OBSERVATIONAL STUDY TO EVALUATE THE EPIDEMIOLOGY OF SURGICAL-INDUCED ACUTE KIDNEY INJURY

ACRONYM

EPIS-AKI

Supported by Baxter, endorsed by ESA

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Study code:

01-AnIt-19

Version 1.2
Date: 2020-06-29

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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.

1.2 Signatures

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Place, date

Signature

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Study Coordinator:
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Place, date

Signature

1.3 Synopsis

Study-ID	01-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
Principal 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
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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 **(biometric evaluation)**	Laura Kerschke 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 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 and to assess the dependence of AKI on preoperative and intraoperative factors. Secondary objectives: to determine the effects of pre- and intraoperative factors on the occurrence of AKI, to determine the impact of AKI on postoperative outcomes including use of renal replacement therapy, all-cause mortality (ICU and hospital) as well as the length of stay (ICU and hospital) and a combination of endpoints summarized as $MAKE_{90}$ (major adverse kidney events at day 90).
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
Primary trial objective	The primary objective of the EPIS-AKI trial is to prospectively evaluate the incidence of AKI within 72h after extended surgical procedures in hospitals using the latest consensus definition for AKI according the KDIGO criteria.
Study endpoints	**Primary endpoint:** Occurrence of AKI within 72h after surgery according the KDIGO criteria **Secondary endpoints:** Secondary endpoints are: • Effect of preoperative risk factors on the incidence of post–operative AKI • Effect of predetermined intraoperative factors on the incidence of post–operative AKI • Biomarkers of AKI (urine for this endpoint will be collected in some centers) • Outcomes: o Use of renal replacement therapy o Length of ICU stay o Length of hospital stay • Survival o ICU mortality o Hospital mortality • $MAKE_{90}$ (major adverse kidney events at day 90): 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
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. Data will be summarized by standard descriptive statistical measures. Normally distributed variables will be reported as mean and standard deviation and non-normally distributed variables as median and lower and upper quartile. Categorical variables will be expressed as proportion. 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, Chi-square tests or Fisher’s exact tests will be used appropriate to the distributional characteristics of the endpoint. 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, point estimates and corresponding 95% confidence intervals will be derived. In further exploratory analyses, the association between secondary outcomes and the type of surgery will be analyzed using appropriate statistical methods. Additionally, subgroup analyses will be performed based on the type of surgery to identify variables that are correlated with the occurrence of AKI in each group. A two-sided p-value of < 0.05 will be considered as statistically significant.
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).

1.4 Abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitors
AKI	Acute Kidney Injury
APACHE	Acute Physiology And Chronic Health Evaluation
ASA	American Society of Anesthesiology
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
eCRF	Electronic Case Report Form
EPIS-AKI	Epidemiology of Surgical-induced Acute Kidney Injury
FPFV	First patient first visit
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IMC	Intermediate Care
ISF	Investigator Site File
KDIGO	Kidney Disease: Improving Global Outcomes
LPFV	Last patient first visit
LPLV	Last patient last visit
MAKE	Major Adverse Kidney Events
OD	operative day
PACU	Post Anesthesia Care Unit
POD	postoperative day
RRT	Renal Replacement Therapy
SOFA	Sequential Organ Failure Assessment
UO	Urine Output

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2 Introduction

Acute kidney injury (AKI) is a severe clinical complication with increasing incidence (1) and it is associated with adverse short- and long-term outcomes resulting in a major health care burden worldwide. (2,3) AKI is now being considered as independent risk factor for adverse outcomes. (4-7) Since the introduction of consensus classification systems (Risk Injury Failure Loss and End stage [RIFLE] (8), Acute Kidney Injury Network [AKIN] (9), and the Kidney Disease: Improving Global Outcomes [KDIGO] criteria (10)), 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. (11) 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.

2.1 Background

Many analyses have been performed to evaluate the epidemiology of AKI in different surgical settings (**Table 1**). Since the introduction of the different classification systems, results were thought to become comparable. Most of the trials, though, are retrospective and therefore limited due to the nature of the trial design. Additionally, AKI is mainly diagnosed by the serum creatinine criterion thereby disregarding urine output. However, it has been recently shown in a general ICU patient cohort that the urine criterion is important for diagnosing and staging AKI. (12) Consequently, the exact incidence of AKI after extended surgical procedures is currently unknown.

Table 1 Summary of epidemiologic studies of surgical associated AKI.

Study	Year	Design	Population (n)	Definition	Incidence (%)
AKI after major abdominal surgery					
Armstrong et al. (13)	2009	Retrospective	Hepatobiliary (1535)	AKIN/ SCr	5.1
Bell et al. (14)	2014	Interrupted time series analysis	Major abdominal/GI (3271)	KDIGO/ SCr	9.8
Bihorac et al. (15)	2009	Retrospective	Major abdominal/GI (2337)	RIFLE/ SCr	39.3*
Biteker et al. (16)	2014	Prospective	Major abdominal/GI (510)	RIFLE/ SCr and GFR	7.1*
Brunelli et al. (17)	2012	Retrospective	Major abdominal/GI (1912)	AKIN/ SCr	26.8*
Causey et al. (18)	2011	Retrospective	Colorectal (339)	RIFLE/ SCr	11.8
Chao et al. (19)	2013	Retrospective	Major abdominal/GI (1972)	AKIN/ SCr	20.2
Cho et al. (20)	2014	Prospective	Hepatobiliary (111)	AKIN/ SCr and UO	1.8*

Coca et al. (21)	2010	Retrospective	Major abdominal/GI (11460)	AKIN/ SCr	18.9*
Study	**Year**	**Design**	**Population (n)**	**Definition**	**Incidence (%)**
AKI after major abdominal surgery					
Correa-Gallego et al. (22)	2015	Retrospective	Hepatobiliary (2116)	RIFLE/ GFR	15.9
Grams et al. (23)	2016	Retrospective	Major abdominal/GI (44597)	KDIGO/ SCr	13.2*
Kambakamba et al. (24)	2015	Retrospective	Hepatobiliary (829)	AKIN/ SCr	8.2
Kim et al. (25)	2013	Retrospective	GI (4718)	KDIGO/ SCr	14.4
Lee et al. (26)	2014	Retrospective	GI (595)	AKIN/ SCr	35.3
Slankamenac et al. (27)	2009	Retrospective	Hepatobiliary (569)	RIFLE/ SCr and UO	15.1
Sun et al. (28)	2015	Retrospective	Major abdominal/GI (1345)	AKIN/ SCr	9.7
Sun et al. (28)	2015	Retrospective	Major gynaecological (865)	AKIN/ SCr	3.1
Teixeira et al. (29)	2014	Retrospective	Major abdominal/GI (450)	KDIGO/ SCr and UO	22.4
Tomozawa et al. (30)	2015	Retrospective	Hepatobiliary (642)	AKIN/ SCr	12.2
Vaught et al. (31)	2014	Retrospective	Major gynaecological (2341)	RIFLE/ SCr	12.6*
AKI after cardiac surgery (extract from latest studies)					
Bernardi et al. (32)	2016	Database analysis	CABG (with or without CPB) (8024)	KDIGO/ SCr	14.7*
Kim et al. (33)	2015	Retrospective	OPCAB (783)	KDIGO/ SCr	3.1
Kim et al. (34)	2015	Retrospective	Cardiac surgery with CPB (590)	KDIGO/ SCr	28.1
Seelhammer et al. (35)	2016	Retrospective	Cardiac surgery (with and without CPB) (4022)	SCr/ GFR	25.6
Xu et al.	2016	Prospective	Cardiac surgery (with and without CPB) (3245)	KDIGO/ SCr and UO	39.9*
AKI after surgery					
Hoste et al. (36)	2015	Prospective	All surgeries (740)	KDIGO/ SCr and UO	53.2

Abbreviations: AKIN, Acute Kidney Injury Network; CABG, Coronary artery bypass graft; CPB, cardiopulmonary bypass; GFR, glomerular filtration rate; GI, gastrointestinal; KDIGO, Kidney Disease: Improving Global Outcomes; OPCAB, Off-pump coronary artery bypass graft; RIFLE, Risk Injury Failure, Loss and End-stage; SCr, serum creatinine; UO, urine output
* Patients with chronic kidney disease excluded

After abdominal surgery, the occurrence rate of AKI ranges from 1.8-39.3%. Recent studies on the incidence of AKI after cardiac surgery demonstrate a range in the AKI incidence from 3.1% to 39.9% (**Table 1**). Hoste et al., though, recently performed a large prospective observational multinational trial including 1802 critically ill (surgical as well as non-surgical) patients in 139 ICUs worldwide to evaluate the epidemiology of AKI. Focusing on surgical patients (n=740), the incidence of AKI according to the KDIGO criteria was 53.2% indicating a considerably higher occurrence when using the latest consensus definition and a standardized data collection instrument. (36)

2.2 Rationale

The epidemiology of surgical induced AKI is currently unknown. However, recent reports on incidences of AKI indicate that every second surgical patient is affected by this complication.

Since AKI is independently associated with adverse outcomes, an exact knowledge of the occurrence is imperatively needed to enhance the awareness for this critical condition, consequently optimize patient management in order to improve patient outcome. Moreover, it has a high impact on health policy and the results are urgently needed for designing new pre-emptive and therapeutic trials, which is the main goal of the RAPNetwork (Renoprotective Network) supported by the European Society of Anesthesiology (Initiator: Univ.-Prof. Dr. med. Alexander Zarbock).

In conclusion, the goal of the EPIS-AKI trial is to gain an exact knowledge on the incidence of AKI in patients undergoing extended surgical procedures in general and in different surgical disciplines. We seek to include patients who are admitted to an observational unit such as ICU or high dependency unit to adequately address both criteria of the KDIGO definition since the assessment of urine output requires a Foley catheter. Based on the high number of included patients, we will use the data to generate new risk scores for surgical patients and for different surgical subpopulations.

3 Objectives and Endpoints

3.1 Objectives

3.1.1 Primary Objective

The primary objective of the EPIS-AKI trial is to prospectively evaluate the epidemiology of AKI within 72 h after extended surgical procedures (≥ 2 h) that require ICU, IMC or PACU admission using the latest consensus definition for AKI according the KDIGO criteria (**Table 2**).

Table 2 KDIGO criteria for the diagnosis of AKI

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 ≥ 12 h
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		

3.1.2 Secondary Objectives

The secondary objectives include ICU and hospital outcome measures such as incidence of renal replacement therapy (RRT), mortality (ICU and hospital) as well as the length of stay (ICU and hospital) and $MAKE_{90}$ (major adverse kidney events at day 90 (37)).

Additionally, we also aim to test the hypothesis that preoperative factors contribute to AKI especially chronological age, frailty and anemia.

Moreover, we will explore the relationship between selected intraoperative factors focusing on the nature of surgery (type, duration, planned vs. emergency) and anesthetic components centered around intraoperative hypotension and vasoplegia) and postoperative AKI.

Finally, in a subset of patients we will link biomarker evolution and the development of surgically induced AKI.

3.1.3 Primary Endpoint

The primary endpoint is defined as the occurrence of AKI within 72h after major surgery according to the KDIGO criteria (**Table 2**).

3.1.4 Secondary Endpoints

Secondary endpoints include:

- Effect of preoperative risk factors on the incidence of post–operative AKI
- Effect of predetermined intraoperative factors on the incidence of post–operative AKI
- Biomarkers of AKI (urine for this endpoint will be collected in some centers)
- Outcomes:
    - Use of renal replacement therapy
    - Length of ICU stay
    - Length of hospital stay
- Survival
    - ICU mortality
    - Hospital mortality
- $MAKE_{90}$ (major adverse kidney events at day 90): combined endpoint consisting of
    - mortality
    - renal replacement therapy
    - persistent renal dysfunction defined as serum-creatinine ≥ 1.5 times as compared to baseline serum-creatinine

4 Study Design

The EPIS-AKI trial is an international, prospective, observational, multi-center, cross-sectional cohort study including 10,000 patients undergoing extended surgical procedures.

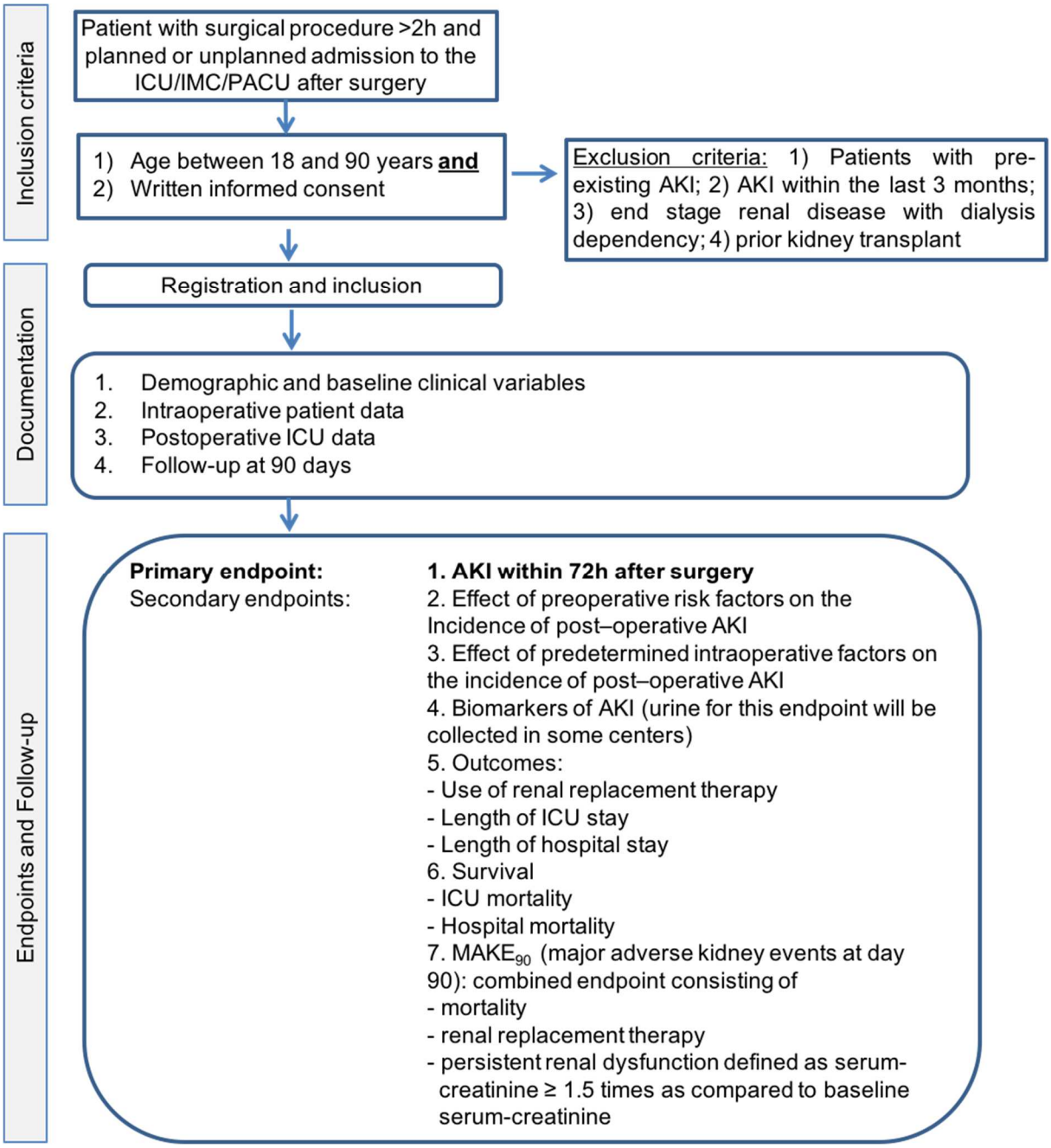

Figure 1: EPIS-AKI Trial Workflow.

5 Study Sites and Study Population

5.1 Study Site Selection

The study will be performed as a prospective epidemiologic multilateral multicenter trial in Europe and the USA. The Department of Anesthesiology, Intensive Care and Pain Medicine at the University Hospital of Muenster will serve as coordinating center and has a lot of experience with randomized-controlled trials. The study team consists of experienced investigators and study nurses. Further qualified trial sites will 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.

5.2 Study Population

5.2.1 Inclusion Criteria

1. Age ≥ 18 years
2. Major elective or emergency surgery procedures with a duration of at least 2 h
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.

5.2.2 Exclusion Criteria

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

5.2.3 Distribution of Gender in the Study Population

We expect a gender distribution of (male: female) 50:50. No patient will be excluded from the study on the basis of gender. Gender will be used for covariate adjustment in a multivariate data analysis. A subgroup analysis will be performed according to gender.

6 Patient Inclusion and Registration

Prior to being included into the study, patients have to complete screening and met all designated inclusion criterions (age ≥ 18 years, major surgeries with a duration of at least 2 h (planned postoperative admission ICU, informed consent), and no exclusion criteria.
A subject identification code will be assigned to the patient with the following format:

EP_XX – YY – ZZZZ

XX represents the country. YY represents the center number and ZZZZ is a continuously increasing number which is uniquely allocated to each patient recruited at the respective study site.

7 Study procedures

Since this is an observational trial, no specific study related procedures are planned. All patients will be treated according to the standards of each center.

7.1 Urine Collection

In some of the participating centers, urine samples will be collected immediately after surgery to analyze biomarkers for the evolution of surgery induced AKI. These samples will be centrifuged immediately at 5000g for 5 min and stored at -80°C. For storage, the same identification code will be used as previously described (chapter 6).

7.2 Data Collection

We will abstract all clinical variables from the medical record (**Table 2**). Demographic and baseline clinical variables will be collected. Data collection will be performed pseudonymously and the patient´s name will not appear on any case report form or in any other clinical trial document. All collected data will be kept confidential. This study will be performed in accordance with the revision of the Declaration of Helsinki (2008). ICH-GCP will be strictly adhered to. The points for adhering to the STROBE statement have been respected in the design of the study.

8 Screening, and Documentation Plan

8.1 Screening

All patients meeting the inclusion criteria will be documented in a screening log.
If a patient fulfills all inclusion criteria and does not have any exclusion criteria ("eligible"), it should be documented in the screening log whether inclusion in the clinical trial has occurred. If the patient is not included in the clinical trial, the cause should be documented in the screening log.

A patient must provide written consent before undergoing any protocol-required assessments.

<u>T1 - Screening (premedication visit)</u>

- Verification of in-/exclusion criteria, including informed consent

8.2 Documentation Plan

<u>T1 - Baseline</u>

- Demographic data, concomitant medication
- Admission diagnosis, source of admission

<u>T2 - Day of operation</u>
Intraoperative data

- Surgical procedure
    - type, priority, duration, blood loss, transfusion, episodes of hypotension (MAP < 55mmHg for more than 5 Minutes), fluid intake, urine output, use of colloids, use of nephrotoxic agents, use of vasopressors, if cardiac: CPB/ aortic X-clamp duration, use of contrast media in the week prior to surgery

<u>T3 - 1st to 3rd post-operative morning</u>
Postoperative data

- APACHE, SAPS, fluid status (fluid balance, fluid intake, urine output, blood loss, transfusion), postoperative complication (sepsis, hemodynamic instability)
- AKI
    - Stage, Definition (urine versus creatinine), RRT, use of nephrotoxic drugs
- Concomitant Medication
    - Pressors, amphotericin, aminoglycosides, cyclosporine, tacrolimus, radiocontrast agents, diuretics

T4 (day 90 after surgery ±7 days)

- Mortality
- Length of primary stay (ICU, Hospital)
- Serum-creatinine
- Renal recovery
- Number of days of RRT/RRT dependence
- MAKE = major adverse kidney events

Table 3 Visit plan

Visit	**S**	**B**	**OD**	**Postop. days 1-3**	**Day 90**
	T1		**T2**	**T3**	**T4**
Inclusion and Exclusion criteria	X				
Demography Age, Gender, Race, Comorbidities (CKD, hypertension, diabetes, COPD), Medication (Diuretics, NSAIDs, ACEi/ARBs, Statins), ASA status, weight; BMI		X			
Admission diagnosis, source of admission		X			
Intraoperative data Surgical procedure (type, priority, duration, episodes of hypotension (MAP < 55mmHg for more than 5 minutes), blood loss, transfusion, fluid intake, urine output, use of colloids, use of nephrotoxic agents, use of vasopressors), if cardiac: CPB/ aortic X-clamp duration			X		
Postoperative data APACHE, SAPS, fluid status (fluid balance, fluid intake, urine output, blood loss, transfusion), postoperative complication (sepsis, hemodynamic instability)				X	
AKI Stage, Definition, RRT, use of nephrotoxic drugs				X	
Concomitant Medication Pressors, amphotericin, aminoglycosides, cyclosporine, tacrolimus, radiocontrast 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; ACEi, angiotensin converting enzyme inhibitors; AKI, Acute Kidney Injury; APACHE, Acute Physiology And Chronic Health Evaluation; ARBs, angiotensin receptor blockers; ASA, American Society of Anesthesiology; CPB, cardiopulmonary bypass; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NSAID, non steroidal anti-inflammatory drugs; RRT, Renal Replacement Therapy; SAPS, Simplified Acute Physiology Score

9 Statistics

9.1 Power analysis

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.[39] Depending on the type of surgery, AKI incidences of 1.8-39.3% are reported in existing literature (**Table 1**, data from abdominal surgeries were used for estimation). 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 (e.g., type/length of surgery, use of blood products, morbidities). 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).

9.2 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.

Data will be summarized by standard descriptive statistical measures. Normally distributed variables will be reported as mean and standard deviation and non-normally distributed variables as median and lower and upper quartile. Categorical variables will be expressed as proportion. 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, Chi-square tests or Fisher’s exact tests will be used appropriate to the distributional characteristics of the endpoint.

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. (38) To detect factors that might be correlated to the occurrence of AKI, exploratory uni- and multivariable logistic regression analyses will be conducted. For secondary outcomes, point estimates and corresponding 95% confidence intervals will be derived. In further exploratory analyses, the association between secondary outcomes and the type of surgery will be analyzed using appropriate statistical methods. Additionally, subgroup analyses will be performed based on the type of surgery to identify variables that are correlated with the occurrence of AKI in each group.

A two-sided p-value of < 0.05 will be considered as statistically significant.

10 Documentation, Data Management, Archiving

10.1 Patient Identification List

All subject data will be collected in a pseudonymized form. Every trial subject can be identified by a unique subject identification code consisting of a two digit country code, a hyphen, two digit center code, a hyphen and four digit numbers. A confidential subject identification list which links the patients’ names with the subject identification code will be stored in the investigator site file at each center.

10.2 Source Data / Source documents

Source data are, within the meaning of the ICH E6 Guideline, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source data will be documented in various source documents (e.g. hospital records, doctor's report, subjects' diaries or evaluation checklists, x-rays) and then entered into the electronic Case Report Form (eCRF).

10.3 Recording of Data / Case Report Form (CRF)

Data will be recorded paper based on CRFs. The CRFs will be provided as multipart forms using non-carbon copy paper and the designated members of the investigator`s staff will complete all CRFs as soon as possible. The original CRFs will be used for further data processing. Copies will be filed at the study site.

The CRFs will be provided as PDF documents by the coordinating study site and will be printed in the study site with pre-populated subject identification code in the header of each CRF page. The original CRFs will be used for further data processing. Copies will be filed at the study site.

Entries must be made with a black ballpoint pen and must be legible. Pencils and correction fluids may not be used. If corrections are necessary, they will be entered by an authorized member of the investigator's staff in the following manner: The wrong entry will be crossed out, but it must remain legible, and the correct entry will be placed next to it. Corrections will be initialed and dated by the person responsible for correcting the entry.

All CRF pages will be reviewed for completeness and correctness by a study team physician. He takes on responsibility for the recorded data by signing and dating..

10.4 Data Management

Prior to entering data into the database, an in-house review will be performed by the study coordinator to clarify missing or non-plausible data by sending queries to the study site.

The original CRFs will be sent to the coordinating study site. Double data entry will be performed by two different persons with consecutive data comparison and reconciliation. Thereafter, electronic data checks will be performed with regard to completeness and plausibility. In case of missing or non-plausible data, queries will be sent to the study center. The queries must be resolved by authorized members of the investigator`s staff in the respective study center in a timely manner. Query responses will be entered into the database and will be stored together with the original CRF.

After completion of data entry and data processing, the database will be locked and the data will be exported for statistical analysis.

10.5 Archiving

After the end of the trial, the originals of all trial-specific documents (Trial Master File) including originals of the CRFs must be stored by the responsible institution for at least 10 years. Furthermore, the investigator stores the ISF (Investigator Site File) including copies of the CRFs for the time period given above.

11 Ethical and Regulatory Requirements

11.1 Declaration of Helsinki and Legal Requirements

The study will be conducted in compliance with the declaration of Helsinki (current version, October 2013, Fortaleza), the current legal provisions regarding data protection, and the principals of Good Clinical Practice.

The present study will not be started before the ethics committee has given a favorable opinion. In case of substantial amendments, a new application will be submitted to the ethics committee. Changes will not be implemented unless the competent ethics committee has given a favorable opinion.

Issues, which always require a favorable opinion of the ethics committee are for example:

- change of the investigator or his deputy,
- changes in any documents addressed to study participants or in any study information addressed to potential study participants.

11.2 Ethical consideration

The study protocol, patient information and informed consent will be submitted to the ethics committee of the University of Muenster for appraisal. Once the protocol is approved, the documents will be submitted to the ethics committee of all participating centers for appraisal. The study will be directly started in those centers, in which the local ethics committee has approved the study.

All translation and Adaptation of the patient information and informed consent should be sent to the coordinating investigator.

Patients will be approached for participation. All patients will receive standard perioperative care. None of the patients will be exposed to additional risks. Participation in this trial will be voluntary and written informed consent will be obtained from all participating patients.

11.3 Patient Information and Informed Consent

Prior to inclusion into the study, the investigator informs each patient about nature, significance and implications of the study as well as about the patient's right to withdraw from study participation at any time point without any resulting disadvantage. Additionally, patients are handed out the patient information sheet and the informed consent form which are provided for this study. Patient consent in study participation must be given in writing. Before informed consent is requested, patients are left sufficient time for consideration. They are provided the opportunity for clarification of any study issues.

The informed consent form is dated and signed by the patient and by the investigator. The originally signed informed consent form is archived in the investigator site file. A copy of the signed informed consent form (or a second original) is handed over to the patient together with a copy of the patient information sheet.

If the patient is unable to write, in exceptional cases, instead of the written consent required, oral consent in the presence of at least one witness, who was also included when the patient was being informed may be given. The witness may not be a member of the investigating team. The orally given consent has to be documented in writing, dated and signed by the witness. In case of an emergency surgery, if the patient is unable to provide informed consent, local regulations provided by the corresponding local ethics committee with respect to patients without capacity to consent, have to be followed. In detail, at the University of Muenster a legally authorized representative may provide written informed consent or a family

member may be asked for patients presumed will to participate in this trial. In case the legally authorized representative/ family member is not available, the investigator has to follow the legal requirements of the local ethics committee. Independent of the opt-in process of the corresponding ethics committee, informed consent of the patient or legally authorized representative needs be obtained as soon as the patient's condition allows it.

In case of any study issue which requires a change of the patient information sheet, patients already included into the study must, if relevant to them, be informed about these issues orally and in writing and their written consent in further study participation must be obtained.

11.4 Adherence to the Protocol

The investigator must adhere to the protocol as detailed in this document. Substantial changes to the protocol will require a written favorable opinion from the corresponding ethics committee prior to implementation. This does not apply when the modification is needed to eliminate an immediate hazard to patients. Any deviations from the protocol must be fully documented in the source documentation and recorded and explained in the CRF (if applicable).

11.5 Data Protection

This study will be performed in compliance with the applicable data protection laws. Study personnel will handle all patient data in a strictly confidential way. To prevent the identification of a person to whom study data belong, study data will be pseudonymized by means of the patient identification number. If patient documents (e.g., examination results) are transferred to an institution outside the study site, copies will be used on which the patient's name and initials are obscured and the patient identification number is indicated.

12 Publication Policy

Any publication will take account of the 'International Committee of Medical Journal Editors' (ICMJE).

Any published data will observe data protection legislation covering the trial subject and investigators.

After submitting grant proposal, recruitment of patients, data acquisition, cleaning and analysis of the data obtained, authorship will be distributed according to differences in investment. Each participating center including at least 30 patients can designate one collaborator that will be mentioned in the publication. Furthermore, for each additional 50 patients included, one more collaborator can be designated. These collaborators will be listed as Collaborators in the manuscript and will be traceable via PubMed. Also, on request, centers will be allowed to use their data. Proposals for substudies and secondary analyses can be submitted to the Steering Committee that will need to approve those analyses and that will revise all papers originating from final analysis prior to submission. Furthermore, the Sponsor of the study (ESA CTN) can use anonymized data for internal analyses and educational purposes.

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14 Appendices

14.1 Steering committee

Name	Center	Country
Alexander Zarbock	Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Münster	Germany
Thomas Rimmelé	Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm	France
Max Bell	Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm	Sweden
Nandor Marczin	Section of Anaesthesia, Pain Medicine and Intensive Care, Imperial College, London	England
Stefano Romagnoli	Department of Anesthesia and Intensive Care, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Florence	Italy
Idit Matot	Division of Anesthesiology and Intensive Care and Pain Medicine, Tel Aviv Sourasky Medical Center, Sackler School of Medicine, Tel Aviv	Israel