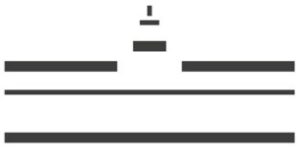


Observational study to evaluate the **EPI**demiology of **S**urgical-induced **A**cute **K**idney **I**njury

Statistical Analysis Plan

Version: Version 1.0
Date: 16.07.2022

EudraCT number: n.a.

ClinicalTrials.gov identifier: NCT04165369

Acronym: EPIS-AKI

Principle investigator:
Univ.-Prof. Dr. med. Alexander Zarbock

Signatures

Principal investigator

Univ.-Prof. Dr. med. Alexander Zarbock,

University Hospital Münster
Department of Anesthesiology, Intensive Care Medicine and Pain Medicine
Albert-Schweitzer-Campus 1
48149 Münster
Germany

Münster, 16.07.2022
Place, date

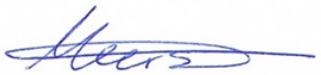
Signature

Medical project management

Prof. Dr. med. Melanie Meersch,

University Hospital Münster
Department of Anesthesiology, Intensive Care Medicine and Pain Medicine
Albert-Schweitzer-Campus 1
48149 Münster
Germany

Münster, 16.07.2022
Place, date

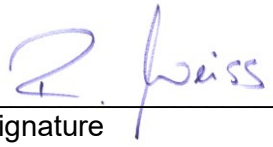


Signature

Dr. med. Raphael Weiss,

University Hospital Münster
Department of Anesthesiology, Intensive Care Medicine and Pain Medicine
Albert-Schweitzer-Campus 1
48149 Münster
Germany

Münster, 16.07.2022
Place, date



Signature

Biostatistician

Dr. rer. medic. Laura Kerschke, M. Sc.,

University of Münster
Institute of Biostatistics and Clinical Research
Schmeddingsstr. 56
48149 Münster
Germany

Münster, 16.07.2022
Place, date

Signature

1 Synopsis

Study-ID	04-AnIt-19
Title of the trial	Observational study to evaluate the **EPI**demiology of **S**urgical-induced **A**cute **K**idney **I**njury
Acronym	EPIS-AKI
Responsible institution	Department of Anesthesiology, Intensive Care and Pain Medicine Albert-Schweitzer-Campus 1, A1 48149 Muenster
Medical condition	Complications after surgery
Principle investigator	**Univ.-Prof. Dr. med. Alexander Zarbock** Department of Anesthesiology, Intensive Care and Pain Medicine University Hospital of Muenster Albert-Schweitzer-Campus 1, A1 48149 Muenster Phone: +49 251/83-47252; Fax: +49 251/83-40501; Email: zarbock@uni-muenster.de
Medical project management	**Prof. Dr. med. Melanie Meersch** Department of Anesthesiology, Intensive Care and Pain Medicine University Hospital of Muenster Albert-Schweitzer-Campus 1, A1 48149 Muenster Phone: +49 251/83-47282; Fax: +49 251/83-40501; Email: meersch@uni-muenster.de **Dr. med. Raphael Weiss** Department of Anesthesiology, Intensive Care and Pain Medicine; University Hospital of Muenster Albert-Schweitzer-Campus 1, A1 48149 Muenster Phone: +49 251/83-47255; Fax: +49 251/83-40501; Email: raphael.weiss@ukmuenster.de
Study coordinator	**Dr. oec. troph. Carola Wempe** Department of Anesthesiology, Intensive Care and Pain Medicine; University Hospital of Muenster Albert-Schweitzer-Campus 1, A1 48149 Muenster Phone: +49 251/83-47267; Fax: +49 251/83-40501; Email: wempe-c@anit.uni-muenster.de
Trial type	International prospective, observational, multi-center, cross-sectional cohort study

Participating centers	This clinical trial will be carried out as an international multicenter observational cohort trial in Europe and the USA. If necessary, further qualified trial sites may be recruited to the trial. The listing of trial sites, principal investigators, sub-investigators, and further trial staff, will be kept and continuously updated in a separate list. The final version of this list will be attached to the final report of the clinical trial.
Biometry	**Dr. rer. medic. Laura Kerschke, M. Sc.** Institute of Biostatistics and Clinical Research University of Muenster Schmeddingstr. 56 48149 Muenster Phone: +49 251/83-53607 Email: laura.kerschke@ukmuenster.de
Funding	Unrestricted research grant from Baxter
Objective(s)	Acute kidney injury (AKI) is a severe clinical complication with increasing incidence and is associated with adverse short- and long-term outcomes resulting in a major health care burden worldwide. The introduction of consensus classification systems has enhanced the awareness for AKI. The evaluation of an accurate occurrence rate for AKI is of great importance for health policy, quality initiatives as well as for designing clinical trials. However, analyzing AKI from existing databases is often limited by missing data elements, especially the inclusion of the urine output criteria. Missing data and the use of different definitions before the consensus classification are the reasons for large variations in reported occurrences of surgical induced AKI. The primary objective of the study is to prospectively evaluate the incidence of AKI within 72 h after extended surgical procedures that require admission to an observation unit (e.g., ICU, IMC, PACU) using the latest consensus definition for AKI (Kidney Disease: Improving Global Outcomes criteria) and a standardized data collection instrument. Secondary objectives are: • to evaluate the severity and duration of post-surgery AKI, as well as the use of renal replacement therapy (RRT), all-cause mortality (ICU and hospital), ICU and hospital length of stay, and the occurrence of MAKE (major adverse kidney events) up to 90 days after extended surgical procedures, • to determine the effects of pre- and intraoperative factors on the occurrence of AKI, • to determine the association between AKI and postoperative outcomes including use of RRT, all-cause mortality, ICU and hospital length of stay, the occurrence of MAKE (major adverse kidney events) and CKD (chronic kidney disease) development or progression up to 90 days after extended surgical

	procedures, • to determine the transition from non-AKI and AKI to CKD (i.e. development or progression; CKD defined by CKD-KDIGO) at day 90 after extended surgical procedures.
Key inclusion and exclusion criteria	***Inclusion criteria:*** 1. Age ≥ 18 years 2. Major surgeries with a duration of at least 2 h 3. Planned or unplanned admission to the ICU, IMC or PACU after surgery 4. Written informed consent ***Exclusion criteria:*** 1. Pre-existing AKI 2. AKI within the last 3 months 3. End stage renal disease with dialysis dependency 4. Kidney transplant
Study endpoints	**Primary endpoint**: Occurrence of AKI within 72h after extended surgery according the KDIGO criteria. **Secondary endpoints:** Secondary endpoints are: • Use of renal replacement therapy • Duration of AKI (transient vs. persistent) • Length of ICU stay • Length of hospital stay • Survival o ICU mortality o Hospital mortality • $MAKE_{90}$ (major adverse kidney events within 90 days): combined endpoint consisting of: o Mortality o renal replacement therapy o persistent renal dysfunction defined as serum-creatinine ≥ 1.5 times as compared to baseline serum-creatinine • Transition from non-AKI and AKI to CKD (i.e. development or progression; CKD defined by CKD-KDIGO) at day 90
Number of subjects	To be analyzed in the trial: n=10,000
Time plan	First patient first visit (FPFV): 01/06/2020 Last patient first visit (LPFV): 30/06/2022 Last patient last visit (LPLV): 30/09/2022 Final study report: 31/12/2022
Statistical analysis	Statistical analyses will be performed according to the principles of the ICH-guideline E9 “Statistical Principles for Clinical Trials” using standard statistical software. Analyses will be performed based on the Full Analysis Set (FAS). In the primary analysis the incidence of AKI will be estimated together with the exact corresponding two-sided 95% confidence interval according to Clopper-Pearson.

	To detect factors that might be correlated to the occurrence of AKI (e.g., type/length of surgery, use of blood products, morbidities), exploratory uni- and multivariable logistic regression analyses will be conducted. For secondary outcomes, descriptive statistics, point estimates and corresponding 95% confidence intervals will be derived. To quantify evidence of differences between groups given by categorical parameters, such as the type of surgery, exploratory inferential analyses will be performed, using statistical tests like t-tests, Mann-Whitney-U tests, Kruskal-Wallis tests, Chi-square tests or Fisher's exact tests, appropriate to the distributional characteristics of the endpoint. Additionally, subgroup analyses will be conducted based on the type of surgery to identify variables that are correlated with the occurrence of AKI in each group.
Power calculation	The primary aim of the study is to estimate the incidence of post-surgery AKI and to derive the corresponding exact two-sided 95% confidence interval according to Clopper-Pearson. Depending on the type of surgery, AKI incidences of 1.8-39.3% are reported in existing literature. As the width of the confidence interval increases, the closer the observed incidence of post-surgery AKI equals 50%, a rate of 40% is assumed, as a conservative approach. Using this assumption, the width of the confidence interval based on a sample size of n = 10,000 patients and a confidence level of 95% is given by 0.019. Thus, with n = 10,000 patients, the incidence of post-surgery AKI can be estimated with at least this precision. The study also aims to detect factors that might be correlated to the occurrence of post-surgery AKI, as e.g. the type of surgery (i.e. cardiac, neurological etc.) and predefined preoperative and intraoperative factors. Therefore, further exploratory analyses such as uni- and multivariable logistic regression analyses will be conducted. Given the relatively large number of different types of surgeries, a sample size of n = 10,000 patients is sufficient to investigate the influence of this parameters on the occurrence of post-surgery AKI in a uni- and multivariable context.
Trial registration	The trial is registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04165369).

2 Abbreviations

ACE	Angiotensin Converting Enzyme
AKI	Acute Kidney Injury
APACHE	Acute Physiology And Chronic Health Evaluation
ARB	Angiotensin Receptor Blocker
ASA	American Society of Anesthesiologists
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
EPIS-AKI	Epidemiology of Surgical-induced Acute Kidney Injury
FPFV	First patient first visit
GFR	Glomerular Filtration Rate
ICH	International Conference on Harmonisation of Technical Requirements
ICU	Intensive Care Unit
IMC	Intermediate Care
KDIGO	Kidney Disease: Improving Global Outcomes
LPFV	Last patient first visit
LPLV	Last patient last visit
MAKE	Major Adverse Kidney Events
NSAID	Nonsteroidal Anti-inflammatory Drug
NYHA	New York Heart Association
OD	Operative Day
PACU	Post Anesthesia Care Unit
POD	Postoperative day
RRT	Renal Replacement Therapy
SAPS	Simplified Acute Physiology Score
SAP	Statistical Analysis Plan
UO	Urine Output

3 General remarks

This SAP was written without knowledge of any study data.

4 Background of the study

Acute kidney injury (AKI) is a severe clinical complication with increasing incidence and it is associated with adverse short- and long-term outcomes resulting in a major health care burden worldwide. AKI is now being considered as independent risk factor for adverse outcomes. Since the introduction of consensus classification systems (Risk Injury Failure Loss and End stage [RIFLE], Acute Kidney Injury Network [AKIN], and the Kidney Disease: Improving Global Outcomes [KDIGO] criteria), the awareness for its importance has grown tremendously and most of the studies use these definitions to report AKI rates.

The establishment of an accurate occurrence rate for AKI is important for health policy, quality initiatives as well as for designing clinical trials. However, analyzing AKI from existing databases in the surgical setting is often limited by missing data elements needed for the application of these definitions, especially the inclusion of the urine output criteria. Additionally, administrative databases are limited since billing codes do not capture many cases of AKI. This might be one explanation for the large variation in occurrence rates of AKI reported in the surgical setting.

The objective of the epidemiology of Surgical-induced Acute Kidney Injury (EPIS-AKI) trial is to prospectively evaluate the epidemiology of AKI after extended surgical procedures in hospitals using the latest consensus definition for AKI and a standardized data collection instrument and to assess the dependence of AKI on preoperative and intraoperative factors (Study protocol[1], version 1.2, 29.06.2020).

5 Study objectives

Primary objective:
The primary objective of the study is to evaluate the incidence of AKI within 72 h after extended surgical procedures that require admission to an observation unit (e.g., ICU, IMC, PACU) using the latest consensus definition for AKI (Kidney Disease: Improving Global Outcomes criteria).

Secondary objectives:
The secondary objectives of the study are:

- to evaluate the severity and duration of post-surgery AKI, as well as the use of renal replacement therapy (RRT), all-cause mortality (ICU and hospital), ICU and hospital length of stay, and the occurrence of MAKE (major adverse kidney events) and CKD (chronic kidney disease) development or progression up to 90 days after extended surgical procedures,
- to determine the effects of pre- and intraoperative factors on the occurrence of AKI,
- to determine the association between AKI and postoperative outcomes including use of RRT, all-cause mortality, ICU and hospital length of stay, and the occurrence of MAKE up to 90 days after extended surgical procedures.
- Transition from non-AKI and AKI to CKD (i.e. development or progression; CKD defined by CKD-KDIGO) at day 90.

6 General study design and plan

The EPIS-AKI trial is an international, prospective, observational, multi-center, cross-sectional cohort study including patients that undergo extended surgical procedures.

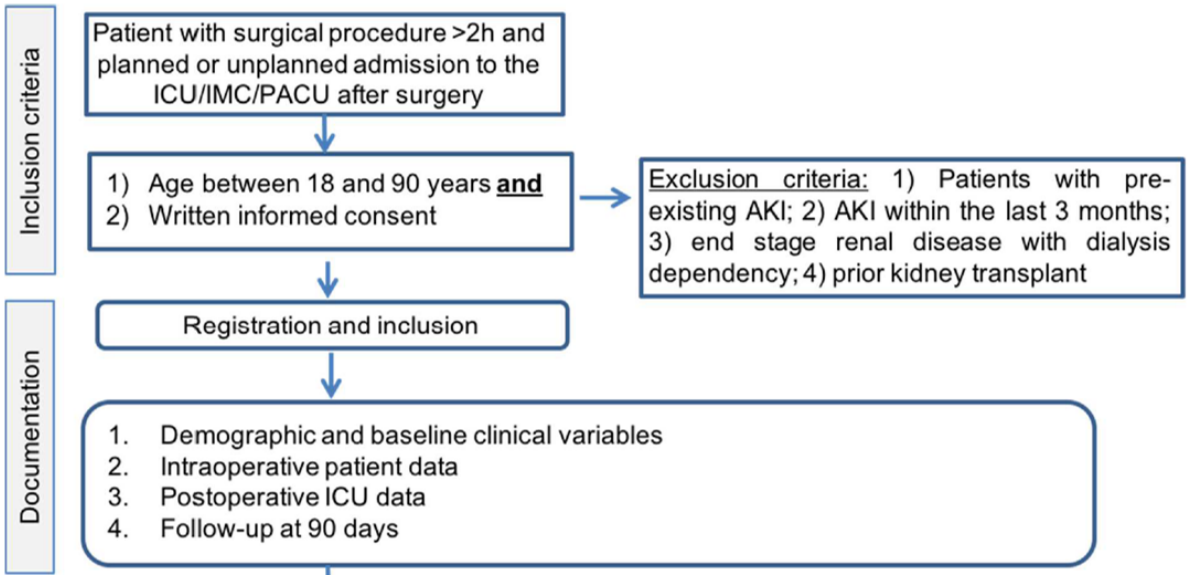


Figure 1: Trial workflow.

Eligible patients, i.e. meeting all inclusion and none of the exclusion criteria, will be enrolled into the study (Figure 1). The visit plan is shown in Table 1.

Visit	S	B	OD	POD 1-3	Day 90
Inclusion and Exclusion criteria	X				
Demography Age, gender, race, height, weight, creatinine, comorbidities, ASA status, medication		X			
Admission diagnosis, source of admission		X			
Intraoperative data Surgical procedure (speciality, type, duration, if cardiac: CPB			X		

/ aortic X-clamp duration), fluid status (fluid intake, transfusion, blood loss, urine output), use of cell saver, episodes of hypotension, drug application, intraoperative complications					
Postoperative data APACHE, SAPS, fluid status, drug application, postoperative complications				X	
AKI Stage, occurrence, duration, diagnosis, RRT				X	
Concomitant Medication Vasopressors, nephrotoxic agents, diuretics				X	
Mortality					X
Length of primary stay (ICU, Hospital)					X
Serum-creatinine					X
Renal recovery					X
Number of days of RRT/RRT dependence					X
MAKE (major adverse kidney events)					X
Abbreviations: S, Screening; B, Baseline, OD, operative day; POD, postoperative day; ASA, American Society of Anaesthesiology; CPB, cardiopulmonary bypass; APACHE, Acute Physiology And Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; ICU, intensive care unit.					

Table 1: Visit plan.

7 Inclusion and exclusion criteria

The inclusion and exclusion criteria of the study are:

Inclusion criteria:

1. Age ≥ 18 years
2. Major elective or emergency surgery procedures with a duration of at least 2h
3. Planned or unplanned admission to the ICU, IMC or PACU after surgery
4. Informed Consent

Major surgeries will be targeted within the broad subgroup domains of neurosurgery, cardiac, vascular, gynecology, thoracic, urology, orthopedics/trauma and abdominal surgery.

Exclusion criteria:

1. Pre-existing AKI
2. AKI within the last 3 months
3. End stage renal disease with dialysis dependency,
4. Kidney transplant

8 Statistical design and sample size calculation

The primary aim of the study is to estimate the incidence of post-surgery AKI and to derive the corresponding exact two-sided 95% confidence interval according to Clopper-Pearson[2].
Depending on the type of surgery, AKI incidences of 1.8-39.3% are reported in existing literature (Table 2). As the width of the confidence interval increases, the closer the observed incidence of post-surgery AKI equals 50%, a rate of 40% is assumed, as a conservative approach. Using this assumption, the width of the confidence interval based on a sample size of n = 10,000 patients and a confidence level of 95% is given by 0.019.
Thus, with n = 10,000 patients, the incidence of post-surgery AKI can be estimated with at least this precision.
The study also aims to detect factors that might be correlated to the occurrence of post surgery AKI for different types of surgical procedures (e.g. cardiac, neurological etc.). Therefore, further exploratory analyses such as uni- and multivariable logistic regression analyses will be conducted. Given the relatively large number of different types of surgeries, a sample size of n = 10,000 patients is sufficient to investigate the influence of this

parameters on the occurrence of post-surgery AKI in a uni- and multivariable context and to conduct corresponding subgroup analyses (e.g. cardiac surgery induced AKI).

Study	Year	Design	Population (n)	Definition	Incidence (%)
AKI after major abdominal surgery					
Armstrong et al. [3]	2009	Retrospective	Hepatobiliary (1535)	AKIN/ SCr	5.1
Bell et al. [4]	2014	Interrupted time series analysis	Major abdominal/GI (3271)	KDIGO/ SCr	9.8
Bihorac et al. [5]	2009	Retrospective	Major abdominal/GI (2337)	RIFLE/ SCr	39.3*
Biteker et al. [6]	2014	Prospective	Major abdominal/GI (510)	RIFLE/ SCr and GFR	7.1*
Brunelli et al. [7]	2012	Retrospective	Major abdominal/GI (1912)	AKIN/ SCr	26.8*
Causey et al. [8]	2011	Retrospective	Colorectal (339)	RIFLE/ SCr	11.8
Chao et al. [9]	2013	Retrospective	Major abdominal/GI (1972)	AKIN/ SCr	20.2
Cho et al. [10]	2014	Prospective	Hepatobiliary (111)	AKIN/ SCr and UO	1.8*
Coca et al. [11]	2010	Retrospective	Major abdominal/GI (11460)	AKIN/ SCr	18.9*
Correa-Gallego et al. [12]	2015	Retrospective	Hepatobiliary (2116)	RIFLE/ GFR	15.9
Grams et al. [13]	2016	Retrospective	Major abdominal/GI (44597)	KDIGO/ SCr	13.2*
Kambakamba et al. [14]	2015	Retrospective	Hepatobiliary (829)	AKIN/ SCr	8.2
Kim et al. [15]	2013	Retrospective	GI (4718)	KDIGO/ SCr	14.4
Lee et al. [16]	2014	Retrospective	GI (595)	AKIN/ SCr	35.3
Slankamenac et al. [17]	2009	Retrospective	Hepatobiliary (569)	RIFLE/ SCr and UO	15.1
Sun et al. [18]	2015	Retrospective	Major abdominal/GI (1345)	AKIN/ SCr	9.7
Sun et al. [18]	2015	Retrospective	Major gynaecological (865)	AKIN/ SCr	3.1
Teixeira et al. [19]	2014	Retrospective	Major abdominal/GI (450)	KDIGO/ SCr and UO	22.4
Tomozawa et al. [20]	2015	Retrospective	Hepatobiliary (642)	AKIN/ SCr	12.2
Vaught et al. [21]	2014	Retrospective	Major gynaecological (2341)	RIFLE/ SCr	12.6*

Abbreviations: AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; GI, gastrointestinal; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk Injury Failure, Loss and End-stage; SCr, serum creatinine; UO, urine output
* Patients with chronic kidney disease excluded

Table 2: Summary of epidemiologic studies used for sample size planning.

9 Timing of the statistical analysis

The statistical analysis will be performed after data entry into the study database and data cleaning has been completed.

10 Analysis populations

All analyses will be performed on the Full Analysis Set (FAS). The Full Analysis Set contains all patients enrolled into the trial.

11 Endpoints

11.1 Primary endpoint

The primary endpoint of the study is the occurrence of AKI within 72 h after extended surgery according to the KDIGO (Kidney Disease: Improving Global Outcomes) criteria (Table 3).

Stage	Serum creatinine	Urine output
1	≥ 0.3 mg/dl in 48 h *or* 1.5-1.9-times baseline within the last 7 days	< 0.5 ml/kg/h for ≥ 6 h
2	2.0-2.9-times baseline	< 0.5 ml/kg/h for ≥ 12h
3	3-times baseline *or* ≥ 4.0 mg/dl *or* initiation of RRT	< 0.3 ml/kg/h for ≥ 24 h *or* anuria for ≥ 12 h
Abbreviations: RRT, renal replacement therapy		

Table 3: KDIGO criteria for the diagnosis of AKI.

11.2 Secondary endpoints

- Severity of post-surgery AKI
- Duration of AKI (transient, < 48h vs. persistent, > 48h)
- Use of renal replacement therapy (RRT) within 90 days after extended surgery
- All-cause mortality 90-days after extended surgery
- Length of ICU stay (time from ICU admission until ICU discharge)
- Length of hospital stay (time from hospital admission until hospital discharge)
- Occurrence of MAKE (major adverse kidney event), defined as combined endpoint consisting of
    - all-cause mortality,
    - use of RRT,
    - persistent renal dysfunction defined as serum-creatinine ≥ 1.5 times as compared to baseline serum-creatinine

  within 90 days after extended surgery ($MAKE_{90}$)
- Transition from non-AKI and AKI to CKD G3 to G5 (i.e. development or progression; CKD defined by CKD-KDIGO, Table 4) at day 90 (CKD_{90})

Stage	eGFR [mL/min/1.73m²)
G1	≥ 90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	< 15
Abbreviations: eGFR, estimated glomerular filtration rate	

Table 4: KDIGO classification for the diagnosis of CKD.

11.3 Variables to be analyzed descriptively

11.3.1 Subject disposition

- Number of patients enrolled (total; per study center)
- Inclusion and exclusion criteria

11.3.2 Demographic and baseline variables

- Age
- Gender
- Ethnicity
- Height
- Weight

- Baseline creatinine

11.3.3 Comorbidities

- Hypertension
- Atrial fibrillation/flutter
- Previous myocardial infarction
- Congestive heart failure / NYHA classification
- Diabetes
- COPD
- CKD / CKD stage
- Peripheral vascular disease
- Previous stroke
- ASA score

11.3.4 Medication

- Aspirin (ASS)
- ACE inhibitors or ARBs
- Beta-blockers
- Diuretics
- NSAIDs (except ASS)
- Statins
- Vasopressors
- Use of contrast media one week prior to surgery

11.3.5 Intraoperative data

- Surgical specialty
- Type of surgery
- Duration of surgery
- If cardiopulmonary bypass (CPB): Total CPB time / Total X-Clamp time
- Intake of Crystalloids / Colloids / Erythrocytes (EC) / Thrombocytes (TC) / Fresh frozen plasma (FFP)
- Use of cell saver
- Total blood loss
- Use of urine catheter
- Total urine output
- Episodes of hypotension (MAP < 55 mmHg for more than 5 minutes)
- Application and type of vasopressors
- Application and type of nephrotoxic agents
- Application of diuretics
- Intraoperative complications / Type of complications

11.3.6 Postoperative data

- APACHE II score
- SAPS
- Cumulative intake of Crystalloids / Colloids / Erythrocytes (EC) / Thrombocytes (TC) / Fresh frozen plasma (FFP)
- Cumulative total blood loss
- Cumulative total urinary output
- Time of urine catheter removal
- Application and type of vasopressors
- Application and type of nephrotoxic agents
- Application of diuretics
- Postoperative complications / Type of complications
- Occurrence of AKI / severity of AKI / duration of AKI / diagnosis (worst case AKI)
- Time of bladder catheter removal
- Use of RRT / Start of RRT / Modality at time of RRT initiation / Indication for initiation of RRT

12 Statistical Analyses

Statistical analyses will be performed according to the principles of the ICH-guideline E9 “Statistical Principles for Clinical Trials” using standard statistical software.

12.1 Summary of study data

Variables listed in section 11 will be analyzed descriptively.

Continuous variables: Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), number of missing values, mean, standard deviation, median, Q25%, Q75%, maximum and minimum. Histograms or boxplots might be used for graphical presentation of the data.

Categorical variables: For categorical variables the frequency and percentages (based on the non-missing sample size) of observed levels will be reported. Bar charts might be used for graphical presentation of the data.

12.2 Primary analysis

In the primary analysis the incidence of AKI will be estimated together with the exact corresponding two-sided 95% confidence interval according to Clopper-Pearson[2].

12.3 Secondary analyses

All secondary analyses are considered exploratory.

Secondary outcomes (see 11.2) will be evaluated based on descriptive statistics, point estimates and corresponding 95% confidence intervals.

To detect factors that might be correlated to the occurrence of AKI, $MAKE_{90}$, CKD_{90} (i.e. development or progression), and a persistent AKI, exploratory uni- and multivariable logistic regression analyses will be conducted (including age, arterial hypertension, diabetes mellitus, sex, type of surgery as explanatory variables).

The association between AKI (overall and by severity, duration) and postoperative outcomes including use of RRT, all-cause mortality, ICU and hospital length of stay, the occurrence of $MAKE_{90,}$ the development or progression of CKD_{90}, and the estimated glomerular filtration rate (eGFR) at day 90 will be assessed descriptively. Subsequent analyses for related risk factors will be undertaken.

The impact of baseline serum-creatinine and urinary output on the occurrence of $MAKE_{90}$ in patients with post-surgical AKI will be assessed by logistic regression analyses.

12.4 Further exploratory analyses

To quantify evidence of differences between groups given by categorical parameters, such as the type of surgery, statistical tests like t-tests, Mann-Whitney-U tests, Kruskal-Wallis tests, Chi-square tests or Fisher’s exact tests will be used, appropriate to the distributional characteristics of the endpoint. P-values from exploratory analyses will be interpreted in Fisher’s sense as a metric weight of evidence against the respective null hypothesis of no effect. Two-sided p-values ≤ 0.05 will be considered statistically noticeable.

Further analyses used for hypotheses generation and exploration might be determined afterwards on demand. Results will be interpreted according to the exploratory level of scientific evidence.

12.5 Subgroup analyses

Exploratory subgroup analyses will be performed based on the type of surgery (e.g. cardiac surgery) to identify variables that are correlated with the occurrence of AKI (overall and by severity) in each group.

13 Interim analyses

No interim analyses will be performed.

14 Treatment of missing values and outliers

14.1 Missing values

No imputation of missing values will be performed.

14.2 Outliers

The primary endpoint is binary. Hence, treatment of outliers is not necessary for the analysis of the primary endpoint. For metric variables that will be analyzed exploratory, it is assumed that the data will be checked thoroughly by the data management and that outliers will be verified. No further outlier detection will be performed.

15 Summary of changes to the protocol

The following changes to the protocol were made:

- Definition of the severity of AKI as a secondary endpoint
- Definition of the duration of AKI (transient vs. persistent) as secondary endpoint
- Definition of transition from non-AKI and AKI to CKD (i.e. development or progression, CKD defined by CKD-KDIGO) as a secondary endpoint

16 Software

Analyses will be performed using R (R Core Team).

17 References

1. EPIS-AKI – Trial Study Protocol, Version 1.2, 29.06.2020. Accesible via http://emah.ukmuenster.de/fileadmin/ukminternet/daten/kliniken/anaesthesiologie/epis/EPIS-AKI_Protocol_V1.1_20-06-29_final.pdf
2. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4), pp.404-413.
3. Armstrong T, Welsh FK, Wells J, Chandrakumaran K, John TG, Rees M. The impact of pre-operative serum creatinine on short-term outcomes after liver resection. *HPB (Oxford).* 2009;11(8):622-628.
4. Bell S, Davey P, Nathwani D, et al. Risk of AKI with gentamicin as surgical prophylaxis. *Journal of the American Society of Nephrology : JASN.* 2014;25(11):2625-2632.
5. Bihorac A, Yavas S, Subbiah S, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Annals of surgery.* 2009;249(5):851-858.
6. Biteker M, Dayan A, Tekkesin AI, et al. Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery. *American journal of surgery.* 2014;207(1):53-59.
7. Brunelli SM, Waikar SS, Bateman BT, et al. Preoperative statin use and postoperative acute kidney injury. *The American journal of medicine.* 2012;125(12):1195-1204 e1193.
8. Causey MW, Maykel JA, Hatch Q, Miller S, Steele SR. Identifying risk factors for renal failure and myocardial infarction following colorectal surgery. *The Journal of surgical research.* 2011;170(1):32-37.
9. Chao CT, Lin YF, Tsai HB, Wu VC, Ko WJ. Acute kidney injury network staging in geriatric postoperative acute kidney injury patients: shortcomings and improvements. *Journal of the American College of Surgeons.* 2013;217(2):240-250.
10. Cho E, Kim SC, Kim MG, Jo SK, Cho WY, Kim HK. The incidence and risk factors of acute kidney injury after hepatobiliary surgery: a prospective observational study. *BMC nephrology.* 2014;15:169.
11. Coca SG, King JT, Jr., Rosenthal RA, Perkal MF, Parikh CR. The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. *Kidney international.* 2010;78(9):926-933.

12. Correa-Gallego C, Berman A, Denis SC, et al. Renal function after low central venous pressure-assisted liver resection: assessment of 2116 cases. *HPB (Oxford).* 2015;17(3):258-264.
13. Grams ME, Sang Y, Coresh J, et al. Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2016;67(6):872-880.
14. Kambakamba P, Slankamenac K, Tschuor C, et al. Epidural analgesia and perioperative kidney function after major liver resection. *The British journal of surgery.* 2015;102(7):805-812.
15. Kim CS, Oak CY, Kim HY, et al. Incidence, predictive factors, and clinical outcomes of acute kidney injury after gastric surgery for gastric cancer. *PloS one.* 2013;8(12):e82289.
16. Lee EH, Kim HR, Baek SH, et al. Risk factors of postoperative acute kidney injury in patients undergoing esophageal cancer surgery. *Journal of cardiothoracic and vascular anesthesia.* 2014;28(4):936-942.
17. Slankamenac K, Breitenstein S, Held U, Beck-Schimmer B, Puhan MA, Clavien PA. Development and validation of a prediction score for postoperative acute renal failure following liver resection. *Annals of surgery.* 2009;250(5):720-728.
18. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology.* 2015;123(3):515-523.
19. Teixeira C, Rosa R, Rodrigues N, et al. Acute kidney injury after major abdominal surgery: a retrospective cohort analysis. *Crit Care Res Pract.* 2014;2014:132175.
20. Tomozawa A, Ishikawa S, Shiota N, Cholvisudhi P, Makita K. Perioperative risk factors for acute kidney injury after liver resection surgery: an historical cohort study. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* 2015;62(7):753-761.
21. Vaught AJ, Ozrazgat-Baslanti T, Javed A, Morgan L, Hobson CE, Bihorac A. Acute kidney injury in major gynaecological surgery: an observational study. *BJOG : an international journal of obstetrics and gynaecology.* 2015;122(10):1340-1348.