) and 1-year mortality after hospital discharge [adjusted hazard ratio (HR) 2.83, 95% CI 1.77–4.51, $P < .001$; Supplementary data online, *Table S11*].

Dynamic changes in PENK levels within the first 12–24 h after presentation were associated with both in-hospital AKI (per 10 pmol/L increase: adjusted OR 1.27, 95% CI 1.15–1.43, $P < .001$; increase vs. decrease: adjusted OR 2.88, 95% CI 1.83–4.57, $P < .001$) and 1-year CKD (per 10 pmol/L increase: adjusted OR 1.09, 95% CI 1.00–1.20, $P = .048$; increase vs. decrease: adjusted OR 1.63, 95% CI 1.12–2.35, $P = .010$; *Figure 1C*, Supplementary data online, *Table S12*) on top of established patient and procedure characteristics including PCI duration and contrast volume. These results were similarly observed in the subgroup of patients undergoing PCI before the second measurement (see Supplementary data online, *Table S13*). Increased PENK after PCI was related to a 2.7-fold increase in AKI risk (OR 2.71, 95% CI 1.44–5.10, $P = .002$).

Circulating PENK at presentation predicted mortality at 30 days (per $\log_2$ increase: adjusted HR 2.73, 95% CI 1.85–4.02, $P < .001$; Q4 vs. Q1–Q3: adjusted HR 4.21, 95% CI 1.85–9.58, $P = .001$) and at 1 year (per $\log_2$ increase: adjusted HR 1.66, 95% CI 1.22–2.26, $P = .001$; Q4 vs. Q1–Q3: adjusted HR 1.68, 95% CI 1.07–2.64, $P = .023$) beyond established risk factors and the GRACE 2.0 risk score, in line with previous evidence (see Supplementary data online, *Table S14*).[17] Similar results were obtained upon internal validation (see Supplementary data online, *Tables S15* and *S16*).

Derivation and external validation of the KID-ACS score

The novel KID-ACS risk score incorporates different variable importance for in-hospital AKI and 30-day mortality and predicts both events with a single set of six variables (*Figure 2*). In the development cohort, the score performed well in predicting in-hospital AKI (AUC .72, 95% CI .68–.76) and 30-day mortality (AUC .91, 95% CI .87–.95; *Figure 2A*, Supplementary data online, *Tables S17–S19*). Similar findings were obtained in subgroups stratified by sex, type of ACS, type of intervention, and baseline renal function (see Supplementary data online, *Table S20* and *S24*). In the external validation cohorts, KID-ACS achieved similarly high performance for in-hospital AKI (Zurich validation cohort AUC .73, 95% CI .70–.77; Czech validation cohort AUC .75, 95% CI .68–.81; German validation cohort AUC .71, 95% CI .55–.87) and 30-day mortality (UK validation cohort AUC .87, 95% CI .83–.91; Czech validation cohort AUC .91, 95% CI .87–.94; German validation cohort AUC .96, 95% CI .92–1.00). KID-ACS showed good calibration and high clinical utility (*Figure 2B*, Supplementary data online, *Figures S2* and *S3*).

KID-ACS improves on established risk scores

The simple six-item KID-ACS score (*Figure 3*) was non-inferior to the CA-AKI risk score and the GRACE 2.0 risk score, which require a total of 15 clinical variables (each $P < .001$). KID-ACS showed significantly improved performance in predicting in-hospital AKI compared to the CA-AKI score (delta AUC .11, 95% CI .07–.16, $P < .001$; NRI .48, 95% CI .34–.62, $P < .001$). Similarly, KID-ACS had significantly higher performance in predicting 30-day mortality compared to the GRACE 2.0 score (delta AUC .05, 95% CI .01–.09, $P = .009$; NRI .67, 95% CI .38–.95, $P < .001$). Similar results were observed in complete case

Table 2 Treatment characteristics of patients with acute coronary syndrome in the Swiss cohort (SPUM-ACS Biomarker Study) according to proenkephalin quartiles

	All patients (*n* = 4311)	PENK quartile 1 <50.1 pmol/L (*n* = 1074)	PENK quartile 2 >50.1–62.7 pmol/L (*n* = 1072)	PENK quartile 3 >62.7–79.9 pmol/L (*n* = 1073)	PENK quartile 4 >79.9 pmol/L (*n* = 1092)	*P*-value
Revascularization strategy						
PCI	3946/4069 (97.0%)	980/1019 (96.2%)	976/1009 (96.7%)	984/1009 (97.5%)	1006/1032 (97.5%)	.224
Door to balloon (min)	78 (45–179)	88 (48–258)	80.5 (45–204)	76 (42–148)	77 (45–141)	.001
PCI duration (min)	29 (19–45)	28.5 (18–45)	28 (18–45)	31 (19–45)	30 (20–46)	.296
Infarct-related artery						.034
RCA	1346/4088 (32.9%)	329/1021 (32.2%)	349/1016 (34.4%)	320/1013 (31.6%)	348/1038 (33.5%)	
LMCA	68/4088 (1.7%)	11/1021 (1.1%)	14/1016 (1.4%)	19/1013 (1.9%)	24/1038 (2.3%)	
LAD	1801/4088 (44.1%)	435/1021 (42.6%)	446/1016 (43.9%)	457/1013 (45.1%)	463/1038 (44.6%)	
LCx	823/4088 (20.1%)	239/1021 (23.4%)	196/1016 (19.3%)	204/1013 (20.1%)	184/1038 (17.7%)	
SVG	50/4088 (1.2%)	7/1021 (.7%)	11/1016 (1.1%)	13/1013 (1.3%)	19/1038 (1.8%)	
Requirement of circulatory support						
Vasopressor use	113/4306 (2.6%)	20/1073 (1.9%)	16/1071 (1.5%)	22/1072 (2.1%)	55/1090 (5.0%)	<.001
Mechanical circulatory support	120/4306 (2.8%)	20/1073 (1.9%)	27/1070 (2.5%)	24/1072 (2.2%)	49/1091 (4.5%)	.001
Contrast volume (mL)						.038
<100	332/4212 (7.9%)	74/1054 (7.0%)	87/1047 (8.3%)	65/1046 (6.2%)	106/1065 (10.0%)	
100–199	2158/4212 (51.2%)	551/1054 (52.3%)	506/1047 (48.3%)	547/1046 (52.3%)	554/1065 (52.0%)	
200–299	1279/4212 (30.4%)	313/1054 (29.7%)	344/1047 (32.9%)	322/1046 (30.8%)	300/1065 (28.2%)	
≥300	443/4212 (10.5%)	116/1054 (11.0%)	110/1047 (10.5%)	112/1046 (10.7%)	105/1065 (9.9%)	
Excessive contrast volume used[a]	578/4198 (13.8%)	72/1046 (6.9%)	86/1043 (8.2%)	132/1045 (12.6%)	288/1064 (27.1%)	<.001
Procedural bleed[b]	443/3987 (11.1%)	88/990 (8.9%)	101/995 (10.2%)	110/992 (11.1%)	144/1010 (14.3%)	.001
Slow flow or no flow post procedure	47/3894 (1.2%)	15/962 (1.6%)	4/967 (.4%)	10/968 (1.0%)	18/997 (1.8%)	.025
Complex anatomy[c]	2151/3664 (58.7%)	520/928 (56.0%)	526/910 (57.8%)	542/902 (60.1%)	563/924 (60.9%)	.131
Duration of hospital stay (days)	3 (1–5)	3 (1–5)	2 (1–5)	2 (1–5)	3 (1–6)	<.001
Left ventricular ejection fraction at discharge (%)	51.7 ± 11.5	53.1 ± 10.8	52.3 ± 11.8	51.7 ± 11.0	49.7 ± 12.3	<.001
Discharge medication						
Aspirin	4226/4266 (99.1%)	1065/1072 (99.3%)	1060/1066 (99.4%)	1057/1067 (99.1%)	1044/1061 (98.4%)	.055
P2Y12 inhibitors	4063/4063 (100.0%)	1018/1018 (100.0%)	1008/1008 (100.0%)	1028/1028 (100.0%)	1009/1009 (100.0%)	1.000

Continued

Table 2 ***Continued***

	All patients ($n = 4311$)	PENK quartile 1 <50.1 pmol/L ($n = 1074$)	PENK quartile 2 >50.1–62.7 pmol/L ($n = 1072$)	PENK quartile 3 >62.7–79.9 pmol/L ($n = 1073$)	PENK quartile 4 >79.9 pmol/L ($n = 1092$)	*P*-value
Beta-blocker	3336/4262 (78.3%)	840/1070 (78.5%)	824/1066 (77.3%)	830/1067 (77.8%)	842/1059 (79.5%)	.631
ACE-inhibitor/ARB	3745/4264 (87.8%)	938/1072 (87.5%)	932/1066 (87.4%)	939/1067 (88.0%)	936/1059 (88.4%)	.895
Vitamin K antagonist/DOAC	304/4311 (7.1%)	61/1074 (5.7%)	63/1072 (5.9%)	76/1073 (7.1%)	104/1092 (9.5%)	.001
Diuretic	999/4265 (23.4%)	195/1072 (18.2%)	211/1066 (19.8%)	220/1067 (20.6%)	373/1060 (35.2%)	<.001
Immunosuppressive drugs	111/4265 (2.6%)	22/1072 (2.1%)	13/1066 (1.2%)	20/1067 (1.9%)	56/1060 (5.3%)	<.001
NSAID	60/4265 (1.4%)	21/1072 (2.0%)	12/1066 (1.1%)	15/1067 (1.4%)	12/1060 (1.1%)	.316
Oral antidiabetics	502/4263 (11.8%)	143/1072 (13.3%)	117/1065 (11.0%)	117/1066 (11.0%)	125/1060 (11.8%)	.282

Categorical data are shown as numbers and percentages (%). Continuous data are presented as median and IQR or as mean ± SD. Groups were compared using analysis of variance, the Kruskal–Wallis test, the χ^2 test, or Fisher's exact test, as appropriate.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; DOAC, direct oral anticoagulant; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMCA, left main coronary artery; NSAID, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; PENK, proenkephalin; RCA, right coronary artery; SVG, saphenous vein graft.
[a]Excessive contrast volume used was defined as the contrast dose to eGFR ratio ≥ 3.7.[2]
[b]Procedural bleed was defined as a decrease in haemoglobin value of >3 g/dL compared to before the procedure.
[c]Complex anatomy was defined as multivessel disease, more than two lesions, high coronary lesion complexity, chronic total occlusion, lesion length >30 mm, or bifurcation.

analyses. Taking into consideration dynamic changes in PENK levels led to slightly improved model performance for predicting in-hospital AKI (see Supplementary data online, *Table S21* and *Figure S4*).

Discussion

Harnessing multiple large prospective ACS cohorts, we (i) show for the first time that circulating PENK offers incremental utility for predicting renal outcomes in patients with ACS, (ii) report for the first time that the occurrence of in-hospital AKI is independently related to long-term renal outcomes in patients with ACS, (iii) identified PENK as a marker of all-cause mortality in line with previous evidence, and (iv) developed and externally validated the first risk score for early assessment of both AKI and mortality risk in patients with ACS (*Structured Graphical Abstract*).

New kidney biomarkers allow for refined prediction of both renal and cardiovascular outcomes.[7,63–65] Circulating PENK, a stable endogenous polypeptide with no protein binding or cleavage known,[5,66] has emerged as an early marker of glomerular dysfunction and tubular damage from a plethora of preclinical and clinical studies.[5,65,67,68] Previous evidence demonstrates that high PENK portends adverse kidney outcomes,[15,32,34,68–72] adverse cardiovascular events,[10,73] and all-cause mortality[71] in different critically ill patient populations highlighting its potential for risk stratification in patients with ACS. In particular, faster increase of PENK plasma levels after kidney stress (within 2–6 h)[14] and their stronger correlation with measured glomerular filtration rate[66,67,74] compared to serum creatinine and cystatin C may help identify individuals who are likely to developed AKI. Thus, the integration of this novel biomarker might have merit to refine personalized and timely treatment strategies in acutely ill patient populations, such as patients with ACS.

Acute kidney injury is a common complication of ACS and occurs due to low cardiac output, renal congestion, or both.[7] In addition, high comorbidity burden and the administration of contrast agents make patients with ACS particularly susceptible to AKI.[3,75,76] Indeed, around 5%–15% of patients with ACS develop AKI during index hospitalization[77–79] with up to 30% of cases considered preventable by timely initiation of adequate supportive measures.[65]

Here, we show that circulating PENK at presentation is a predictor of AKI development, sustained kidney damage, and fatal events during follow-up beyond established risk factors in patients with ACS (*Figure 1A* and *B*). High PENK at presentation was associated with 1.6-fold increased risk of in-hospital AKI and 1.6-fold increased risk of CKD at 1-year (see Supplementary data online, *Table S4*). Of note, we found that the occurrence of AKI during index hospitalization is strongly related to adverse long-term renal outcomes in patients with ACS, matching observations in other patient populations[80,81] (see Supplementary data online, *Table S11*). Moreover, in-hospital AKI conferred increased mortality risk, in line with previous studies.[3,82]

As recommended for the evaluation of AKI biomarkers,[65] we explored PENK trajectories using serial biomarker measurements. Our results indicate that dynamic changes in PENK levels within the first 12–24 h are tightly linked to the development of in-hospital AKI in patients with ACS who underwent PCI in the vast majority of cases. Dynamic increases in PENK translated into 2.9-fold increased AKI risk. These results were similarly observed in the subgroup of patients undergoing PCI suggesting that peri-procedural changes in PENK may refine early post-PCI risk assessment (*Figure 1C*).

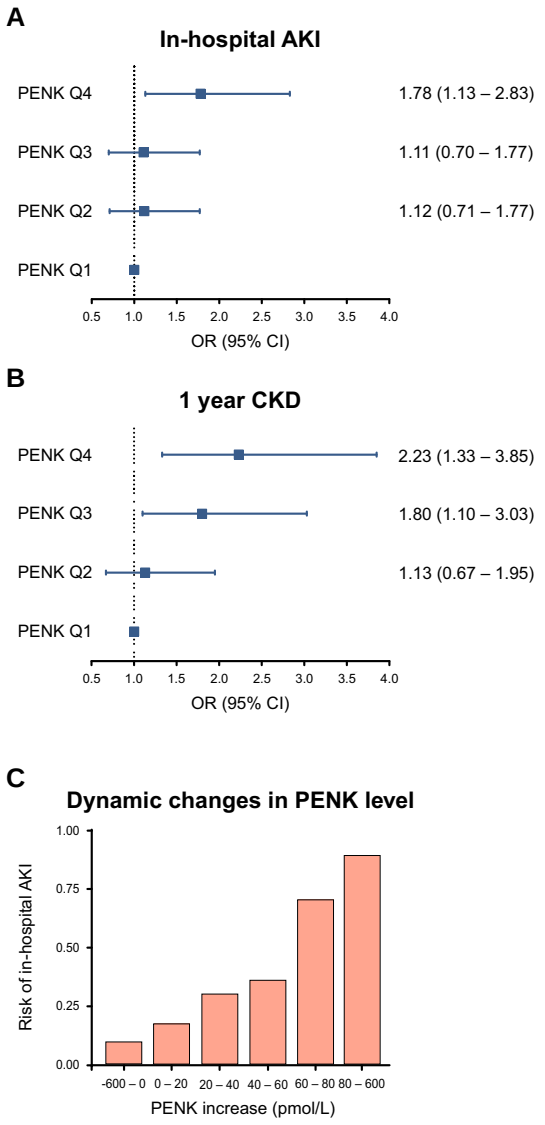


Figure 1 Circulating proenkephalin predicts renal outcomes in acute coronary syndrome. (*A*) Multivariable-adjusted odds ratio for in-hospital acute kidney injury according to proenkephalin quartile (Q). (*B*) Multivariable-adjusted odds ratio for incident chronic kidney disease at 1 year after the index acute coronary syndrome according to proenkephalin quartile. (*C*) Dynamic increases of proenkephalin within the first 12–24 h after presentation relate to the risk to develop in-hospital acute kidney injury. The fully adjusted regression model for in-hospital acute kidney injury included sex, body mass index, systolic blood pressure, and the contrast-associated acute kidney injury risk score (Model 1). The fully adjusted regression model for 1-year chronic kidney disease included sex, body mass index, history of smoking, and the Framingham Risk Score for the Development of Chronic Kidney Disease.[43] Squares indicate the mean estimates of the odds ratio, and line lengths equal corresponding 95% confidence intervals

In addition to the assessment of mortality risk, accurate prediction of AKI risk in patients with ACS is important for treatment stratification and tailored surveillance. Previous risk scores for AKI were mostly derived from US patient populations[3,83,84] using single-centre PCI registries[3,83] or retrospective analysis of healthcare records,[84] showed limited external validity,[85,86] required a multitude of patient variables,[3,83,84] and fell short of relevant biomarkers.[3,83,84]

According to current recommendations,[1,65] a combination of kidney and non-kidney biomarkers along with clinical information should guide ACS management including the timing and type of interventions, preventive measures, and supportive care. The KID-ACS score is informed by patient age, cardiac arrest status, kidney damage (PENK),[68] congestion (NT-proBNP),[87] inflammation (leucocyte count),[88] and stress response (glucose)[89] with varying contribution of the individual variables, depending on the predicted outcome (*Figure 2C*). KID-ACS shows excellent predictive performance and clinical utility for both in-hospital AKI and 30-day mortality (see Supplementary data online, *Figure S3*).

Previous studies have shown the safety and efficacy of biomarker-guided patient management to reduce the incidence and severity of AKI in other clinical settings.[65,90,91] The newly developed biomarker-enhanced KID-ACS score could be used to support future decision-making regarding the timing of invasive treatment and kidney protection in patients with ACS. Specifically, refined assessment of renal and of mortality risk will support (i) personalized pre-, intra-, and post-procedural fluid management, (ii) patient triage and timing of coronary interventions in patients with non-ST-elevation ACS,[92] (iii) avoidance of nephrotoxic substances,[93–95] (iv) adapted dosing of renally eliminated drugs,[94–96] and (v) effective monitoring during hospitalization.[1,93]

Simultaneous prediction of multiple clinically relevant endpoints by a single risk tool facilitates the integration of personalized risk assessment into clinical practice (*Figure 3*).[97] In particular, in time-sensitive situations, a single score informed by six variables promises higher utility than a combination of different risk scores[3,4] requiring a total of 15 or more different variables. The geographical and sociocultural diversity of the external validation cohorts of prospectively enrolled patients supports the generalizability of our results.

In conclusion, circulating PENK is a useful predictor of renal outcomes and mortality in patients with ACS on top of established risk factors. The KID-ACS score integrates PENK levels and provides a contemporary simple tool for early assessment of both renal and mortality risk in patients presenting with ACS. Further external validation of KID-ACS is warranted.

Strengths and limitations

This study has several strengths. First, the multinational design involving external validation of the results in independent prospective ACS cohorts from different countries ensures high external validity and allows to account for regional differences in ACS phenotypes and healthcare systems. The SPUM-ACS Biomarker Study constitutes one of the largest and best characterized cohorts of patients with ACS worldwide. It provides in-depth patient characterization, an extensive blood biobank, information on renal function during long-term follow-up, and external adjudication of clinical outcomes. The prospective multicentre design of SPUM-ACS together with its contemporary patient population undergoing guideline-based treatment approaches grants for high quality of the collected data. Furthermore, a longitudinal blood sampling strategy enabling exploration of temporal dynamics in biomarker levels constitutes a rare resource for the characterization of risk factor profiles in patients with ACS. In addition, the central assessment of established biomarkers (hs-TnT, NT-proBNP, and high-sensitivity C-reactive protein) in the core laboratory at the University Hospital Zurich and

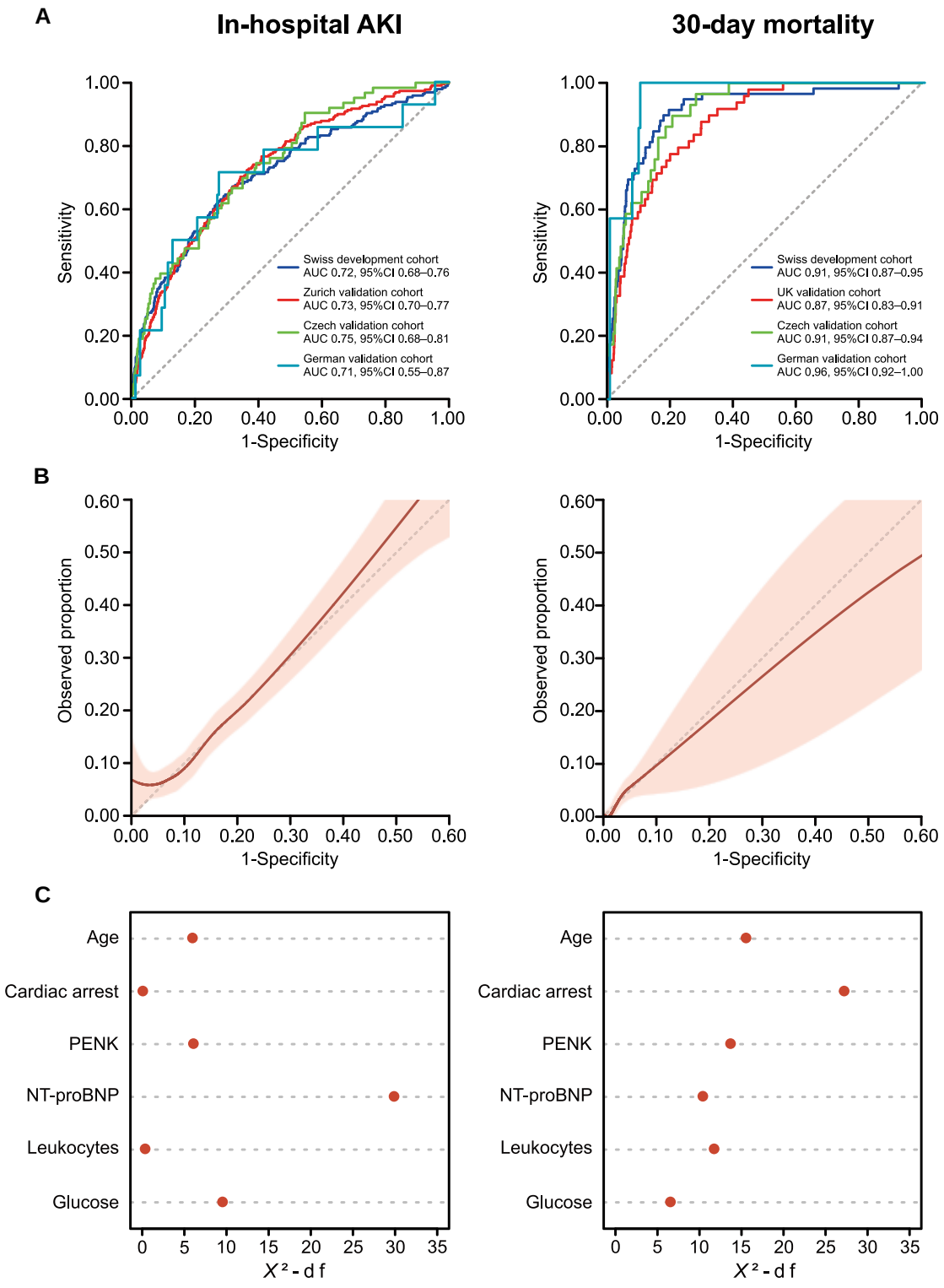


Figure 2 Performance of the KID-ACS score. (A) Receiver operating characteristics curves of the KID-ACS score for predicting in-hospital acute kidney injury (left) and 30-day mortality (right). (B) Smoothed calibration plot of the KID-ACS score for predicting in-hospital acute kidney injury (left) and 30-day mortality (right). (*C*) Importance of KID-ACS score features in the model prediction of in-hospital acute kidney injury (left) and 30-day mortality (right) measured by partial Wald χ^2 minus the degrees of freedom. AUC, area under the receiver operating characteristic curve; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide

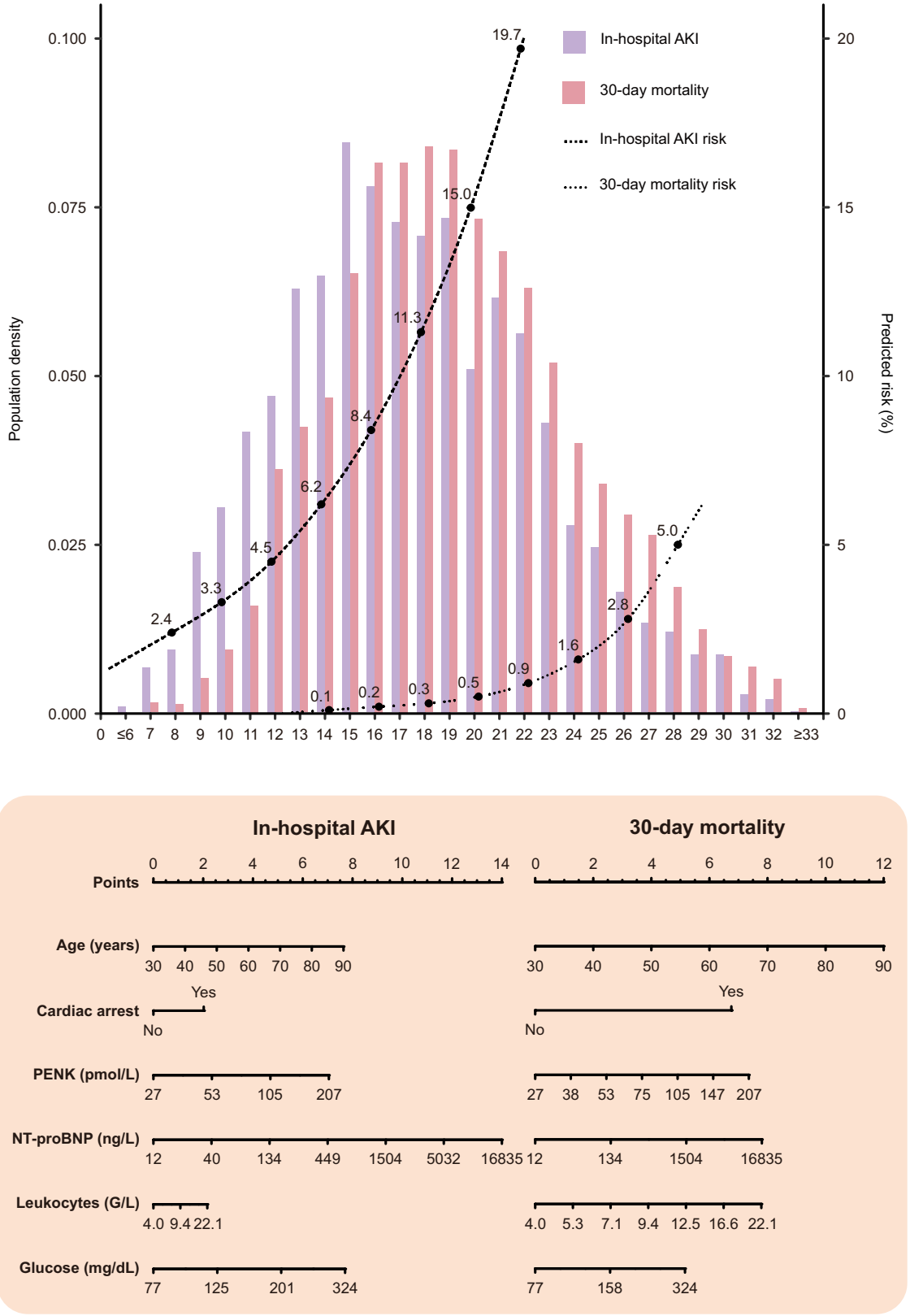


Figure 3 The KID-ACS score nomogram for bedside application. Risk curves refer to in-hospital acute kidney injury (left) and 30-day mortality (right). The histogram shows the KID-ACS score distribution in the derivation cohort with adjacent bars referring to in-hospital acute kidney injury and to 30-day mortality, respectively. NT-proBNP, N-terminal pro-B-type natriuretic peptide; PENK, proenkephalin

blinded measurement of PENK using a validated assay guarantees highest analytical accuracy. Further, external adjudication of diagnoses at time of presentation and clinical outcomes during follow-up by an independent clinical event adjudication committee ward off assessment bias.

Our study has limitations. First, the all-cause mortality rate in the Swiss cohort was moderate, which might be due to demographic, socioeconomic, and geographic factors given that other ACS cohorts in Switzerland are characterized by similar mortality rates.[18,98] However, sufficient statistical power was confirmed by sample size estimations. Second, data on the KID-ACS score endpoint in-hospital AKI were lacking in the UK cohort. Yet, the availability of four ACS cohorts permitted external validation for each endpoint of KID-ACS in independent patient data. Third, serial blood sampling was only performed in the Swiss cohort preventing from the exploration of dynamic changes in PENK levels in the other cohorts. However, established internal validation strategies confirmed the relationship between early trajectories of circulating PENK and AKI development in patients with ACS, consistent with previously conducted studies in other critically ill patient populations.[14,99] Fourth, as no repeated measurements of creatinine at 12–24 h were routinely documented, development of in-hospital AKI occurring exclusively after this time point could not be assessed. Next, the lack of information on albuminuria precluded the inclusion of this AKI-associated parameter[100] in our multivariable models. Further, due to restricted availability of cystatin C, analyses including this variable could only be performed in a subcohort of patients. These analyses should be interpreted with caution, yet they are in agreement with the main results. In addition, due to a lack of repeated renal function testing at 1 year of follow-up, CKD was ascertained by a single eGFR value without accounting for variations in serum creatinine levels and the estimation method. Moreover, no time-dependent data on 1-year CKD were available, and thus, potential censoring due to fatal events after index ACS could not be considered. Furthermore, our results primarily apply to patients with atherosclerotic ACS pathobiology and the validity of the findings in ACS types that are not due to macrovascular atherosclerotic lesions, such as Takotsubo syndrome and myocardial infarction with non-obstructive coronary arteries, is not warranted. Finally, the extended seven-item post-procedural KID-ACS score adds predictive value but can only be applied in patients with both measurements available (see Supplementary data online, *Figure S4*).

Future directions

Incorporation of biomarkers into clinical risk assessment holds promise to refine personalized treatment strategies. Additional clinical studies on the role of PENK in acutely ill cardiovascular patient populations are warranted to better understand its clinical merits. The newly developed KID-ACS score provides a tool for early cardio-renal risk stratification, which may guide patient selection and targeted interventions in patients presenting with ACS in future trials. Further external validation is essential to evaluate the performance of the KID-ACS score in other populations. Collectively, more evidence on the assessment of kidney risk and its application to individualized management of patients with ACS is needed.

Conclusions

We show that circulating PENK adds incremental value to the prediction of renal outcomes and mortality in patients presenting with ACS. Moreover, we found an association of AKI development during index hospitalization with long-term renal outcomes and mortality after ACS, highlighting the importance of risk-tailored patient management. The novel 6-item KID-ACS risk score integrates PENK and predicts both in-hospital AKI and 30-day mortality above and beyond established risk models. KID-ACS provides a simple tool for early risk assessment in patient with ACS.

Acknowledgements

We gratefully acknowledge the crucial contribution of all clinicians, administrative personnel, data managers, and study participants participating in the involved study cohorts. In particular, we would like to express our gratitude towards the independent event adjudication committee of the SPUM-ACS Biomarker Study (Matthias Pfisterer, Lukas Kappenberger, Tiziano Moccetti, David Carballo, Baris Gencer, and Philippe Meyer). We thank Isabelle Peereboom, Carola Kälin-Weeke, and Monika Seiler for the coordination and supervision of the measurements in the SPUM-ACS core laboratory. We further express our gratitude towards all involved lab technicians, all study nurses, data managers, and finally all members of the local catheter laboratory teams for their tireless and valuable work.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

F.A.W. received financial support from the Theodor und Ida Herzog-Egli Foundation, the Foundation for Cardiovascular Research—Zurich Heart House, the Kurt und Senta Herrmann Foundation, the Research Funding for excellent research by the University of Zurich, the European Society of Cardiology, the Swiss Heart Foundation, the Swiss Society of Cardiology, the Fonds zur Förderung des akademischen Nachwuchses of the University of Zurich, and the Medical University of Graz. Further, he received travel support from the Swiss Society of Cardiology, the SphingoTec GmbH, the 4TEEN4 Pharmaceuticals GmbH, and the PAM Theragnostics GmbH. P.W. was funded by the China Scholarship Council. J.P. received research grants from the Ministry of Health of the Czech Republic, Roche, and Siemens and declares consulting fees from AstraZeneca and Boehringer Ingelheim and payment or honoraria from Amgen, Bayer, and Novartis. D.J.L.J. received funding support from the UK National Institute for Health Research Biomedical Research Centre (NIHR-BRC). F.B. received speaker honoraria from Chiesi, Daiichi Sankyo, and Boston Scientific. O.H. is employed by SphingoTec GmbH, which holds patents for the PENK biomarker. S.K. received research grants to the institution from the Jubiläumsstiftung SwissLife, the Lindenhof Foundation, the Novartis Foundation for Medical-Biological Research, the Swiss Heart Foundation, the Swiss Society of Cardiology, and the Theodor und Ida Herzog-Egli Foundation and travel support from the European Atherosclerosis Society, the European Society of Cardiology, the European Society of Clinical Investigation, SphingoTec GmbH, the 4TEEN4 Pharmaceuticals GmbH, and PAM Theragnostics GmbH. F.K. was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), the European Research Area Network on Cardiovascular Diseases (ERA-CVD and BMBF), and the European Foundation for the Study

of Diabetes (EFSD)/Novo Nordisk Foundation. F.K. received financial support by Novo Nordisk, PricewaterhouseCoopers/Strategy&, DGK-Akademie, AstraZeneca, Thieme, AMGEN, Boehringer Ingelheim, Lilly, Bayer, and SphingoTec/4TEEN4. K.W.O. received funding support from the UK National Institute for Health Research Biomedical Research Centre (NIHR-BRC). S.M. declares support by the Swiss Heart Foundation. L.L. and G.G.C. are coinventors on the International Patent WO/2020/226993 filed in April 2020; the patent relates to the use of antibodies that specifically bind interleukin-1a to reduce various sequelae of ischemia-reperfusion injury to the central nervous system. G.G.C. is a consultant to Sovida Solutions Limited and is the recipient of a Sheikh Khalifa's Heart Research Foundation Assistant Professorship at the Faculty of Medicine, University of Zurich. G.G.C. received financial support by the Alfred and Annemarie von Sick Grants for Translational and Clinical Research Cardiology and Oncology and by the Swiss Heart Foundation. A.B. was CSO of SphingoTec GmbH and is a partial owner of the company. L.L. has received financial support from the Swiss Heart Foundation and the Novartis Foundation for Medical-Biological Research. J.K.S. received funding support from the UK National Institute for Health Research Biomedical Research Centre (NIHR-BRC). T.O. received research grant from the Ministry of Health of the Czech Republic. M.R. received consulting fees from Bayer Healthcare and Siemens and payment and Declarations Form honoraria from Bayer Healthcare and Siemens. M.R. received institutional grants from Cordis, Biotronik, Boston Scientific, Medtronic, and Terumo. L.R. received funding from Abbott, Sanofi, Regeneron, Boston Scientific, and HeartFlow, consulting fees from Abbott, Amgen, AstraZeneca, Canon, Novo Nordisk, Medtronic, and Sanofi, and payment or honoraria from Abbott, Occlutech, and Sanofi and is a stock holder of Verve Therapeutics. T.H.C. declares funding support from the National Institute for Health and Care Research. C.G.J. received speaker honoraria from Daiichi Sankyo, AstraZeneca, Bayer, Bristol Myers Squibb, Boston Scientific, and Medtronic. Further, C.G.J. received research grants from the Deutsche Herzstiftung. Also, he received travel support from Bayer and Zoll. L.L.N. received funding support from the British Heart Foundation and the UK National Institute for Health Research Biomedical Research Centre (NIHR-BRC). T.F.L. has no conflicts of interest related to this manuscript, but received educational and research grants from Abbott, Ablative Solutions, Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Sanofi, Servier, and Vifor and honoraria from Amgen, Dacadoo, Daiichi Sankyo, Glaxo, Smith & Kline, Firalis, Menarini Foundation, NeuroImmune, and Novo Nordisk. The hs-CRP, hs-TnT, and NT-proBNP assays reported in this study were kindly provided by Roche Diagnostics (Boehringer Mannheim, Indianapolis, IN, USA). The other authors report no conflicts of interest.

Data Availability

The data underlying this article cannot be shared publicly due to data protection regulations related to the different patient cohorts involved in this study. Requests for the data and additional documents related to this study should be made to the corresponding authors.

Funding

The SPUM-ACS registry has been primarily supported by the Swiss National Science Foundation (SPUM 33CM30-124112 and 32473B_163271) and the Swiss Heart Foundation (both to T.F.L.). Additional support for the SPUM-ACS registry was received from AstraZeneca (Baar, Switzerland), Eli Lilly (Indianapolis, IN, USA), Roche Diagnostics (Boehringer Mannheim, Indianapolis, IN, USA), Medtronic (Münchenbuchsee, Switzerland), Merck Sharp and Dohme (Lucerne, Switzerland), sanofi-aventis (Vernier, Switzerland), and St Jude Medical AG (Zurich, Switzerland). F.A.W. is supported by the Theodor und Ida Herzog-Egli Foundation, the Foundation for Cardiovascular Research—Zurich Heart House, the Kurt und Senta Herrmann Foundation, and the Research Funding for excellent research by the University of Zurich. The LAMP study was supported by the British Heart Foundation. Proenkephalin measurements were performed by SphingoTec GmbH. The research by J.P. and T.O. was supported by a grant from the Ministry of Health of the Czech Republic—conceptual development of research organization (FNBr, 65269705; funding was given to the University Hospital Brno).

Ethical Approval

The present study was carried out in accordance with the Declaration of Helsinki and approved by local Ethics Committees (reference number: EK-1688/2019-01809).

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT01000701.

References

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al.* 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. https://doi.org/10.1093/eurheartj/ehad191
2. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165. https://doi.org/10.1093/eurheartj/ehy394
3. Mehran R, Owen R, Chiarito M, Baber U, Sartori S, Cao D, *et al.* A contemporary simple risk score for prediction of contrast-associated acute kidney injury after percutaneous coronary intervention: derivation and validation from an observational registry. *Lancet* 2021;**398**:1974–83. https://doi.org/10.1016/S0140-6736(21)02326-6
4. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, *et al.* Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;**4**:e004425. https://doi.org/10.1136/bmjopen-2013-004425
5. Khorashadi M, Beunders R, Pickkers P, Legrand M. Proenkephalin: a new biomarker for glomerular filtration rate and acute kidney injury. *Nephron* 2020;**144**:655–61. https://doi.org/10.1159/000509352
6. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, *et al.* The definition of acute kidney injury and its use in practice. *Kidney Int* 2015;**87**:62–73. https://doi.org/10.1038/ki.2014.328
7. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet* 2019;**394**:1949–64. https://doi.org/10.1016/S0140-6736(19)32563-2
8. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple!. *Nephron* 2017;**136**:302–8. https://doi.org/10.1159/000469669
9. Ronco C, Bellomo R, Kellum J. Understanding renal functional reserve. *Intensive Care Med* 2017;**43**:917–20. https://doi.org/10.1007/s00134-017-4691-6
10. Doehner W, von Haehling S, Suhr J, Ebner N, Schuster A, Nagel E, *et al.* Elevated plasma levels of neuropeptide proenkephalin a predict mortality and functional outcome in ischemic stroke. *J Am Coll Cardiol* 2012;**60**:346–54. https://doi.org/10.1016/j.jacc.2012.04.024
11. Zarbock A, Nadim MK, Pickkers P, Gomez H, Bell S, Joannidis M, *et al.* Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. *Nat Rev Nephrol* 2023;**19**:401–17. https://doi.org/10.1038/s41581-023-00683-3
12. Stark M, Danielsson O, Griffiths WJ, Jornvall H, Johansson J. Peptide repertoire of human cerebrospinal fluid: novel proteolytic fragments of neuroendocrine proteins. *J Chromatogr B Biomed Sci Appl* 2001;**754**:357–67. https://doi.org/10.1016/s0378-4347(00)00628-9
13. Marino R, Struck J, Hartmann O, Maisel AS, Rehfeldt M, Magrini L, *et al.* Diagnostic and short-term prognostic utility of plasma pro-enkephalin (pro-ENK) for acute kidney injury in patients admitted with sepsis in the emergency department. *J Nephrol* 2015;**28**:717–24. https://doi.org/10.1007/s40620-014-0163-z
14. Shah KS, Taub P, Patel M, Rehfeldt M, Struck J, Clopton P, *et al.* Proenkephalin predicts acute kidney injury in cardiac surgery patients. *Clin Nephrol* 2015;**83**:29–35. https://doi.org/10.5414/cn108387

15. Hollinger A, Wittebole X, Francois B, Pickkers P, Antonelli M, Gayat E, *et al.* Proenkephalin A 119-159 (Penkid) is an early biomarker of septic acute kidney injury: the kidney in sepsis and septic shock (Kid-SSS) study. *Kidney Int Rep* 2018;**3**:1424–33. https://doi.org/10.1016/j.ekir.2018.08.006
16. KDIGO. KDIGO clinical practice guideline for acute kidney injury (AKI) and acute kidney disease (AKD) update 2023, 2023. https://kdigo.org/wp-content/uploads/2023/10/KDIGO-AKI-Guideline_Scope-of-Work_25Oct2023_Final.pdf (2 May 2024, date last accessed).
17. Ng LL, Sandhu JK, Narayan H, Quinn PA, Squire IB, Davies JE, *et al.* Proenkephalin and prognosis after acute myocardial infarction. *J Am Coll Cardiol* 2014;**63**:280–9. https://doi.org/10.1016/j.jacc.2013.09.037
18. Wenzl FA, Kraler S, Ambler G, Weston C, Herzog SA, Raber L, *et al.* Sex-specific evaluation and redevelopment of the GRACE score in non-ST-segment elevation acute coronary syndromes in populations from the UK and Switzerland: a multinational analysis with external cohort validation. *Lancet* 2022;**400**:744–56. https://doi.org/10.1016/S0140-6736(22)01483-0
19. Wenzl FA, Bruno F, Kraler S, Klingenberg R, Akhmedov A, Ministrini S, *et al.* Dipeptidyl peptidase 3 plasma levels predict cardiogenic shock and mortality in acute coronary syndromes. *Eur Heart J* 2023;**44**:3859–71. https://doi.org/10.1093/eurheartj/ehad545
20. Arrigo M, Parenica J, Ganovska E, Pavlusova M, Mebazaa A. Plasma bio-adrenomedullin is a marker of acute heart failure severity in patients with acute coronary syndrome. *Int J Cardiol Heart Vasc* 2019;**22**:174–6. https://doi.org/10.1016/j.ijcha.2019.02.011
21. Kubena P, Arrigo M, Parenica J, Gayat E, Sadoune M, Ganovska E, *et al.* Plasma levels of soluble CD146 reflect the severity of pulmonary congestion better than brain natriuretic peptide in acute coronary syndrome. *Ann Lab Med* 2016;**36**:300–5. https://doi.org/10.3343/alm.2016.36.4.300
22. Reynen S, Schlossbauer M, Hubauer U, Hupf J, Mohr A, Orso E, *et al.* Urinary N-terminal pro-brain natriuretic peptide: prognostic value in patients with acute chest pain. *ESC Heart Fail* 2021;**8**:2293–305. https://doi.org/10.1002/ehf2.13332
23. Davies A, Wenzl FA, Li XS, Winzap P, Obeid S, Klingenberg R, *et al.* Short and medium chain acylcarnitines as markers of outcome in diabetic and non-diabetic subjects with acute coronary syndromes. *Int J Cardiol* 2023;**389**:131261. https://doi.org/10.1016/j.ijcard.2023.131261
24. Kraler S, Wenzl FA, Georgiopoulos G, Obeid S, Liberale L, von Eckardstein A, *et al.* Soluble lectin-like oxidized low-density lipoprotein receptor-1 predicts premature death in acute coronary syndromes. *Eur Heart J* 2022;**43**:1849–60. https://doi.org/10.1093/eurheartj/ehac143
25. Wenzl FA, Luscher TF. Application of a sex-specific GRACE score in practice—authors' reply. *Lancet* 2023;**401**:23. https://doi.org/10.1016/S0140-6736(22)02457-6
26. Kraler S, Wenzl FA, Vykoukal J, Fahrmann JF, Shen M-Y, Chen D-Y, *et al.* Low-density lipoprotein electronegativity and risk of death after acute coronary syndromes: a case-cohort analysis. *Atherosclerosis* 2023;**376**:43–52. https://doi.org/10.1016/j.atherosclerosis.2023.05.014
27. Bruno F, Adjibodou B, Obeid S, Kraler SC, Wenzl FA, Akhtar MM, *et al.* Occlusion of the infarct-related coronary artery presenting as acute coronary syndrome with and without ST-elevation: impact of inflammation and outcomes in a real-world prospective cohort. *Eur Heart J Qual Care Clin Outcomes* 2023;**9**:564–74. https://doi.org/10.1093/ehjqcco/qcad027
28. Winzap PA, Kraler S, Obeid S, Wenzl FA, Templin C, Klingenberg R, *et al.* Initial systolic blood pressure associates with systemic inflammation, myocardial injury, and outcomes in patients with acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care* 2023;**12**:437–50. https://doi.org/10.1093/ehjacc/zuad047
29. Kraler S, Balbi C, Vdovenko D, Lapikova-Bryhinska T, Camici GG, Liberale L, *et al.* Circulating GDF11 exacerbates myocardial injury in mice and associates with increased infarct size in humans. *Cardiovasc Res* 2023;**119**:2729–42. https://doi.org/10.1093/cvr/cvad153
30. Bruno F, Wenzl FA, De Filippo O, Kraler S, Giacobbe F, Roffi M, *et al.* Safety and effectiveness of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: insights from the SPUM-ACS study. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:391–402. https://doi.org/10.1093/ehjcvp/pvae024
31. Ernst A, Kohrle J, Bergmann A. Proenkephalin A 119-159, a stable proenkephalin A precursor fragment identified in human circulation. *Peptides* 2006;**27**:1835–40. https://doi.org/10.1016/j.peptides.2006.03.008
32. Emmens JE, Ter Maaten JM, Damman K, van Veldhuisen DJ, de Boer RA, Struck J, *et al.*Proenkephalin, an opioid system surrogate, as a novel comprehensive renal marker in heart failure. *Circ Heart Fail* 2019;**12**:e005544. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005544
33. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;**120**:c179–184. https://doi.org/10.1159/000339789
34. Depret F, Hollinger A, Cariou A, Deye N, Vieillard-Baron A, Fournier MC, *et al.* Incidence and outcome of subclinical acute kidney injury using penKid in critically ill patients. *Am J Respir Crit Care Med* 2020;**202**:822–9. https://doi.org/10.1164/rccm.201910-1950OC
35. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators. Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med* 2017;**376**:11–20. https://doi.org/10.1056/NEJMoa1611391
36. Levey AS, James MT. Acute kidney injury. *Ann Intern Med* 2017;**167**:ITC66–80. https://doi.org/10.7326/AITC201711070
37. James MT, Levey AS, Tonelli M, Tan Z, Barry R, Pannu N, *et al.* Incidence and prognosis of acute kidney diseases and disorders using an integrated approach to laboratory measurements in a universal health care system. *JAMA Netw Open* 2019;**2**:e191795. https://doi.org/10.1001/jamanetworkopen.2019.1795
38. Bianchi NA, Stavart LL, Altarelli M, Kelevina T, Faouzi M, Schneider AG. Association of oliguria with acute kidney injury diagnosis, severity assessment, and mortality among patients with critical illness. *JAMA Netw Open* 2021;**4**:e2133094. https://doi.org/10.1001/jamanetworkopen.2021.33094
39. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
40. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, *et al.* Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;**384**:129–39. https://doi.org/10.1056/NEJMoa2030186
41. Hayek SS, Sever S, Ko Y-A, Trachtman H, Awad M, Wadhwani S, *et al.* Soluble urokinase receptor and chronic kidney disease. *N Engl J Med* 2015;**373**:1916–25. https://doi.org/10.1056/NEJMoa1506362
42. Bash LD, Coresh J, Kottgen A, Parekh RS, Fulop T, Wang Y, *et al.* Defining incident chronic kidney disease in the research setting: the ARIC Study. *Am J Epidemiol* 2009;**170**:414–24. https://doi.org/10.1093/aje/kwp151
43. O'Seaghdha CM, Lyass A, Massaro JM, Meigs JB, Coresh J, D'Agostino RB Sr, *et al.* A risk score for chronic kidney disease in the general population. *Am J Med* 2012;**125**:270–7. https://doi.org/10.1016/j.amjmed.2011.09.009
44. Wali RK, Iyengar M, Beck GJ, Chartyan DM, Chonchol M, Lukas MA, *et al.* Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. *Circ Heart Fail* 2011;**4**:18–26. https://doi.org/10.1161/CIRCHEARTFAILURE.109.932558
45. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305. https://doi.org/10.1056/NEJMoa041031
46. Stamatelopoulos K, Mueller-Hennessen M, Georgiopoulos G, Sachse M, Boeddinghaus J, Sopova K, *et al.* Amyloid-beta (1-40) and mortality in patients with non-ST-segment elevation acute coronary syndrome: a cohort study. *Ann Intern Med* 2018;**168**:855–65. https://doi.org/10.7326/M17-1540
47. Hung J, Roos A, Kadesjö E, McAllister DA, Kimenai DM, Shah ASV, *et al.* Performance of the GRACE 2.0 score in patients with type 1 and type 2 myocardial infarction. *Eur Heart J* 2021;**42**:2552–61. https://doi.org/10.1093/eurheartj/ehaa375
48. Serra-Burriel M, Juanola A, Serra-Burriel F, Thiele M, Graupera I, Pose E, *et al.* Development, validation, and prognostic evaluation of a risk score for long-term liver-related outcomes in the general population: a multicohort study. *Lancet* 2023;**402**:988–96. https://doi.org/10.1016/S0140-6736(23)01174-1
49. Wu X, Yuan X, Wang W, Liu K, Qin Y, Sun X, *et al.* Value of a machine learning approach for predicting clinical outcomes in young patients with hypertension. *Hypertension* 2020;**75**:1271–8. https://doi.org/10.1161/HYPERTENSIONAHA.119.13404
50. Zweck E, Spieker M, Horn P, Iliadis C, Metze C, Kavsur R, *et al.* Machine learning identifies clinical parameters to predict mortality in patients undergoing transcatheter mitral valve repair. *JACC Cardiovasc Interv* 2021;**14**:2027–36. https://doi.org/10.1016/j.jcin.2021.06.039
51. Levi R, Carli F, Arevalo AR, Altinel Y, Stein DJ, Naldini MM, *et al.* Artificial intelligence-based prediction of transfusion in the intensive care unit in patients with gastrointestinal bleeding. *BMJ Health Care Inform* 2021;**28**:e100245. https://doi.org/10.1136/bmjhci-2020-100245
52. Neuberger U, Vollmuth P, Nagel S, Schonenberger S, Weyland CS, Gumbinger C, *et al.* Optimal thresholds to predict long-term outcome after complete endovascular recanalization in acute anterior ischemic stroke. *J Neurointerv Surg* 2021;**13**:1124–7. https://doi.org/10.1136/neurintsurg-2020-016997
53. Shipe ME, Deppen SA, Farjah F, Grogan EL. Developing prediction models for clinical use using logistic regression: an overview. *J Thorac Dis* 2019;**11**:S574–84. https://doi.org/10.21037/jtd.2019.01.25
54. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X
55. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J* 2014;**35**:1925–31. https://doi.org/10.1093/eurheartj/ehu207
56. Ceglarek U, Schellong P, Rosolowski M, Scholz M, Willenberg A, Kratzsch J, *et al.*The novel cystatin C, lactate, interleukin-6, and N-terminal pro-B-type natriuretic peptide (CLIP)-based mortality risk score in cardiogenic shock after acute myocardial infarction. *Eur Heart J* 2021;**42**:2344–52. https://doi.org/10.1093/eurheartj/ehab110
57. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837–45. doi: https://doi.org/10.2307/2531595

58. Stamatelopoulos K, Mueller-Hennessen M, Georgiopoulos G, Lopez-Ayala P, Sachse M, Vlachogiannis NI, *et al.* Cathepsin S levels and survival among patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2022;**80**: 998–1010. https://doi.org/10.1016/j.jacc.2022.05.055
59. Wenzl FA, Mengozzi A, Mohammed SA, Pugliese NR, Mongelli A, Gorica E, *et al.* Circulating long noncoding RNA signatures associate with incident diabetes in older adults: a prospective analysis from the VITA cohort study. *Diabetes Care* 2023;**46**: 1239–44. https://doi.org/10.2337/dc23-0012
60. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin J, Reitsma GP, *et al.* Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;**368**:m441. https://doi.org/10.1136/bmj.m441
61. Simonsson M, Winell H, Olsson H, Szummer K, Alfredsson J, Hall M, *et al.* Development and validation of a novel risk score for in-hospital major bleeding in acute myocardial infarction:—the SWEDEHEART score. *J Am Heart Assoc* 2019;**8**: e012157. https://doi.org/10.1161/JAHA.119.012157
62. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, *et al.* Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;**162**: W1–73. https://doi.org/10.7326/M14-0698
63. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, *et al.* The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016; **387**:2302–11. https://doi.org/10.1016/S0140-6736(16)00741-8
64. Batra G, Lindback J, Becker RC, Harrington RA, Held C, James SK, *et al.* Biomarker-based prediction of recurrent ischemic events in patients with acute coronary syndromes. *J Am Coll Cardiol* 2022;**80**:1735–47. https://doi.org/10.1016/j.jacc.2022.08.767
65. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, *et al.* Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. *JAMA Netw Open* 2020;**3**: e2019209. https://doi.org/10.1001/jamanetworkopen.2020.19209
66. Beunders R, Donato LJ, van Groenendael R, Arlt B, Carvalho-Wodarz C, Schulte J, *et al.* Assessing GFR with proenkephalin. *Kidney Int Rep* 2023;**8**:2345–55. https://doi.org/10.1016/j.ekir.2023.08.006
67. Beunders R, van Groenendael R, Leijte GP, Kox M, Pickkers P. Proenkephalin compared to conventional methods to assess kidney function in critically ill sepsis patients. *Shock* 2020;**54**:308–14. https://doi.org/10.1097/shk.0000000000001510
68. Lin L-C, Chuan M-H, Liu J-H, Liao H-W, Ng LL, Magnusson M, *et al.* Proenkephalin as a biomarker correlates with acute kidney injury: a systematic review with meta-analysis and trial sequential analysis. *Crit Care* 2023;**27**:481. https://doi.org/10.1186/s13054-023-04747-5
69. Beunders R, Struck J, Wu AHB, Zarbock A, Somma D, Mehta S, *et al.* Proenkephalin (PENK) as a novel biomarker for kidney function. *J Appl Lab Med* 2017;**2**:400–12. https://doi.org/10.1373/jalm.2017.023598
70. Rosenqvist M, Bronton K, Hartmann O, Bergmann A, Struck J, Melander O. Proenkephalin a 119-159 (penKid)—a novel biomarker for acute kidney injury in sepsis: an observational study. *BMC Emerg Med* 2019;**19**:75. https://doi.org/10.1186/s12873-019-0283-9
71. Ng LL, Squire IB, Jones DJL, Cao TH, Chan DCS, Sandhu JK, *et al.* Proenkephalin, renal dysfunction, and prognosis in patients with acute heart failure: a GREAT network study. *J Am Coll Cardiol* 2017;**69**:56–69. https://doi.org/10.1016/j.jacc.2016.10.038
72. Hartman SJF, Zwiers AJM, van de Water NEC, van Rosmalen J, Struck J, Schulte J, *et al.* Proenkephalin as a new biomarker for pediatric acute kidney injury—reference values and performance in children under one year of age. *Clin Chem Lab Med* 2020;**58**: 1911–9. https://doi.org/10.1515/cclm-2020-0381
73. Molvin J, Jujic A, Navarin S, Melander O, Zoccoli G, Hartmann O, *et al.* Bioactive adrenomedullin, proenkephalin A and clinical outcomes in an acute heart failure setting. *Open Heart* 2019;**6**:e001048. https://doi.org/10.1136/openhrt-2019-001048
74. Smeets NJL, Hartmann O, Schulte J, Schreuder MF, de Wildt SN. Proenkephalin A as a marker for glomerular filtration rate in critically ill children: validation against gold standard iohexol GFR measurements. *Clin Chem Lab Med* 2023;**61**:104–11. https://doi.org/10.1515/cclm-2022-0545
75. Kooiman J, Pasha SM, Zondag W, Sijpkens YWJ, van der Molen AJ, Huisman MV, *et al.* Meta-analysis: serum creatinine changes following contrast enhanced CT imaging. *Eur J Radiol* 2012;**81**:2554–61. https://doi.org/10.1016/j.ejrad.2011.11.020
76. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 2006;**69**:S11–15. https://doi.org/10.1038/sj.ki.5000368
77. Landi A, Branca M, Leonardi S, Frigoli E, Vranckx P, Tebaldi M, *et al.* Transient vs in-hospital persistent acute kidney injury in patients with acute coronary syndrome. *JACC Cardiovasc Interv* 2023;**16**:193–205. https://doi.org/10.1016/j.jcin.2022.10.009
78. Marenzi G, Cosentino N, Bartorelli AL. Acute kidney injury in patients with acute coronary syndromes. *Heart* 2015;**101**:1778–85. https://doi.org/10.1136/heartjnl-2015-307773
79. Parikh CR, Coca SG, Wang Y, Masoudi FA, Krumholz HM. Long-term prognosis of acute kidney injury after acute myocardial infarction. *Arch Intern Med* 2008;**168**: 987–95. https://doi.org/10.1001/archinte.168.9.987
80. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012;**81**:442–8. https://doi.org/10.1038/ki.2011.379
81. Mizuguchi KA, Huang CC, Shempp I, Wang J, Shekar P, Frendl G. Predicting kidney disease progression in patients with acute kidney injury after cardiac surgery. *J Thorac Cardiovasc Surg* 2018;**155**:2455–2463.e5. https://doi.org/10.1016/j.jtcvs.2018.01.093
82. Ortega-Hernandez J, Springall R, Sanchez-Munoz F, Arana-Martinez JC, Gonzalez-Pacheco H, Bojalil R. Acute coronary syndrome and acute kidney injury: role of inflammation in worsening renal function. *BMC Cardiovasc Disord* 2017;**17**: 202. https://doi.org/10.1186/s12872-017-0640-0
83. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, *et al.* A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;**44**:1393–9. https://doi.org/10.1016/j.jacc.2004.06.068
84. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2013;**61**:2242–8. https://doi.org/10.1016/j.jacc.2013.03.026
85. Landi A, Chiarito M, Branca M, Frigoli E, Gagnor A, Calabro P, *et al.* Validation of a contemporary acute kidney injury risk score in patients with acute coronary syndrome. *JACC Cardiovasc Interv* 2023;**16**:1873–86. https://doi.org/10.1016/j.jcin.2023.06.015
86. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, *et al.* Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc* 2014;**3**:e001380. https://doi.org/10.1161/JAHA.114.001380
87. Pandhi P, Ter Maaten JM, Anker SD, Ng LL, Metra M, Samani NJ, *et al.* Pathophysiologic processes and novel biomarkers associated with congestion in heart failure. *JACC Heart Fail* 2022;**10**:623–32. https://doi.org/10.1016/j.jchf.2022.05.013
88. Foy BH, Sundt TM, Carlson JCT, Aguirre AD, Higgins JM. Human acute inflammatory recovery is defined by co-regulatory dynamics of white blood cell and platelet populations. *Nat Commun* 2022;**13**:4705. https://doi.org/10.1038/s41467-022-32222-2
89. Losser MR, Damoisel C, Payen D. Bench-to-bedside review: glucose and stress conditions in the intensive care unit. *Crit Care* 2010;**14**:231. https://doi.org/10.1186/cc9100
90. Gocze I, Jauch D, Gotz M, Kennedy P, Jung B, Zeman F, *et al.* Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK study. *Ann Surg* 2018;**267**:1013–20. https://doi.org/10.1097/SLA.0000000000002485
91. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, *et al.* Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;**43**:1551–61. https://doi.org/10.1007/s00134-016-4670-3
92. Kite TA, Kurmani SA, Bountziouka V, Cooper NJ, Lock ST, Gale CP, *et al.* Timing of invasive strategy in non-ST-elevation acute coronary syndrome: a meta-analysis of randomized controlled trials. *Eur Heart J* 2022;**43**:3148–61. https://doi.org/10.1093/eurheartj/ehac213
93. Bagai J, Beavers CJ. Quality initiatives for prevention of contrast-induced acute kidney injury. https://scai.org/quality-initiatives-prevention-contrast-induced-acute-kidney-injury (2 May 2024, date last accessed).
94. Lewington A, MacTier R, Hoefield R, Sutton A, Smith D, Downes M. *Prevention of Contrast Induced Acute Kidney Injury (CI-AKI) in Adult Patients*. The Royal College of Radiologists, 2013. https://ukkidney.org/sites/renal.org/files/Prevention_of_Contrast_Induced_Acute_Kidney_Injury_CI-AKI_In_Adult_Patients.pdf (3 August 2024, date last accessed).
95. Arribas JM, Alegria-Barrero E. How to prevent contrast-induced nephropathy in patients undergoing invasive cardiac procedures. *e-J Cardiol Pract* 2009;**7**. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-7/How-to-prevent-contrast-induced-nephropathy-in-patients-undergoing-invasive-card (3 August 2024, date last accessed).
96. Ostermann M, Bellomo R, Burdmann EA, Doi K, Endre ZH, Goldstein SL, *et al.* Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney Int* 2020;**98**:294–309. https://doi.org/10.1016/j.kint.2020.04.020
97. Wenzl FA, Fox KAA, Luscher TF. Towards personalized cardiovascular care: Global Registry of Acute Coronary Events 3.0 score heralds artificial intelligence era. *Eur Heart J* 2023;**44**:4615–6. https://doi.org/10.1093/eurheartj/ehad597
98. Zanchin C, Ueki Y, Zanchin T, Haner J, Otsuka T, Stortecky S, *et al.* Everolimus-eluting biodegradable polymer versus everolimus-eluting durable polymer stent for coronary revascularization in routine clinical practice. *JACC Cardiovasc Interv* 2019;**12**:1665–75. https://doi.org/10.1016/j.jcin.2019.04.046
99. Breidthardt T, Jaeger C, Christ A, Klima T, Mosimann T, Twerenbold R, *et al.* Proenkephalin for the early detection of acute kidney injury in hospitalized patients with chronic kidney disease. *Eur J Clin Invest* 2018;**48**:e12999. https://doi.org/10.1111/eci.12999
100. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol* 2010;**21**:1757–64. https://doi.org/10.1681/asn.2010010128