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EPIdemiology of Surgery-Associated Acute Kidney Injury (EPIS-AKI): study protocol for a multicentre, observational trial

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To cite: Weiss R, Saadat-Gilani K, Kerschke L, *et al*. EPIdemiology of Surgery-Associated Acute Kidney Injury (EPIS-AKI): study protocol for a multicentre, observational trial. *BMJ Open* 2021;**11**:e055705. doi:10.1136/bmjopen-2021-055705

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-055705).

Received 21 July 2021
Accepted 26 November 2021

Check for updates

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ABSTRACT

Introduction More than 300 million surgical procedures are performed each year. Acute kidney injury (AKI) is a common complication after major surgery and is associated with adverse short-term and long-term outcomes. However, there is a large variation in the incidence of reported AKI rates. The establishment of an accurate epidemiology of surgery-associated AKI is important for healthcare policy, quality initiatives, clinical trials, as well as for improving guidelines. The objective of the Epidemiology of Surgery-associated Acute Kidney Injury (EPIS-AKI) trial is to prospectively evaluate the epidemiology of AKI after major surgery using the latest Kidney Disease: Improving Global Outcomes (KDIGO) consensus definition of AKI.

Methods and analysis EPIS-AKI is an international prospective, observational, multicentre cohort study including 10 000 patients undergoing major surgery who are subsequently admitted to the ICU or a similar high dependency unit. The primary endpoint is the incidence of AKI within 72 hours after surgery according to the KDIGO criteria. Secondary endpoints include use of renal replacement therapy (RRT), mortality during ICU and hospital stay, length of ICU and hospital stay and major adverse kidney events (combined endpoint consisting of persistent renal dysfunction, RRT and mortality) at day 90. Further, we will evaluate preoperative and intraoperative risk factors affecting the incidence of postoperative AKI. In an add-on analysis, we will assess urinary biomarkers for early detection of AKI.

Ethics and dissemination EPIS-AKI has been approved by the leading Ethics Committee of the Medical Council North Rhine-Westphalia, of the Westphalian Wilhelms-University Münster and the corresponding Ethics Committee at each participating site. Results will be disseminated widely and published in peer-reviewed journals, presented at conferences and used to design further AKI-related trials.

Trial registration number NCT04165369.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial will be conducted as an international prospective, observational, multicentre, cohort study investigating the epidemiology of surgery-associated acute kidney injury (AKI) according to the current Kidney Disease: Improving Global Outcomes definition of AKI.
⇒ The trial has several strengths: a large cohort of patients, an international setting with diverse continents, regions and countries participating as well as the large different types of surgeries and patients allow a universal analysis of the epidemiology of surgery-associated AKI.
⇒ An add-on study will evaluate novel biomarkers for early detection of AKI and to distinguish between transient and persistent AKI.
⇒ Given the large number of patients and participating study sites the trial is highly depending on the compliance and accuracy of the involved sites which is a limitation of the study.

INTRODUCTION

More than 300 million surgical procedures are performed each year and acute kidney injury (AKI) is a common complication after major surgery with increasing incidence.[1 2] This syndrome is associated with adverse short- and long-term outcomes, resulting in a major healthcare burden worldwide.[3–6] Although the incidence varies depending on the patient population and type of surgery, AKI is now being considered as an independent risk factor for adverse outcomes such as chronic kidney disease, chronic dialysis dependency, as well as higher mortality rates.[7–9] Although major surgery is the second most common cause of AKI, there is a large variability in the reported incidences of surgery-associated AKI.[10] After abdominal surgery, the incidence rate of AKI ranges from 1.8% to 39.3%.[11–14] Recent studies in cardiac surgery patients reported a broad range in the incidence of AKI from 3.1% to 39.9%.[15–18] After introducing a uniform definition, results were thought to become comparable. Most of the trials, though, are retrospective and therefore their message is limited due to the nature of

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the trial design. Additionally, AKI is mainly diagnosed by the serum creatinine criterion, whereas the urine output (UO) criterion is often disregarded. However, it has been shown in intensive care unit (ICU) patients as well as in cardiac surgery patients that the urine criterion is important for diagnosing and staging AKI.[19 20] As such, a retrospective cohort study including 4229 patients undergoing major non-cardiac surgery showed an increase of AKI from 8.1% to 64.0% when considering both serum creatinine and UO in contrast to serum creatinine alone.[21] Patients meeting both AKI-criteria showed significantly higher mortality rates and need for renal replacement as compared with patients with AKI solely or predominantly diagnosed by one criterion.[19] Furthermore, it could be demonstrated that patients diagnosed with AKI based on UO had significantly longer ICU and hospital stays as compared with those patients with to serum creatinine-based AKI.[22]

Though research regarding AKI is performed nearly worldwide, the vast majority of data derives from studies conducted in high developed countries making it difficult to compare their results to data from low-income/middle-income countries. Low-income and middle-income countries often neither have the resources nor infrastructure to conduct large prospective trials. Furthermore, data quality and study design are crucial points as most of the studies are conducted retrospectively, used different classifications and lack standardisation. A meta-analysis from 2013 included 312 studies from 2004 to 2012 of which only 154 adopted a Kidney Disease: Improving Global Outcomes (KDIGO) equivalent AKI definition. This diversity underlines the difficulty. The pooled overall AKI rate in critically ill adult patients according to KDIGO was 31.7%. However, the incidence in different regions varied noteworthily: Northern Europe 14.7%, Western Europe 20.1%, Southern Europe 31.5%, Northern America 24.5%, Southern America 29.6%, Western Asia 16,7%, Eastern Asia 14.7%. While the vast majority of included patients derived from high-income countries (ie, approximately 1.9 million from North America and Europe), only 3000 subjects from South America could be included. Nevertheless it could be demonstrated that the AKI-associated mortality was inversely related to income of countries and percentage of gross domestic product spent on total health expenditure.[23] Another systemic review and meta-analysis from 2020 considering critically ill patients presented similar results. Although AKI incidences were similar between developed (38 studies, 39.3%) and developing countries (18 studies, 35.1%), patients in the latter had worse outcomes regarding ICU stay, need for dialysis and mortality.[24]

Considering recent studies from Germany and elsewhere, 57%–75.6% of AKI cases go undetected, undiagnosed and/or undocumented.[25–27] This demonstrates that AKI seems not to receive adequate recognition or attention even in high developed countries. Given the fact that many regions in low-income/middle-income countries additionally suffer from lower living conditions, limited capabilities due to poverty, lack of education and limited access to healthcare and equipment, such as electronic health data and patient files,[28–32] the numbers of AKI cases and AKI-associated complications, such as mortality, are likely underestimated.

Consequently, the exact incidence of AKI after major surgery is currently unknown.

Epidemiology of Surgery-associated Acute Kidney Injury (EPIS-AKI) is designed to prospectively evaluate the global epidemiology of AKI after major surgery using the latest KDIGO consensus definition. Further, the trial aims at assessing preoperative and intraoperative risk associated with surgery-associated AKI.

Objectives and aims

Aim 1

To prospectively evaluate the epidemiology of AKI within 72 hours (defined by the KDIGO criteria) after major surgery that requires admission to an ICU or a similar high dependency unit.

Aim 2

To assess preoperative and intraoperative risk factors for the development of surgery-associated AKI and evaluate modifiable risk factors.

Aim 3

We aim to evaluate and validate novel biomarkers for early detection of surgery-associated AKI and to differentiate between transient (<48 hours) and persistent (>48 hours) AKI in an add-on analysis.

METHODS AND ANALYSIS

Design and setting

The EPIS-AKI trial is an international prospective, observational, multicentre, cohort study conducted at more than 90 centres across the world (online supplemental table 1). The final version of the participating centres will be attached to the final report of the clinical trial.

The protocol follows the principles of 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) and the Declaration of Helsinki (version Fortaleza 2013). The flow chart is summarised in figure 1.

Patient and public involvement

EPIS-AKI is an investigator initiated observational trial that was designed by investigators of the Department for Anesthesiology, Intensive Care and Pain Medicine at the University Hospital Münster. No other institutions nor patients were involved in the trial design. However, patients will be asked for their participation in this trial to collect corresponding data (see the Consent process section). Furthermore, national coordinators and different societies (box 1) helped to promote the study in their respective countries and to translate prepared documents into several languages. Especially, the European Society of Anesthesiology and Intensive Care provided support in recruiting national coordinators. Study results

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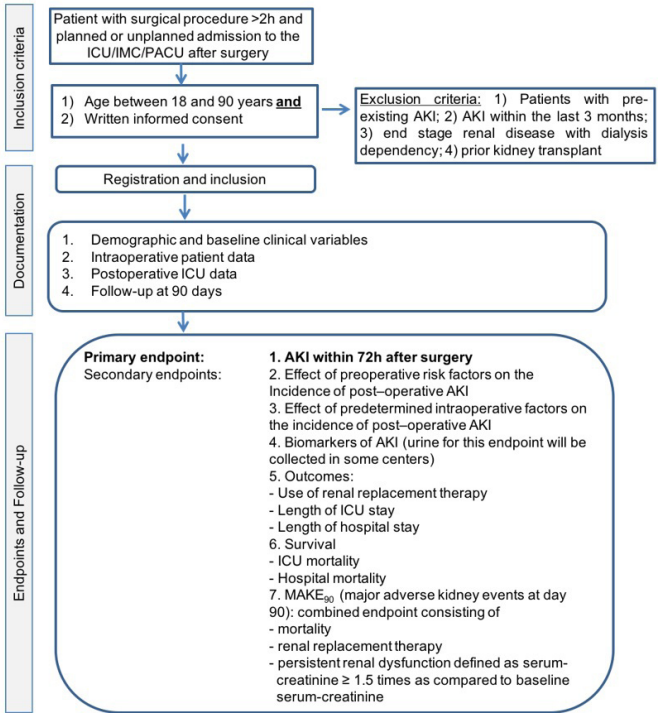


Figure 1 EPIS-AKI Trial Workflow Research coordinators will screen patients for eligibility on a daily basis and then ask patients for study participation. After surgery, inclusion/exclusion criteria will be rechecked and if still eligible (especially duration of surgery ≥2 hours, admission to ICU or similar), patients will be enrolled and included in the trial. All subjects will be treated according to the standards of the local centres. Patients will be monitored closely for the first postoperative 72 hours during their stay on a high dependency unit. In addition, in selected study sites urine samples will be collected directly from the routinely inserted urine catheter immediately after surgery. AKI, acute kidney injury; EPIS-AKI, Epidemiology of Surgery-associated Acute Kidney Injury; ICU, intensive care unit, PACU; post anesthesia care unit, MAKE90; major adverse kidney events at day 90.

will be published in a peer-reviewed journal. At request, patients and/or their representatives will be informed about the results of the trial.

Participants

All adult patients (age ≥18 years) undergoing major surgery for at least 2 hours and who are admitted to an ICU or a similar high dependency unit will be asked for study participation and will be included in this trial. Subjects who fulfil one of the exclusion criteria ((1) pre-existing AKI, (2) AKI within last 3 months, (3) end-stage renal disease with dialysis dependency and (4) kidney transplant) will not be included. Two major inclusion criteria were chosen (major surgery defined as surgery >2 hours plus a subsequent ICU admission) to exclude patients undergoing minor surgeries on the one hand and to exclude revision surgeries of critically ill patients on the other hand. The combination of the duration of surgery and the subsequent admission to an ICU is the important component to only include patients at risk. All surgical patients independent of surgical specialty may be considered (including elective and emergency surgery) as long as patients fulfil all the inclusion and none of the exclusion criteria. Due to the nature of the surgical procedures, some specialties will be more present than others. Therefore, subgroup analyses will be performed to focus on the incidence of AKI in different specialties. In addition, in selected centres, urine samples will be collected immediately after surgery from routinely placed urinary catheters.

We expect an evenly distributed sex ratio. No patient will be excluded from the study based on sex, ethnicity or religion. Sex will be used for covariate adjustment in a multivariate data analysis.

Box 1 Supporting societies

Name of participating societies
Colegio Mexicano de Medicina Crítica
Colombian Association of Surgery
Czech Society of Anesthesiology and Intensive Care
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin
European Society of Anaesthesiology and Intensive Care
Korean Society of Anesthesiologists
Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva
Société Française d'Anesthésie et de Réanimation
South African Society of Anaesthesiologists
Spanish Perioperative Audit and Research Network
Turkish Anaesthesiology and Reanimation Society

Consent process

Country-specific requirements, including ethics approval and/or study registration at local authorities, have to be fulfilled prior to starting patient enrolment. All patients will be approached and informed before participation, usually during their anaesthesia previsit, and will be asked to give written informed consent according to local regulations. This is a two-step process. After surgery has been performed, patients have to be finally proven for eligibility according to study criteria. Participation in this trial is voluntary. All patients will receive standard perioperative care. None of the patients is exposed to additional risks. All data will be kept confidential and stored in a pseudonymised form. The patient has the right to withdraw from the study at any time without providing a reason and without medical treatment being affected.

Observation

All included patients will be treated according to the standard of care at each participating site. Patients will be closely monitored for the first 72 hours after surgery and during ICU stay. This time period will give the possibility to distinguish between rapid recovery (<48 hours) and persistent AKI (>48 hours). Data regarding routine clinical management will be collected, especially data regarding demographics, comorbidities, type of surgical procedure, complications and administered medication (table 1). Furthermore, AKI stages will be documented according to KDIGO criteria and assessed by serum-creatinine (SCr) and UO. Once the inlaying urine

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Table 1 Collected data and information

Patient data	Medical history	Preoperative medication	Intraoperative data	Postoperative data	Outcomes	Follow-up
Age	Hypertension	Aspirin (ASA/ASS)	Surgical specialty	Start/end of documentation	Date of ICU discharge	Date of follow-up
Gender	Atrial fibrillation/flutter	ACE inhibitors or ARBs	Type of surgery	APACHE II score	Date of hospital discharge	Patient condition
Ethnicity	Previous myocardial infarction	Beta-blockers	Surgical procedure as listed by ICHI	SAPS score	Condition of hospital discharge (alive/death)	RRT
Height	Congestive heart failure according to NYHA classification	Diuretics	Duration of surgery	Fluid intake (crystalloids, colloids, blood products)	Date of death	SCr level
Weight	Diabetes	NSAIDs (except ASA/ASS)	Total time of cardiopulmonary bypass	Fluid output (total blood loss, urinary output)	SCr level at ICU discharge and hospital discharge	
SCr baseline	Chronic obstructive disease	Statins	Total X-Clamp time	Removal of urine catheter	RRT at hospital discharge	
Date of hospital admission	Chronic kidney disease (Stages)	Vasopressors	Fluid intake (crystalloids, colloids, blood products)	Application of vasopressors	Days of RRT in hospital	
Date of surgery	Peripheral vascular disease	Use of contrast media on week prior to surgery	Fluid output (total blood loss, urinary output)	Application of nephrotoxic agents		
Date of ICU admission	Previous stroke		Episodes of hypotension (MAP <55 mm Hg for more than 5 min)	Application of diuretics		
	ASA Score		Application of vasopressors	Postoperative complications		
			Application of nephrotoxic agents	AKI according to KDIGO classification		
			Application of diuretics	Severity of AKI		
			Intraoperative complications	Occurence of AKI		
				Duration of AKI (transient <48 hour vs Persistent >48 hour)		
				Diagnosis (worst case AKI) via SCr, UO, both		
				RRT		
				Start of RRT		
				Modality of RRT at initiation		
				Indication for RRT		

ACE, Angiotensin converting enzyme inhibitors; AKI, acute kidney injury; APACHE, Acute physiology and chronic health evaluation; ARBs, angiotensin-receptor blockers; ASA, American Society of Anesthesiologists; ASA/ASS, acetylsalicylic acid; ICHI, International classification of health interventions; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, Mean arterial pressure; NSAID, Nonsteroidal anti-inflammatory drugs; NYHA, New York Heart Association; RRT, renal replacement therapy; RRT, Renal replacement therapy; SAPS, Simplified acute physiology score; SCr, Serum-creatinine; UO, Urine output; UO, urine output .

catheter is removed, the urine criterion will no longer be used to diagnose and stage an AKI.

After 90 days, a follow-up will be performed by telephone call contacting the patient or the general practitioner.

Outcomes

The primary outcome of the trial is the incidence of AKI within the first 72 hours after surgery according to KDIGO criteria (including the distribution of stages):

Kidney Disease: Improving Global Outcomes 1

SCr: ≥0.3 mg/dL (26.52 µmol/L) within 48 hours or 1.5–1.9 times baseline within 7 days.

UO:<0.5 mL/kg/hour for 6–12 hours.

Kidney Disease: Improving Global Outcomes 2

SCr: 2–2.9 times baseline within 7 days.

UO:<0.5 mL/kg/hour for ≥12 hours.

Kidney Disease: Improving Global Outcomes 3

SCr:≥4.0 mg/dL (353.60 µmol/L) or ≥3 times baseline within 7 days.

UO:<0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours.

The secondary outcomes include:

- Use of renal replacement therapy.
- Length of ICU stay
- Length of hospital stay.
- Transient (<48 hours) vs persistent (>48 hours) AKI.

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- Renal recovery (SCr value within the <1.5 times range of the baseline SCr at day 90).
- Survival
  - ICU mortality.
  - Hospital mortality.
- Major adverse kidney events at day 90 ($MAKE_{90}$): combined endpoint consisting of
  - Mortality.
  - Renal replacement therapy.
  - Persistent renal dysfunction defined as SCr≥1.5 times as compared with baseline SCr.

Furthermore, secondary analyses will be performed for

- Effect of preoperative risk factors on the incidence of postoperative AKI.
- Effect of predetermined intraoperative factors on the incidence of postoperative AKI.
- Predictive value of different AKI biomarkers (urine for this endpoint will be collected in some centres).

Data collection

Clinical data will be collected from the patient charts of each participating site in an electronic case report form (eCRF) (Research Electronic Data Capture, V.10.6.22, respectively up-to-date version, Vanderbilt University) in a pseudonymised form. Patient identifiable information will not be available for data-analysis. Investigators will be given secure login credentials (username and password). Data transmission and storage of web-based information is encrypted and will be stored and backed up at the Westfalian Wilhelms University of Münster.

Data quality

Each study team will be instructed on how to use the data entry system and how to interpret the protocol. A frequently asked questions summary describing crucial parts of the trial is handed out to the participating sites. Furthermore, every team has to be guided by at least one local qualified doctor to ensure medical understanding. The current KDIGO criteria are also included and displayed in the eCRF to make it as easy and reliably as possible for the onsite staff to classify AKI stages.

However, each team will be provided an emergency contact number and mail address to ask for help regarding medical, technical or protocolary issues. The study organising team will offer rapid support throughout the entire study period. Furthermore, protocol and study materials are translated into common languages to facilitate processes and to avoid uncertainties. Close contact will be held especially to national coordinators as well as to each single study site on a routinely manner, enabling participants to resolve any unclarities straightforwardly, rapidly and directly with the organising study team. This will ensure collaborators are able to collect accurate data.

Sample size

Depending on the type of surgery, AKI incidences of 1.8%–39.3% are reported in existing literature.

We aim for a high quality, prospective, large-scale, multi-centre, observational trial to estimate the incidence of post-surgery AKI (primary aim) with high precision. That is, to obtain a small width of the corresponding 95% (Clopper-Pearson) CI. The width of the Clopper-Pearson CI for a proportion increases (ie, the precision decreases) the closer the incidence of surgery-associated AKI is to 50%. Assuming that the incidence of surgery-associated AKI does not exceed 40% (which is in line with the previous reported rates), we calculated the width of the CI under the worst-case scenario (ie, scenario with maximum CI width/lowest precision). This is realised, if the incidence of surgery-associated AKI is at the very top of the reported rates (ie, 40%). The precision will be as calculated, if the incidence of surgery-associated AKI is 40%, or higher, if the incidence is less than 40%. Using this approach, the width of the CI 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 surgery-associated AKI can be estimated with at least this precision.

The study also aims to detect factors that might be correlated to the occurrence of surgery-associated AKI, as for example, the type of surgery, age, country income and predefined preoperative/intraoperative factors. Therefore, further exploratory analyses such as univariable and multivariable logistic regression analyses will be conducted. Given the fact that the study does neither include interventions nor additional risks for patients but there is a relatively large number of different types of surgeries, a sample size of n=10 000 patients is reasonable to investigate the influence of this parameters on the occurrence of surgery-associated AKI in a univariable and multivariable context.

Biomarker samples

To further investigate and compare the performance of biomarkers to predict surgery-associated AKI in a clinical background urine samples are collected in selected study centres as an add-on study. We will measure common new biomarkers as tissue inhibitor of metalloproteinases 2 and insulin like growth factor binding protein 7 ([TIMP2]*[IGFBP7]), kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), fatty-acid-binding protein (FABP-1), C-C chemokine ligand 14 (CCL14) and assess whether the biomarkers can predict the development of an AKI ([TIMP2]*[IGFBP7], KIM-1, NGAL, FABP-1) or syndrome progression (CCL14). This will help to better understand biomarker kinetics, to evaluate their significance and demonstrate their relation to AKI development. Parameters will be determined by using commercially available assays prepared according to the respective manufactures protocol.

Statistical analysis

Calculations are carried out in cooperation with the local Institute of Biostatistics and Clinical Research and are intended to answer the question of the research

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project and to provide scientific evidence using statistical methods. Statistical analyses will be performed according to the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-guideline E9 'Statistical Principles for Clinical Trials' using standard statistical software.

Data will be summarised by standard descriptive statistical measures. Normally distributed variables will be reported as mean and SD and non-normally distributed variables as median and lower and upper quartile. Categorical variables will be expressed as proportion. For primary and secondary outcomes point estimates and 95% CIs will be given. Data presentation will follow the STROBE guideline.

In the primary statistical analysis, the incidence of AKI will be estimated together with the exact corresponding two-sided 95% CI according to Clopper-Pearson. The prespecified secondary outcomes will be evaluated based on descriptive statistics, point estimates and corresponding 95% CIs.

In order to evaluate the impact of factors that might be correlated to the occurrence of surgery-associated AKI, as for example, the type of surgery (ie, cardiac, orthopaedic, etc), preoperative and intraoperative factors (eg, length of surgery, use of blood products, morbidities), and country income group, univariable and multivariable logistic regression analyses will be conducted. Furthermore, the ability of novel biomarkers to predict the occurrence of surgery-associated AKI will be assessed using logistic regression analyses. Results from logistic regression analyses will be presented as ORs, corresponding 95% CIs and p values.

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, χ^2 tests or Fisher's exact tests will be used appropriate to the distributional characteristics of the endpoint.

Additionally, subgroup analyses will be performed based on the type of surgery (elective vs emergency surgery; surgical specialty).

All inferential statistics are intended to be exploratory (ie, hypothesis generating) and will be interpreted accordingly. A two-sided $p < 0.05$ will be considered as statistically noticeably.

Ethics and dissemination

EPIS-AKI has been approved by the leading Ethics Committee of the Medical Council North Rhine-Westphalia and of the Westphalian Wilhelms-University Münster (2019-424f-S) and the corresponding Ethics Committee at each participating site. The results will be presented at national as well as international conferences. The final manuscript will be published in a peer-reviewed journal and results will be used to design further AKI related studies.

CONCLUSION

The EPIS-AKI trial is a large international observational trial with the aim to investigate the epidemiology of surgery-associated AKI. Currently, there is a large variability in the reported rates of AKI after major surgery. After abdominal surgery, the incidence of AKI ranges from 1.8% to 39.3%.[11–14] Recent published studies in cardiac surgery demonstrated a range in the incidence of AKI from 3.1% to 39.9%.[15–18] In a surgical critical care setting, the incidence rate was reported to be 53.2%.[30] These variabilities are in part a result of the different definitions used for diagnosing AKI. On the other hand, there is a large number of unreported AKIs meaning that the actual incidence of AKI may even be higher.[23–26] Since AKI is independently associated with adverse outcomes, an exact knowledge of the incidence is imperatively needed to enhance the awareness for this critical syndrome and consequently optimise patient management in order to improve patient outcomes. The EPIS-AKI trial is the first large international observational trial focusing on surgery-associated AKI defined by the KDIGO criteria. The results of this trial will enhance the awareness for this critical condition and is ultimately needed to design new trials that focus on prevention and management of AKI.

Acknowledgements The authors would like to thank all participating centres and their investigators as well as assisting societies, especially the ESAIC, for their continuous support and work.

Collaborators Hichem Makhloufi, Anis Cherak,Lamine Lakhel Ghanem, Zohier Gouaglia, Dina Nasrine Guadouri, Fayrouz Naouel Hama, Mustafa Kara, Omayma Saadi (Constantine, Algeria, Constantine Centre Hospitalier Universitaire, Department of Anesthesiology and Resuscitation); Rachida Sakhraoui, Fadila Bourou, Abdelhadi Cherifi, Rahmoune Ghania Sadaoui (Alger, Algeria, Etablissement Hospitalier Spécialisé Salim Zemirli El Harrach, Department of Anesthesiology and Resuscitation); Amel Ouyahia (Sétif, Algeria, Saadna Abdenour Teaching Hospital, Department of Anesthesia); Ilhem Ouahab, Souad Bouaoud, Meriem Abdoun (Sétif, Algeria, University Hospital of Sétif, Department of Epidemiology, Department of General Surgery); Anisse Tidjane, Benali Tabeti, Nabil Boudjenan-Serradj (Oran, Algeria, University Hospital 1st November 1954, Department of General Surgery); Carlos Jose Pérez Rivera, Paulo Cabrer, Julián Corso, Juan Pablo García, Sharon Idarraga, Christopher Montoya (Bogotá, Colombia, Universidad El Bosque, Fundación Cardioinfantil, Clinical Research Coordinator, Department of General Surgery); Rafael Figueroa, Eduar Aldana, María Alejandra Torrado (Ibagué, Colombia, Avidanti Clinic Ibaqué, Department of Anesthesiology); Ke Peng, Zheng-min Ma, Yu-fan Yang, Ya-juan Zhu (Jiangsu, China, First Affiliated Hospital of Soochow University, Department of Anesthesiology); Peter Sklienka, Michal Frelich, Vojtech Jarkulis, Pavel Sevcik, Vojtech Vodicka (Ostrava, Czech Republic, University Hospital Ostrava, Department of Anesthesia and Intensive Care); Mohamed Gamal Elbahnasawy, Shady Elsalhawy, Sara Motawea, Zeinab Othman, Mohamed Sahma (Tanta, Egypt, Tanta University Faculty of Medicine, Department for Emergency medicine and traumatology); Ahmed Mahmoud Nafea (Alexandria, Egypt, Alexandria University Main Hospital, Department of Anesthesiology); Nermin Ahmed, Doaa Ali Attia (Alexandria, Egypt, Alexandria University, Medical Research Institute); Moataz Maher Emara,Mohamed Mamdouh Bonna, Mohamed Ahmed Gabr, Amany Ismail Tarbay (Mansoura, Egypt, Mansoura University, Faculty of Medicine, Liver Transplant - Gastrointestinal Surgical Center, Department of Anesthesiology and Intensive Care); Ibrahim Abdelmonaem Abdehaleem, Esraa Elsayed Mohamed, Amr Mahmoud Eldeeb (Sharkia, Egypt, Zagazig University Hospital, Department of Anesthesiology); Ahmed Mohamed Abbas, John Ashraf Magdy, Zyad Hassan Hamed, Hany Mostafa Esmaeil Osman, Mostafa Samy Abbas (Assiut, Egypt, Assiut University Hospitals, Department of Anesthesia and Intensive Care); Oliver Joannes-Boyau, Nicolas Barraud, Corentin Berthelot, Thibault Camus, Anissa Dahmi, Mylène Defaye, Sébastien Derville, Younes El-Boustani, Elsa Deloge, Hélène Jacob, Simon Monziols, Fred Priem, Jean-Jacques Robin (Bordeaux, France, Centre Hospitalier Universitaire de Bordeaux, Department of Anesthesiology and Intensive Care); Vincent Legros,

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Contributors RW performed the trial and designed the manuscript; KS-G performed the trial and designed the manuscript; EPIS-AKI Investigators performed the study. LK helped design the trial and draft the manuscript; CW helped design the trial, performed study coordination and drafted the manuscript; MM conceived the study, designed the trial and drafted the manuscript; AZ conceived the study, designed the trial and drafted the manuscript. MM and AZ shared last authorship.

Funding This work was supported by an unrestricted research grant from Baxter and the German Research Foundation (KFO342/1, ZA428/18-1, and ZA 428/21-1 to AZ; ME5413/1-1 to MM).

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

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Provenance and peer review Not commissioned; externally peer reviewed.

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