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

Raphael Weiss,[1] Khaschayar Saadat-Gilani,[1] Laura Kerschke,[2] Carola Wempe,[1] Melanie Meersch ,[1] Alexander Zarbock ,[1] the EPIS-AKI Investigators

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[1]Department of Anaesthesiology, Intensive Care and Pain Medicine, Universitätsklinikum Münster, Münster, Germany
[2]Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany

Correspondence to
Dr Alexander Zarbock;
zarbock@uni-muenster.de

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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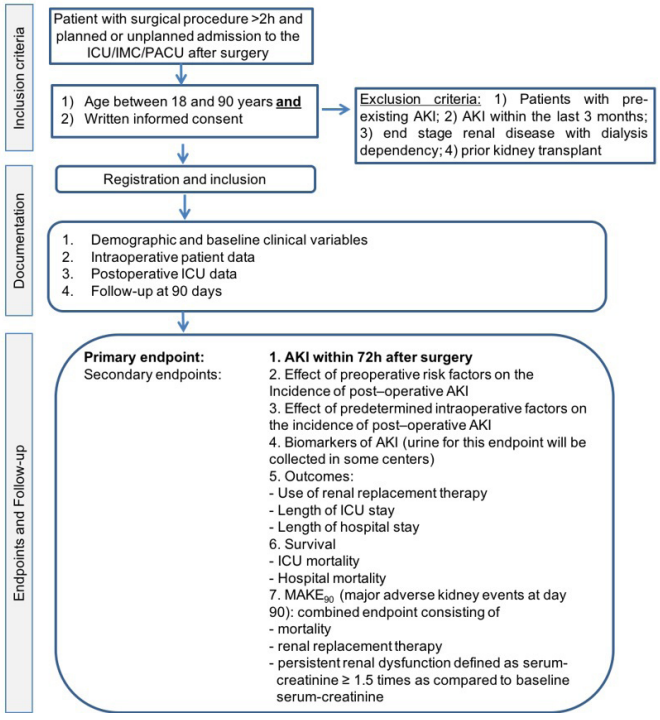


Figure 1 EPIS-AKI Trial Workflow Research coordinators will screen patients for eligibility on a daily basis and then ask patients for study participation. After surgery, inclusion/exclusion criteria will be rechecked and if still eligible (especially duration of surgery ≥2 hours, admission to ICU or 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

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

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.

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.

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Therry Floch, Salvatore Muccio (Reims, France, Centre Hospitalier Universitaire de Reims, Hôpital Maison Blanche, Surgical Intensive Care Unit); Claire Geneve, Marie Lim Legouge, Stéphanie Tao Mauny, Willy Mfam, Léa Pascot (Orléans, France, Centre Hospitalier Universitaire de Orléans, Department of Anesthesiology and Critical Care Medicine); Christophe Aveline, Mireille Chartier, Benjamin Duteurtre, Jean Francois Gautier, Aidren Le Cousin, Pierre Vautier (Cesson-Sévigné, France, Hôpital Privé Sévigné, Department of Anesthesiology and Critical Care Medicine); Julien Nadaud, Nathalie Begel, Claire-Annissa Chekirine, Vincent Derlon, Elodie Grein, Marie-Annick Lehair, Laurent Magazzeni, Philippe Magazzeni, Carsten Potter, Catherine Roth, Florence Voivret (Vantoux, France, Hôpital Robert Schuman-Groupe UNEOS, Department of Anesthesiology and Critical Care Medicine); Thomas Rimmelé, Valérie Cerro (Lyon, France, Hôpital Edouard Herriot, Department of Anesthesiology and Critical Care Medicine); Stéphanie Suria, Jamil Elmawieh, Annabelle Stoclin (Villejuif, France, Gustave Roussy Cancer Center, Postoperative Intensive Care Unit); Cédric Cirenei, Gregoire Andrieu, Sven Couloumy, Jeremy Falcone, Marion Fajardy, Arsène Gagneuil, Emeline Girardet, Agnès Mazereeuw (Lille, France, Centre Hospitalier Universitaire de Lille, Hôpital Huriez, Department of Anesthesiology and Intensive Care); Sébastien Ponsonnard (Limoges, France, Polyclinique de Limoges, Clinique François Chénieux, Department of Anesthesiology and Intensive Care); Pierre-Yves Egreteau, Mélanie Bertel, Simon Bocher, Vanessa Carn, Lenaïg Le Guen, Guillaume Le Loup, Montaine Lefevre (Morlaix, France, Centre Hospitalier des Pays de Morlaix, Department of Intensive Care Medicine); Carole Ichai, Amanita Diop (Nice, France, Centre Hospitalier Universitaire de Nice Hôpital Pasteur 2, Department of Intensive Care Medicine); Vanessa Jean-Michel, Sylvie Devlieger, Juliette Duthoit, Mohamed El Kadiri (Tourcoing, France, Centre Hospitalier Dron Tourcoing, Department of Intensive Care Medicine); Maxime Léger, Viviane Cassisa, Sigismond Lasocki, Charline Masson, Emmanuel Rineau (Angers, France, Centre Hospitalier Universitaire d'Angers, Department of Anesthesiology and Intensive Care); Pierre Verrier, Axel Coquerel (Caen, France, Centre François Baclesse, Postoperative Intensive Care Unit); Philippe Montravers, Enora Atchade (Paris, France, Hôpital Bichat, Department of Anaesthesiology and Surgical Intensive Care); Charles-Edouard Rochon, Céline Delerue (Blois, France, Centre Hospitalier Simone Veil de Blois, Department of Anesthesiology and Intensive Care); Vidal Quentin, Vanessa Latry (Tarbes, France, Centre Hospitalier de Bigorre, Department of Anesthesiology and Critical Care Medicine); Nina Queixalos, Vincent Cottenceau (Centre Hospitalier Universitaire de Bordeaux, Site Pellegrin, Surgical and Traumatologic Intensive Care); Thierry Braun, Saad Bouzoubaa, Basile Christ, Audrey Geiger, Joachim Gomille, Vianney Kieffer, Simone Mangeant, Christelle Prochilo, Christian Schmitt, Stefan Skwirba (Strasbourg, France, Clinique Sainte Anne, Department of Anesthesiology and Intensive Care); Hubert Grand, Frédérique Boury (Libourne, France, Centre Hospitalier Libourne, Department of Intensive Care); Nicolas Mayeur, Marie Pasquie (Toulouse, France, Clinique Pasteur, Cardiovascular and Thoracic Surgery Unit and Intensive Care Unit); Pierre Garçon (Jossigny, France Centre Hospitalier de Marne-La-Vallée, Intensive Care Unit); Vincent Bruckert, Vincent Arnould, Mona Bonciu, Thibault Chapelle, Luc Facchino, Florence Fagot-Gandet, Andrea Iachim, Elena Mannu, Olivier Perus, Rémi Plattier, Romain Rozier (Nice, France, Centre Hospitalier Universitaire de Nice, Department of Anesthesiology and Intensive Care); Gaël Pradel, Michel Boudinaud, Marie-Hélène Hausermann, My Hue Nguyen (Aurillac, France, Centre Hospitalier Henri Mondor d'Aurillac, Department of Intensive Care Medicine); Andersen Ramorasata, Amélie Barreau, Anne-Hélène Boivin (Mont de Marsan, France, Centre Hospitalier Mont de Marsan, Department of Anesthesiology and Intensive Care); Céline Ravry (Dax, France, Centre Hospitalier de Dax, Department of Anesthesiology and Intensive Care); Nicolas Mottard, Johanne Beuvelot, Florence Prunier Bossion, Olivier Desebbe (Lyon, France, Clinique de la Sauvegarde, Department of Anesthesiology and Critical Care); Alexander Zarbock, Christian Dörr, Thilo Caspar von Groote, Mira Küllmar, Christina Massoth, Melanie Meersch, Khaschayar Saadat-Gilani, Raphael Weiss, Carola Wempe (Münster, Germany, University Hospital Münster, Department of Anesthesiology, Intensive Care and Pain Medicine); Sebastian Ziemann, Linda Grüßer, Ana Kowark, Pia Wittig (Aachen, Germany, University Hospital RWTH Aachen, Department of Anesthesiology and Intensive Care); Timo Brandenburger, Thomas Dimski, Niklas Döhmen, Laura Huthmann, Daniela Kaierle, Claude Pelletier, Manon Schleß (Düsseldorf, Germany, University Hospital Düsseldorf, Department of Anesthesiology and Intensive Care); Andreas Hohn, Sebastian Cleophas, Stephanie Haunhorst, Marina Jansen, Alexandra Schmitt, Julia Soisch, Kilian Sturm (Mönchengladbach, Germany, Kliniken Maria Hilf Mönchengladbach, Department of Anesthesiology and Intensive Care); Peter Rosenberger, Alexander Bendig, Lena Flohr, Helene Häberle, Pascal Hofmann, Jonathan Kuhle, Nora Michaela Leser, Kathrin Pfister, Stefanie Prohaska, Franziska Sennholz, Lena Stetz, Kathrin Weber (Tübingen, Germany, University Hospital Tübingen, Department of Anesthesiology and Intensive Care); Sebastian Stehr (Leipzig, Germany, University Hospital Leipzig, Department of Anesthesiology and Intensive Care); Stephan Klaus, Marco Sadlo (Münster, Germany, Herz-Jesu-Krankenhaus, Department of Anesthesiology and Intensive Care); Matthias Boschin, Christian Sengelhoff (Sendenhorst, Germany, St. Josef-Stift Sendenhorst, Department of Anesthesiology and Intensive Care); Ulrich Michael Göbel, Jan Gerrit Haaker, Carina-Kristin Göttker, Matthias Gründel (Münster, Germany, Sankt Franziskus Hospital, Department of Anesthesiology and Intensive Care); Matthias Heringlake, Romina Baumgärtel, Astrid Berggren, Madeleine Gülzow, Lennart Muras, Hauke Paarmann (Karlsburg, Germany, Hospital Karlsburg, Department of Anesthesiology and Intensive Care); Serge Thal, Alexander Bentley, Dschamil El-Masri, Anne Sebastiani (Wuppertal, Germany, University Witten/Herdecke, Helios University Hospital Wuppertal, Department of Anesthesiology and Intensive Care); Eleni Arnaoutoglou, Maria Ntalouka (Larissa, Greece, University of Thessaly, University Hospital Larissa, Department of Anesthesiology); Paula Stratigopoulou, Anastasia Analytis, Efthymios Mavrommatis (Athens, Greece, Laiko General Hospital of Athens, Department of Anesthesiology); Petros Tzimas, Agathi Karakosta, Danai Pantazi (Ioannina, Greece, University of Ioannina, University Hospital Ioannina, Department of Anesthesiology); Antonia Dimakopoulou, Katerina Dimitropoulou (Athens, Greece, 'G. Gennimatas' General Hospital of Athens, Department of Anesthesiology); Orestis Ioannidis (Thessaloniki, Greece, General Hospital G. Papanikolaou, Department of General Surgery of A.U.TH); Humam Jalaawiy (Al-Diwaniyah, Iraq, Al-Diwaniyah Hospital, Department of General Surgery); Aeshah Anwar (Bagdad, Iraq, Bagdad Medical City Hospital, Department of General Surgery); Hashim Talib Hashim (Thi Qar, Iraq, Al-Nassiryah Teaching Hospital); Hogir Imad Rasheed Aldawoody (Khanaqeen, Iraq, Khanaqeen General Hospital, Department of General Surgery); Andrea Cortegiani, Giulia Catalisano, Gilia Ingoglia, Mariachiara Ippolito (Palermo, Italy University of Palermo, Policlinico Paolo Giaccone, Department of Anesthesia and Intensive Care); Silvia De Rosa, Lucia Cattin (Vicenza, Italy, Vicenza Hospital, Department of Anesthesia and Intensive Care, International Renal Research Institute of Vicenza (IRRIV)); Andrea Bianchin, Marisa Barone (Montebelluna, Italy, Montebelluna City Hospital, Department of Anesthesia and Intensive Care); Gianluca Paternoster (Potenta, Italy, San Carlo Regional Hospital, Department of Anesthesia and Intensive Care, Branch Cardioanesthesia); Salvatore Lucio Cutuli, Andrea Russo, Liliana Sollazzi, Laura Cascarano, Massimo Antonelli, Paola Aceto, Bruno Romanò (Rome, Italy, Gemelli University General Hospital, Department of Anesthesia, Intensive Care and Emergency Medicine); Savino Spadaro (Ferrara, Italy, University of Ferrara, Faculty of Medicine, Department Morphology, Surgery and Experimental Medicine); Vincenzo Francesco Tripodi, Michele Rossi, Rosamaria Scappatura, Maria Cristina Vadalà (Calabria, Italy, Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Department of Anesthesia and Intensive Care, Branch Cardioanesthesia); Diego Fiume (Rome, Italy, Sant'Eugenio Hospital, Department of Anesthesia and Intensive Care); Maria Teresa Strano, Giulia Oddo (Palermo, Italy, Public Hospital Cristina Benfratelli, Department of Anesthesia and Intensive Care); Clemente Santorsola (Esine, Italy, General Hospital Vallecamonica-Sebino ASL Vallecamonica-Sebino, Department of Anesthesia, Intensive Care and Emergency Medicine); Bilal Abu Hussain, Adnan Raed Alnaser, Anas Hassouneh Ghassan, Khaled Hasanein, Mohammed Theab (Amman, Jordan, Al-Basheer Hospital, Amman, Departmet of Surgery); Seokyung Shin, Seungho Jung, Kyuho Lee (Seoul, Korea, Yonsei University College of Medicine, Department of Anesthesiology and Pain Medicine); Sung Mee Jung, Jongyoon Baek (Daegu, Korea, Yeungnam University School of Medicine, University Hospital Yeungnam, Department of Anesthesiology and Pain Medicine); Muhammed K. Elhadi (Tripoli, Libya, University of Tripoli, Faculty of Medicine); Wafa Wafa O.Aldressi, Issa Abuzeid, Mohammed Albaraesi, Sarah Aldressi (Benghazi, Libya Benghazi Medical Center, Departmet of General Surgery); Wegdan Khalel, Eman Abdulwahed, Akram Abdulhamid Ashur Abujrad, Amer Almaghrabi, Muhand Mohammed Alteleeb, Entisar Ahmed Ali Alshareea, Marwa Isa Biala, Abdulqudus Deeknah, Dooua Ali Gheddim, Reem Ghmagh, Nawras Salih Ali Abu Ikhrays, Marwa Sinan (Tripoli, Libya, Tripoli Central Hospital, Department of Anesthesiology); Enas Soula, Sumayyah Ghayth Bahroun, Khawla Derwish, Aya Munir Mohamed, Eman Sayed Younes (Sabratha, Libya, National Cancer Institute); Rayet Al Islam Benjouira, Mohamed Aliwa, Najwa Abdullah Altashani, Mohammed Omar Alteb (Tripoli, Libya, National Heart Center Tripoli, Department of Anesthesiology); Ahmed Msherghi, Fatima Alagelli, Sufyan Albarouni, Ahmed Albishti, Sarah Aljamal, Mohamed Alsori, Taha Ekhuja, Suha Elzwai, Mohammed Ghula, Tahani Mustafa, Ahmed Tuwaib, Haifa Zriba (Tripoli, Libya, University Hospital Tripoli, Department of Anesthesiology); Hamza Mahmoud Agilla (Tripoli, Libya, AboSleem Hospital, Department of Anesthesiology and Intensive Care); Toky Andriamahefa Rafanomezantsoa (Toamasina, Madagascar Centre Hospitalier Universitaire de Analankininina Toamasina, Department of Anesthesiology); Anne Marie Camilleri Podesta, Denise Mifsud Bonnici, Tiziana Pirotta (Msida, Malta, University of Malta, Mater Dei Hospital, Department of Anesthesiology and Intensive Care); Gilberto Adrián Gasca López (Ixtapaluca, Mexik, Regional Hospital of High Specialty of Ixtapaluca, Department of Anesthesiology); Maja Mojsova Mijovska, Tatjana Davitkovska,

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Aleksandra Gavrilovska, Sanja Lukikj, Marija Vesova, Dina Zafirova (Skopje, North Macedonia, University Hospital Skopje Mother Theresa, Department for Anesthesia Reanimation and Intensive Care); Sarah Amro (Hebron, Palestine Princess Alia Governmental Hospital, Department of Anesthesiology); Baraa N. F. Hajjaj, Muawia Alkhazendar, Yousuf Barakat, Sewar Abdulaziz Elejla, Ahmed Elhissi, Ahmed Khader, Ali Salem (Gaza, Palestine, Palestinian Ministry of Health - Al-Shifa Medical Complex, Department of Anesthesiology); Rita de Freitas Regufe,André Filipe de Oliveira Eloy, Lisbete Marisa Neto Cordeiro Perdigão (Setúbal, Portugal, Central Hosptial de Setúbal, Department for Anesthesiology); Evgeny Grigoriev, Artem Ivkin, Roman Kornelyuk (Kemerovo, Russia, Kemerovo Cardiology Centre, Department of Anesthesiology); Michael Yaroustovsky, Marina Abramyan, Ekaterina Komardina (Moscow, Russia, Bakulev Scientific Center for Cardiovascular Surgery, Department of Anesthesiology); Nataliya Lesteva, Medina Aybazova, Elmira Kumykova, Svetlana Lesina, Gennady Rybakov, Alexey Shestov (St. Petersburg, Russia, Almazov National Medical Research Centre, Polenov Neurosurgical Institute, Department of Anesthesiology and Intersive care); Abdulnaser Ahmad Ahmad Barmou, Bushra Lotfi Altayeb Ahmed, Aisha Mohammad Eliyas, Yousra Emadeldin (Al Khobar, Saudi Arabia, Almana General Hospital Al-Khobar, Department of Cardiology); Alexander Kaserer,Clara Castellucci, Julian Rössler, Samira Akbas (Zürich, Switzerland, University Hospital Zürich, Institute for Anesthesiology); Andreja Möller Petrun, Irena Gregorcic, Vesna Sok (Maribor, Slovenia, University Medical Centre Maribor, Department of Anesthesiology and Intensive Care); Roman Čičak (Murska Sobota, Slovenia, General Hospital of Murska Sobota, Department of Anesthesiology and Perioperative Medicine); Elizabeth Bárcena, Antonio Guisado, Ismail Wi (Granada, Spain, University Hospital Vrigen de las Nieves, Department of Anaesthesia, Critical Care and Pain Therapy); Javier Ripollés Melchor (Madrid, Spain, University Hospital Infanta Leonor, Department of Anesthesiology and Intensive Care); Ángel Becerra-Bolaños, Sergio Cabrera-Doreste, Ancor Domínguez-Arbelo, María Candelaria Delgado-Alonso, Virginia Muiño-Palomar, Aurelio Rodríguez-Pérez (Gran Canaria, Spain, University Hospital Gran Canaria Doctor Negrín, Department of Anesthesiology and Intensive Care); Javier Mata Estévez, Maria Begona Covas Munoz, Juan Mulet Matas, Sara Perez Palao, Maria Dolores Mira Quirós, Alisia Cezara Teslev (Palma de Mallorca, Spain University Hospital Son Llàtzer, Department of Anesthesiology and Pain Medicine); Mercedes Garcia Alvarez, Marga Argilaga, María Campos, Albert Bainac, Astrid Batalla, Mercedes Garcia Alvarez, Marta Giné, Gracia Herránz, Ignacio Hinojal (Barcelona, Spain, University of Barcelona, Hospital de Sant Pau, Department of Anesthesiology and Pain Medicine); Margarita Logroño Ejea, Noelia de la Rosa Ruiz, María Gastaca Abasolo, Carla Rosario Houhton Acuna, Ibai Iriarte Zaranton, Ana Mendigurenmurua, María José Munoz Sanz, Erika Olea de la Fuente, María Pilar Pérez Vaquero, Ana Soto Iglesias, Ana Ugarte Mieres, Alaitz Urtiaga Urrestizala (Vitoria-Gasteiz, Spain, University Hospital Araba (Txagorritxu Hospital Álava); Department of Anesthesiology and Intensive Care); Lourdes Ferreira, Félix Lobato, Marta Aguado Sevilla (Logroño (La Rioja); Spain, San Pedro Hospital, Department of Anesthesiology); Andres Erazo, Pere Miró, Sergi Sabaté, Diana Vernetta (Barcelona, Spain, Fundación Puigvert, Department of Anesthesiology and Intensive Care); Berta Castellano Paulis, Anabel Adell Perez, Marta Aseguinolaza Pagola, Berta Castellano Paulis, Elena del Val Peciña, Ainhoa Garmendia Odriozola, Amaia Lopetegi Aizpurua, Olatz Pavón Piquer, Pilar Plou Garcia, Paula Ortega Rezola, Antia Osorio Lopez (Donostia, Spain, University Hospital Donostia, Department of Anesthesiology, Intensive Care and Pain Medicine); Isabel de la Calle Gil, Rosalía Navarro Casado (Madrid, Spain, Hospital 12 de Octubre, Department of Anesthesiology and Intensive Care); Peter Adamove, Roser Bayona Domenge, Francho Miguel Blasco Blasco, Adriana Alexandra Rueda Villamizar, Maria Antonia Perelló Llaneras (Barcelona, Spain, University Hospital Bellvitge, Department of Anesthesiology); Jose Ignacio García-Sánchez, Laura Fernandez Téllez, Sara García Zamorano, Natalia Gijón Herreros, Andrea Rodriguez Esteve (Madrid, Spain, University Hospital Fundacion Alcorcón, Departament of Anesthesiology and Critical Care); Pablo Monedero Rodríguez, Isabel García Trigo, Agustín Alcaraz, Andrea Lara Jiménez, Iñigo Rubio, Nuria García, Raquel Callejas (Navarra, Spain, University Hospital Navarra, Departament of Anesthesiology and Critical Care); Angel Manuel Candela Toha, Eli Claros, Pilar Cobeta, Pascual Crespo,Trini Dorado, Elena Elías, Javier Felices, Diego Gil, María Gómez, Nuria Mané, María Martín, Adolfo Martínez, Lucía Pereira, Alberto Balvis Noemí Samaranch, Ana Serrano, Carlos Tiscar, Judith VillaHoz (Madrid, Spain, University Hospital Ramón y Cajal, Department of Anesthesiology and Intensive Care, Branch Cardiovascular and Thoracic Anesthesia); Patricia Galán Menéndez, Elena Cardona, Anna Conesa, Veronica Estepa, Patricia Galán, Laura Llinares Espí, Yuri Loaiza Aldeán, Susana Manrique, Víctor Morales Ariza, Laura Villarino Villa (Barcelona, Spain, University Hospital Vall d'Hebron, Department of Anesthesiology and Critical Care); Elfayadh Saidahmed Mohamed Amed Suliman, Hytham Hamid (Omdurman, Sudan, Shargh Alneel Hospital, Military Hospital Omdurman, Department of Anesthesia); Ahmed Mohamed Ibrahim, Modather Mohamed Saeed (Al-Qadarif, Sudan, Gadarif Teaching Hospital, Department of Anesthesia); Orhan Sungur Mukadder, Demet Altun, Nur Canbolat, Müşerref Beril Dinçer, Tulay Özkan Seyhan (Istanbul, Turkey, Istanbul University, Istanbul Faculty of Medicine, Department of Anesthesiology); Serap Aktaş Yıldırım (Istanbul, Turkey, Acıbadem Altunizade Hospital, Department of Anesthesiology); Müzeyyen İyigün (Istanbul, Turkey, Acibadem Atakent Hospital, Department of Anesthesiology); Davut Yapıcı, Levent Özdemir, Aslinur Sagun (Mersin University, School of Medicine, Department of Anesthesiology and Intensive Care); Neval Boztug, Yesim Cetintas, Bora Dinc, Emel Gündüz (Antalya, Turkey, University Hospital Akdeniz, Department of Anesthesiology); Hakkı Ünlügenç, Demet Lafli Tunay (Adana, Turkey, Çukurova University, Department of Anesthesiology); Deniz Karakaya, Burhan Dost, Ozgur Komurcu (Samsun, Turkey, Mayıs University, Department of Anesthesiology); Özlem Korkmaz Dilmen, Eren Fatma Akcil, Özlem Korkmaz Dilmen, Yusuf Tunali (Istanbul, Turkey, Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Anesthesiology and Intensive Care Medicine); Gülay Ok, Eda Tok Alsina, Özge Hakli (Manisa, Turkey, Manisa Celal Bayar University, Medical Faculty, Department of Anesthesiology and Reanimation); Cengiz Polat, Namigar Turgut (Istanbul, Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Department of Anesthesiology); Nurcan Kızılcık, Özge Köner (Istanbul, Turkey, Yeditepe University, Faculty of Medicine); Öznur Şen, Nurdan Aydin, Burcu Basaran, Emre Sertac Bingul (Istanbul, Turkey, Haseki Sultangazi Research and Training Hospital, Department of Anesthesiology and Intensive Care); Yavuz Gürkan, Kamil Darcin, Semra Ugur (Istanbul, Turkey, University Hospital Koç, Department of Anesthesiology and Reanimation); Kemal Tolga Saracoglu (Istanbul, Turkey, Health Sciences University Kartal Dr. Lutfi Kirdar Training and Research Hospital, Department of Anesthesiology and Intensive Care); Asli Demir, Özgök Aysegül, Eda Balci, Behic Girgin, Aygun Guler, Ümit Karadeniz, Nihal Özaslan, Yigit Özay Hülya, Namik Ozcan, Aysun Postaci, Mehmet Sahap, Nevriye Salman (Ankara, Turkey, Ankara City Hospital, Department of Anesthesiology); Özlem Sağır, Bulent Atik, Murat Bicakcioglu, Hafize Fisun Demir, Ugün Fatih, Nazan Kocaoglu (Balikesir, Turkey Balikesir University, Department of Anesthesiology and Intensive Care); Hüseyin ilksen Toprak, Duygu Demiröz Aslan, Yusuf Ziya Colak (Malatya, Turkey, University Hospital Inonu, Department of Anaesthesiology and Reanimation); Mustafa Soner Ozcan (Isparta, Turkey, Suleyman Demirel University School of Medicine, Department: Anesthesiology and Reanimation); Mehmet Yilmaz (Department of Anesthesiology and Reanimation, Health Sciences University Medical School, Derince, Kocaeli, Turkey); Umran Karaca (Bursa, Turkey, University of Health Sciences Turkey, Yuksek Ihtisas Training and Research Hospital, Department of Anesthesiology and Reanimation); Sevtap Hekimoglu Sahin (Edirne, Turkey, Trakya University, Faculty of Medicine Department of Anesthesiology and Reanimation); Özlem Ersoy Karka, Gizem Demir Şenoğlu (Düzce, Turkey, Düzce University, Department of Anesthesiology and Reanimation); Süheyla Erkoç Karadağ, Neslihan Alkis (Ankara, Turkey, Ankara University School of Medicine, İbni Sina Hospital); Volkan Baytaş (Ankara, Turkey, Ankara University School of Medicine, Cebeci Hospital); Engin Erturk, Ali Akdogan, Ahmet Besir, Engin Erturk, Dilek Kutanis, Sedat Saylan, Ersagun Tugcugil (Trabzon, Turkey, Karadeniz Technical University, Faculty of Medicine, Department of Anesthesiology and Intensive Care); Pinar Ayvat (Izmir, Turkey, Izmir Democracy University School of Medicine, Department of Anesthesiology and Reanimation Department); Berrin Günaydın, Beyza Mehri Büyükgebiz (Ankara, Turkey, Gazi University School of Medicine, Department of Anesthesiology); Omer Faruk Boran, Feyza Calisir, Yavuz Orak (Kahramanmaraş, Turkey, Kahramanmaras Sutcu Imam University Faculty of Medicine, Department of Anesthesiology and Reanimation); Bahar Kuvaki Balkan, Bahar Kuvaki Balkan, Sibel Büyükcoban, Erol Gökel, Sakize Ferim Günenc, Sule Özbilgin (Izmir, Turkey, Dokuz Eylül Üniversitesi, Department of Anesthesiology and Reanimation); Suna Göre, Selcan Akesen, Seda Cansabuncu (Bursa, Turkey, Bursa Uludag University, Medical Faculty, Department of Anaesthesiology and Reanimation); Natalia Momot, Anna Panchenko (Zaporizhzhia, Ukraine, Zaporizhzhia State Medical University Hospital, Department of Anesthesiology and Intensive Care); Jean-Francois Pittet, Kristen Rutledge (Birmingham, USA University of Alabama, Department of Anesthesiology and Perioperative Medicine).

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ORCID iDs
Melanie Meersch http://orcid.org/0000-0002-6011-8049
Alexander Zarbock http://orcid.org/0000-0002-2124-1714

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Supplementary table 1: EPIS-AKI-Trial site investigators

ALGERIA		
Constantine, Algeria Constantine Centre Hospitalier Universitaire, Department of Anesthesiology and Resuscitation	PI: Hichem Makhloufi Anis Cherak Lamine Lakhel Ghanem Zohier Gouaglia Dina Nasrine Guadouri Fayrouz Naouel Hama Mustafa Kara Omayma Saadi	Ethics Committee of the University Hospital of Constantine
Alger, Algeria Etablissement Hospitalier Spécialisé Salim Zemirli El Harrach, Department of Anesthesiology and Resuscitation	PI: Rachida Sakhraoui Fadila Bourou Abdelhadi Cherifi Rahmoune Ghania Sadaoui	No ethics approval needed.
Sétif, Algeria Saadna Abdenour Teaching Hospital, Department of Anesthesia	PI: Amel Ouyahia	Ethics Committee of the Saadna Abdenour Teaching Hospital
Sétif, Algeria University Hospital of Sétif, Department of Epidemiology, Department of General Surgery	Ilhem Ouahab Souad Bouaoud Meriem Abdoun	Ethics Committee of the University Hospital of Sétif
Oran, Algeria University Hospital 1st November 1954 Department of General Surgery	Anisse Tidjane Benali Tabeti Nabil Boudjenan-Serradj	Ethics Committee of the University Hospital 1st November 1954
COLOMBIA		
Bogotá, Colombia Universidad El Bosque, Fundación Cardioinfantil, Clinical Research Coordinator, Department of General Surgery	PI: Carlos Jose Pérez Rivera Paulo Cabrer Julián Corso Juan Pablo García Sharon Idarraga Christopher Montoya	Research Ethics Committee at the University Hospital El Bosque Bogotá
Ibagué, Colombia Avidanti Clinic Ibaqué	PI: Rafael Figueroa Eduar Aldana María Alejandra Torrado	Research Ethics Committee at the Clínica Avidanti Ibagué
CHINA		
Jiangsu, China, First Affiliated Hospital of Soochow University, Department of Anesthesiology	PI: Ke Peng Zheng-min Ma Yu-fan Yang Ya-juan Zhu	Research Ethics Committee at the Soochow University
CZECH REPUBLIC		
Ostrava, Czech Republic University Hospital Ostrava, Department of Anesthesia and Intensive Care	PI: Peter Sklienka Michal Frelich Vojtech Jarkulis Pavel Sevcik Vojtech Vodicka	Ethical Committee at the University Hospital of Ostrava

EGYPT		
Tanta, Egypt Tanta University Faculty of Medicine, Department for Emergency medicine and traumatology	PI: Mohamed Gamal Elbahnasawy Shady Elsalhawy Sara Motawea Zeinab Othman Mohamed Sahma	Research Ethics Committee of the Medical Faculty of the Tanta University
Alexandria, Egypt Alexandria University Main Hospital	PI: Ahmed Mahmoud Nafea	Research Ethics Committee of the Medical Faculty of the University of Alexandria
Alexandria, Egypt Alexandria University, Medical Research Institute	PI: Nermin Ahmed Doaa Ali Attia	Research Ethics Committee of the Medical Faculty of the University of Alexandria
Mansoura, Egypt Mansoura University, Faculty of Medicine, Liver Transplant - Gastrointestinal Surgical Center, Department of Anesthesiology and Intensive Care	PI: Moataz Maher Emara Mohamed Mamdouh Bonna Mohamed Ahmed Gabr Amany Ismail Tarbay	Research Ethics Committee of the Medical Faculty of the University of Mansoura
Sharkia, Egypt Zagazig University Hospital	PI: Ibrahim Abdelmonaem Abdehaleem Esraa Elsayed Mohamed Amr Mahmoud Eldeeb	Institutional Review Board, Zagazig University Hospital
Assiut, Egypt Assiut University Hospitals, Department of Anesthesia and Intensive Care	PI: Ahmed Mohamed Abbas John Ashraf Magdy Zyad Hassan Hamed Hany Mostafa Esmaeil Osman Mostafa Samy Abbas	Ethics Committee of the Medical Faculty of the Assiut University
FRANCE		
Bordeaux, France Centre Hospitalier Universitaire de Bordeaux, Department of Anesthesiology and Intensive Care	PI: 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	Central study declaration, no ethics approval needed
Reims, France Centre Hospitalier Universitaire de Reims, Hôpital Maison Blanche, Surgical Intensive Care Unit	PI: Vincent Legros Therry Floch Salvatore Muccio	Central study declaration, no ethics approval needed
Orléans, France Centre Hospitalier Universitaire de Orléans, Department of Anesthesiology and Critical Care Medicine	PI: Claire Geneve Marie Lim Legouge Stéphanie Tao Mauny Willy Mfam Léa Pascot	Central study declaration, no ethics approval needed

Cesson-Sévigné, France Hôpital Privé Sévigné, Department of Anesthesiology and Critical Care Medicine	PI: Christophe Aveline Mireille Chartier Benjamin Duteurtre Jean Francois Gautier Aidren Le Cousin Pierre Vautier	Central study declaration, no ethics approval needed
Vantoux, France Hôpital Robert Schuman-Groupe UNEOS, Department of Anesthesiology and Critical Care Medicine	PI: Julien Nadaud Nathalie Begel Claire-Annissa Chekirine Vincent Derlon Elodie Grein Marie-Annick Lehair Laurent Magazzeni Philippe Magazzeni Carsten Potter Catherine Roth Florence Voivret	Central study declaration, no ethics approval needed
Lyon, France Hôpital Edouard Herriot, Department of Anesthesiology and Critical Care Medicine	PI: Thomas Rimmelé Valérie Cerro	Central study declaration, no ethics approval needed
Villejuif, France Gustave Roussy Cancer Center, Postoperative Intensive Care Unit	PI: Stéphanie Suria Jamil Elmawieh Annabelle Stoclin	Central study declaration, no ethics approval needed
Lille, France Centre Hospitalier Universitaire de Lille, Hôpital Huriez, Department of Anesthesiology and Intensive Care	PI: Cédric Cirenei Gregoire Andrieu Sven Couloumy Jeremy Falcone Marion Fajardy Arsène Gagneuil Emeline Girardet Agnès Mazereeuw	Central study declaration, no ethics approval needed
Limoges, France Polyclinique de Limoges, Clinique François Chénieux, Department of Anesthesiology and Intensive Care	PI: Sébastien Ponsonnard	Central study declaration, no ethics approval needed
Morlaix, France Centre Hospitalier des Pays de Morlaix, Department of Intensive Care Medicine	PI: Pierre-Yves Egreteau Mélanie Bertel Simon Bocher Vanessa Carn Lenaïg Le Guen Guillaume Le Loup Montaine Lefevre	Central study declaration, no ethics approval needed
Nice, France Centre Hospitalier Universitaire de Nice Hôpital Pasteur 2, Department of Intensive Care Medicine	PI: Carole Ichai Amanita Diop	Central study declaration, no ethics approval needed
Tourcoing, France Centre Hospitalier Dron Tourcoing, Department of Intensive Care Medicine	PI: Vanessa Jean-Michel Sylvie Devlieger Juliette Duthoit Mohamed El Kadiri	Central study declaration, no ethics approval needed
Angers, France	PI: Maxime Léger Viviane Cassisa Sigismond Lasocki	Central study declaration, no ethics approval needed

Centre Hospitalier Universitaire d'Angers, Department of Anesthesiology and Intensive Care	Charline Masson Emmanuel Rineau	
Caen, France Centre François Baclesse, Postoperative Intensive Care Unit	PI: Pierre Verrier Axel Coquerel	Central study declaration, no ethics approval needed
Paris, France Hôpital Bichat, Department of Anaesthesiology and Surgical Intensive Care	PI: Philippe Montravers Enora Atchade	Central study declaration, no ethics approval needed
Blois, France Centre Hospitalier Simone Veil de Blois, Department of Anesthesiology and Intensive Care	PI: Charles-Edouard Rochon Céline Delerue	Central study declaration, no ethics approval needed
Tarbes, France Centre Hospitalier de Bigorre, Department of Anesthesiology and Critical Care Medicine	PI: Vidal Quentin Vanessa Latry	Central study declaration, no ethics approval needed
Centre Hospitalier Universitaire de Bordeaux, Site Pellegrin, Surgical and Traumatologic Intensive Care	PI: Nina Queixalos Vincent Cottenceau	Central study declaration, no ethics approval needed
Strasbourg, France Clinique Sainte Anne, Department of Anesthesiology and Intensive Care	PI: Thierry Braun Saad Bouzoubaa Basile Christ Audrey Geiger Joachim Gomille Vianney Kieffer Simone Mangeant Christelle Prochilo Christian Schmitt Stefan Skwirba	Central study declaration, no ethics approval needed
Libourne, France Centre Hospitalier Libourne, Department of Intensive Care	PI: Hubert Grand Frédérique Boury	Central study declaration, no ethics approval needed
Toulouse, France Clinique Pasteur, Cardiovascular and Thoracic Surgery Unit and Intensive Care Unit	PI: Nicolas Mayeur Marie Pasquie	Central study declaration, no ethics approval needed
Jossigny, France Centre Hospitalier de Marne-La-Vallée, Intensive Care Unit	PI: Pierre Garçon	Central study declaration, no ethics approval needed
Nice, France Centre Hospitalier Universitaire de Nice, Department of Anesthesiology and Intensive Care	PI: Vincent Bruckert Vincent Arnould Mona Bonciu Thibault Chapelle Luc Facchino Florence Fagot-Gandet Andrea Iachim Elena Mannu Olivier Perus Rémi Plattier Romain Rozier	Central study declaration, no ethics approval needed

Aurillac, France Centre Hospitalier Henri Mondor d'Aurillac, Department of Intensive Care Medicine	PI: Gaël Pradel Michel Boudinaud Marie-Hélène Hausermann My Hue Nguyen	Central study declaration, no ethics approval needed
Mont de Marsan, France Centre Hospitalier Mont de Marsan, Department of Anesthesiology and Intensive Care	PI: Andersen Ramorasata Amélie Barreau Anne-Hélène Boivin	Central study declaration, no ethics approval needed
Dax, France Centre Hospitalier de Dax, Department of Anesthesiology and Intensive Care	PI: Céline Ravry	Central study declaration, no ethics approval needed
Lyon, France Clinique de la Sauvegarde, Department of Anesthesiology and Critical Care	PI: Nicolas Mottard Johanne Beuvelot Florence Prunier Bossion Olivier Desebbe	Central study declaration, no ethics approval needed
GERMANY		
Münster, Germany University Hospital Münster Department of Anesthesiology, Intensive Care and Pain Medicine	PI: Alexander Zarbock Christian Dörr Thilo Caspar von Groote Mira Küllmar Christina Massoth Melanie Meersch Khaschayar Saadat-Gilani Raphael Weiss Carola Wempe	Ethics Committee of the Medical Council North Rhine-Westphalia and of the Westphalian Wilhelms-University Münster
Aachen, Germany University Hospital RWTH Aachen Department of Anesthesiology and Intensive Care	PI: Sebastian Ziemann Linda Grüßer Ana Kowark Pia Wittig	Ethics Committee of the Medical Faculty of the Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen
Düsseldorf, Germany University Hospital Düsseldorf, Department of Anesthesiology and Intensive Care	PI: Timo Brandenburger Thomas Dimski Niklas Döhmen Laura Huthmann Daniela Kaierle Claude Pelletier Manon Schleß	Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf
Mönchengladbach, Germany Kliniken Maria Hilf Mönchengladbach, Department of Anesthesiology and Intensive Care	PI: Andreas Hohn Sebastian Cleophas Stephanie Haunhorst Marina Jansen Alexandra Schmitt Julia Soisch Kilian Sturm	Ethics Committee of the Medical Council North-Rhine
Tübingen, Germany University Hospital Tübingen, Department of Anesthesiology and Intensive Care	PI: Peter Rosenberger Alexander Bendig Lena Flohr Helene Häberle Pascal Hofmann Jonathan Kuhle Nora Michaela Leser Kathrin Pfister Stefanie Prohaska	Ethics Committee of the Medical Faculty of the Eberhard-Karls-University and University Hospital Tübingen

	Franziska Sennholz Lena Stetz Kathrin Weber	
Leipzig, Germany University Hospital Leipzig, Department of Anesthesiology and Intensive Care	PI: Sebastian Stehr	Ethics Committee of the Medical Faculty of the University of Leipzig
Münster, Germany Herz-Jesu-Krankenhaus Department of Anesthesiology and Intensive Care	PI: Stephan Klaus Marco Sadlo	Ethics Committee of the Medical Council North Rhine-Westphalia and of the Westphalian Wilhelms-University Münster
Sendenhorst, Germany St. Josef-Stift Sendenhorst, Department of Anesthesiology and Intensive Care	PI: Matthias Boschin Christian Sengelhoff	Ethics Committee of the Medical Council North Rhine-Westphalia and of the Westphalian Wilhelms-University Münster
Münster, Germany Sankt Franziskus Hospital, Department of Anesthesiology and Intensive Care	PI: Ulrich Michael Göbel Jan Gerrit Haaker Carina-Kristin Göttker Matthias Gründel	Ethics Committee of the Medical Council North Rhine-Westphalia and of the Westphalian Wilhelms-University Münster
Karlsburg, Germany Hospital Karlsburg, Department of Anesthesiology and Intensive Care	PI: Matthias Heringlake Romina Baumgärtel Astrid Berggren Madeleine Gülzow Lennart Muras Hauke Paarmann	Ethics Committee of the University Hospital Greifswald
Wuppertal, Germany University Witten/Herdecke, Helios University Hospital Wuppertal, Department of Anesthesiology and Intensive Care	PI: Serge Thal Alexander Bentley Dschamil El-Masri Anne Sebastiani	Ethics Committee of the University Witten/Herdecke
GREECE		
Larissa, Greece University of Thessaly, University Hospital Larissa, Department of Anesthesiology	PI: Eleni Arnaoutoglou Maria Ntalouka	Ethics Committee of the University and University Hospital Larissa
Athens, Greece Laiko General Hospital of Athens, Department of Anesthesiology	PI: Paula Stratigopoulou Anastasia Analytis Efthymios Mavrommatis	Ethics Committee of the University Hospital Athens
Ioannina, Greece University of Ioannina, University Hospital Ioannina, Department of Anesthesiology	PI: Petros Tzimas Agathi Karakosta Danai Pantazi	Ethics Committee of the University Hospital Ioannina
Athens, Greece 'G. Gennimatas' General Hospital of Athens, Department of Anesthesiology	PI: Antonia Dimakopoulou Katerina Dimitropoulou	Ethics Committee of the University Hospital Athens
Thessaloniki, Greece General Hospital G. Papanikolaou, Department of General Surgery of A.U.TH	PI: Orestis Ioannidis	Ethics Committee of the University Hospital Thessaloniki
IRAQ		
Al-Diwaniyah, Iraq Al-Diwaniyah Hospital, Department of General Surgery	PI: Humam Jalaawiy	Al Diwaniyah Government/Health Office

Bagdad, Iraq Bagdad Medical City Hospital, Department of General Surgery	PI: Aeshah Anwar	Ethics Committee of the Medical City Hospital
Thi Qar, Iraq Al-Nassiryah Teaching Hospital	PI: Hashim Talib Hashim	Ethics Committee of the Al-Nassiryah Teaching Hospital
Khanaqeen, Iraq Khanaqeen General Hospital, Department of General Surgery	PI: Hogir Imad Rasheed Aldawoody	No need for local ethics approval.
ITALY		
Palermo, Italy University of Palermo, Policlinico Paolo Giaccone, Department of Anesthesia and Intensive Care	PI: Andrea Cortegiani Giulia Catalisano Gilia Ingoglia Mariachiara Ippolito	Ethics Committee of the University Palermo
Vicenza, Italy Vicenza Hospital, Department of Anesthesia and Intensive Care, International Renal Research Institute of Vicenza (IRRIV)	PI: Silvia De Rosa Lucia Cattin	Clinical Research Ethics Committee of the Vicenza Region
Montebelluna, Italy Montebelluna City Hospital, Department of Anesthesia and Intensive Care	PI: Andrea Bianchin Marisa Barone	Research Ethics Committee of the Asolo District
Potenta, Italy San Carlo Regional Hospital, Department of Anesthesia and Intensive Care, Branch Cardioanesthesia	PI: Gianluca Paternoster	Ethics Committee of the Basilicata Region
Rome, Italy Gemelli University General Hospital, Department of Anesthesia, Intensive Care and Emergency Medicine	PI: Salvatore Lucio Cutuli Andrea Russo Liliana Sollazzi Laura Cascarano Massimo Antonelli Paola Aceto Bruno Romanò	Ethics Committee of the Gemelli University General Hospital
Ferrara, Italy University of Ferrara, Faculty of Medicine, Department Morphology, Surgery and Experimental Medicine	PI: Savino Spadaro	Ethics Committee of the Vasta Emilia Centro/Emilia-Romagna Region
Calabria, Italy Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Department of Anesthesia and Intensive Care, Branch Cardioanesthesia	PI: Vincenzo Francesco Tripodi Michele Rossi Rosamaria Scappatura Maria Cristina Vadalà	Ethics Committee of the Calabria Region
Rome, Italy Sant'Eugenio Hospital, Department of Anesthesia and Intensive Care	PI: Diego Fiume	Ethics Committee of the Lazio Region
Palermo, Italy Public Hospital Cristina Benfratelli Department of Anesthesia and Intensive Care	PI: Maria Teresa Strano Giulia Oddo	Ethics Committee of the University Palermo
Esine, Italy General Hospital Vallecamonica-Sebino	PI: Clemente Santorsola	Ethics Committee of the Lombardia Region

ASL Vallecamonica-Sebino, Department of Anesthesia, Intensive Care and Emergency Medicine		
JORDAN		
Amman, Jordan Al-Basheer Hospital, Amman Departmet of Surgery	Bilal Abu Hussain Adnan Raed Alnaser Anas Hassouneh Ghassan Khaled Hasanein Mohammed Theab	Head of the Al-Basheer Hospital
KOREA		
Seoul, Korea Yonsei University College of Medicine, Department of Anesthesiology and Pain Medicine	PI: Seokyung Shin Seungho Jung Kyuho Lee	Institutional Review Board of the Yonsei University
Daegu, Korea Yeungnam University School of Medicine, University Hospital Yeungnam, Department of Anesthesiology and Pain Medicine	PI: Sung Mee Jung Jongyoon Baek	Institutional Review Board of the Yeungnam University Hospital
LIBYA		
Tripoli, Libya University of Tripoli, Faculty of Medicine	PI: Muhammed K. Elhadi	Ministry of Higher Education & Scientific Research, Authority of Natural Science Research and Technology
Benghazi, Libya Benghazi Medical Center Departmet of General Surgery	PI: Wafa Wafa O.Aldressi Issa Abuzeid Mohammed Albaraesi Sarah Aldressi	Ethics Committee of the Benghazi Medical Center
Tripoli, Libya Tripoli Central Hospital	PI: Wegdan Khalel Eman Abdulwahed Akram Abdulhamid Ashur Abujrad Amer Almaghrabi Muhand Mohammed Alteleeb Entisar Ahmed Ali Alshareea Marwa Isa Biala Abdulqudus Deeknah Dooua Ali Gheddim Reem Ghmagh Nawras Salih Ali Abu Ikhrays Marwa Sinan	Ministry of Health
Sabratha, Libya National Cancer Institute	PI: Enas Soula Sumayyah Ghayth Bahroun Khawla Derwish Aya Munir Mohamed Eman Sayed Younes	Research Ethics Review Committee of the National Cancer Institute - Sabratah - Libya
Tripoli, Libya National Heart Center Tripoli	PI: Rayet Al Islam Benjouira Mohamed Aliwa Najwa Abdullah Altashani Mohammed Omar Alteb	Ministry of Health

Tripoli, Libya University Hospital Tripoli	PI: Ahmed Msherghi Fatima Alagelli Sufyan Albarouni Ahmed Albishti Sarah Aljamal Mohamed Alsori Taha Ekhuja Suha Elzwai Mohammed Ghula Tahani Mustafa Ahmed Tuwaib Haifa Zriba	Ministry of Health, Ministry of Higher Education & Scientific Research, Authority of Natural Science Research and Technology
Tripoli, Libya AboSleem Hospital, Department of Anesthesiology and Intensive Care	PI: Hamza Mahmoud Agilla	Ministry of Health
MADAGASCAR		
Toamasina, Madagascar Centre Hospitalier Universitaire de Analankininina Toamasina	PI: Toky Andriamahefa Rafanomezantsoa	No ethics approval needed.
MALTA		
Msida, Malta University of Malta, Mater Dei Hospital, Department of Anesthesiology and Intensive Care	PI: Anne Marie Camilleri Podesta Denise Mifsud Bonnici Tiziana Pirotta	Ethics Committee of the University of Malta
MEXICO		
Ixtapaluca, Mexiko Regional Hospital of High Specialty of Ixtapaluca	PI: Gilberto Adrián Gasca López	Research Ethics Review Committee of the Regional Hospital of High Specialty of Ixtapaluca
NORTH MACEDONIA		
Skopje, North Macedonia University Hospital Skopje Mother Theresa, Department for Anesthesia Reanimation and intensive Care	PI: Maja Mojsova Mijovska Tatjana Davitkovska Aleksandra Gavrilovska Sanja Lukikj Marija Vesova Dina Zafirova	Medical Ethics Committee of the University of Skopje
PALESTINE		
Hebron, Palestine Princess Alia Governmental Hospital	PI: Sarah Amro	Ministry of Health, No ethics approval needed
Gaza, Palestine Palestinian Ministry of Health - Al-Shifa Medical Complex	PI: Baraa N. F. Hajjaj Muawia Alkhazendar Yousuf Barakat Sewar Abdulaziz Elejla Ahmed Elhissi	Ministry of Health, No ethics approval needed

	Ahmed Khader Ali Salem	
PORTUGAL		
Setúbal, Portugal Central Hosptial de Setúbal, Department for Anesthesiology	PI: Rita de Freitas Regufe André Filipe de Oliveira Eloy Lisbete Marisa Neto Cordeiro Perdigão	Research and Development Office of the Central Hospital Sebútal
RUSSIA		
Kemerovo, Russia Kemerovo Cardiology Centre, Department of Anesthesiology	PI: Evgeny Grigoriev Artem Ivkin Roman Kornelyuk	Ministry of Science and Higher Education of the Russian Federation, Local Ethics Committee (Institutional Review Board) Kemerovo
Moscow, Russia Bakulev Scientific Center for Cardiovascular Surgery	PI: Michael Yaroustovsky Marina Abramyan Ekaterina Komardina	Ministry of Science and Higher Education of the Russian Federation, Local Ethics Committee (Institutional Review Board) Moscow
St. Petersburg, Russia Almazov National Medical Research Centre, Polenov Neurosurgical Institute, Department of Anesthesiology and Intersive care	PI: Nataliya Lesteva Medina Aybazova Elmira Kumykova Svetlana Lesina Gennady Rybakov Alexey Shestov	Ministry of Science and Higher Education of the Russian Federation, Local Ethics Committee (Institutional Review Board), St. Petersburg
SAUDI ARABIA		
Al Khobar, Saudi Arabia Almana General Hospital Al-Khobar, Department of Cardiology	PI: Abdulnaser Ahmad Ahmad Barmou Bushra Lotfi Altayeb Ahmed Aisha Mohammad Eliyas Yousra Emadeldin	Ethics Committee of the Almana General Hospital
SWITZERLAND		
Zürich, Switzerland University Hospital Zürich, Institute for Anesthesiology	PI: Alexander Kaserer Clara Castellucci Julian Rössler Samira Akbas	Ethics Committee of the Canton Zürich
SLOVENIA		
Maribor, Slovenia University Medical Centre Maribor, Department of Anesthesiology and Intensive Care	PI: Andreja Möller Petrun Irena Gregorcic Vesna Sok	Medical Ethics Committee of the Republic of Slovenia
Murska Sobota, Slovenia General Hospital of Murska Sobota, Department of Anesthesiology and Perioperative Medicine	PI: Roman Čičak	Medical Ethics Committee of the Republic of Slovenia
SPAIN		

Granada, Spain University Hospital Vrigen de las Nieves, Department of Anaesthesia, Critical Care and Pain Therapy	PI: Elizabeth Bárcena Antonio Guisado Ismail Wi	Research Ethics Committee of the Government of Andalucia
Madrid, Spain University Hospital Infanta Leonor, Department of Anesthesiology and Intensive Care	PI: Javier Ripollés Melchor	Research Ethics Committee of the University Hospital Infanta Leonor and Hospital Virgen de la Torre
Gran Canaria, Spain University Hospital Gran Canaria Doctor Negrín, Department of Anesthesiology and Intensive Care	PI: Ángel Becerra-Bolaños Sergio Cabrera-Doreste Ancor Domínguez-Arbelo María Candelaria Delgado-Alonso Virginia Muiño-Palomar Aurelio Rodríguez-Pérez	Research Ethics Committee of the University Hospital Gran Canaria Doctor Negrín
Palma de Mallorca, Spain University Hospital Son Llàtzer, Department of Anesthesiology and Pain Medicine	PI: Javier Mata Estévez Maria Begona Covas Munoz Juan Mulet Matas Sara Perez Palao Maria Dolores Mira Quirós Alisia Cezara Teslev	Research Ethics Committee of the University Hospital Son Llàtzer
Barcelona, Spain University of Barcelona, Hospital de Sant Pau, Department of Anesthesiology and Pain Medicine	PI: Mercedes Garcia Alvarez Marga Argilaga María Campos Albert Bainac Astrid Batalla Mercedes Garcia Alvarez Marta Giné Gracia Herránz Ignacio Hinojal	Research Ethics Committee of the Hospital de la Santa Creu and Sant Pau de Barcelona
Vitoria-Gasteiz, Spain University Hospital Araba (Txagorritxu Hospital Álava), Department of Anesthesiology and Intensive Care	PI: Margarita Logroño Ejea Noelia de la Rosa Ruiz María Gastaca Abasolo Carla Rosario Houhton Acuna Ibai Iriarte Zaranton Ana Mendigurenmurua María José Munoz Sanz Erika Olea de la Fuente María Pilar Pérez Vaquero Ana Soto Iglesias Ana Ugarte Mieres Alaitz Urtiaga Urrestizala	Research Ethics Committee of the Government of the Basque Region
Logroño (La Rioja), Spain San Pedro Hospital, Department of Anesthesiology	PI: Lourdes Ferreira Félix Lobato Marta Aguado Sevilla	Research Ethics Committee of La Rioja
Barcelona, Spain Fundación Puigvert, Department of Anesthesiology and Intensive Care	PI: Andres Erazo Pere Miró Sergi Sabaté Diana Vernetta	Research Ethics Committee of the Fundació Puigvert
Donostia, Spain	PI: Berta Castellano Paulis Anabel Adell Perez Marta Aseguinolaza Pagola	Research Ethics Committee of the Government of the Basque Region

University Hospital Donostia, Department of Anesthesiology, Intensive Care and Pain Medicine	Berta Castellano Paulis Elena del Val Peciña Ainhoa Garmendia Odriozola Amaia Lopetegi Aizpurua Olatz Pavón Piquer Pilar Plou Garcia Paula Ortega Rezola Antia Osorio Lopez	
Madrid, Spain Hospital 12 de Octubre, Department of Anesthesiology and Intensive Care	PI: Isabel de la Calle Gil Rosalía Navarro Casado	Research Ethics Committee of the Hospital 12 de Octubre
Barcelona, Spain University Hospital Bellvitge, Department of Anesthesiology	PI: Peter Adamove Roser Bayona Domenge Francho Miguel Blasco Blasco Adriana Alexandra Rueda Villamizar Maria Antonia Perelló Llaneras	Research Ethics Committee of the University Hospital Bellvitge
Madrid, Spain University Hospital Fundacion Alcorcón Departament of Anesthesiology and Critical Care	PI: Jose Ignacio García-Sánchez Laura Fernandez Téllez Sara García Zamorano Natalia Gijón Herreros Andrea Rodriguez Esteve	Research Ethics Committee of the University Hospital Fundacion Alcorcón
Navarra, Spain University Hospital Navarra, Departament of Anesthesiology and Critical Care	PI: Pablo Monedero Rodríguez Isabel García Trigo, Agustín Alcaraz Andrea Lara Jiménez Iñigo Rubio Nuria García Raquel Callejas	Research Ethics Committee of the University Hospital Navarra
Madrid, Spain University Hospital Ramón y Cajal, Department of Anesthesiology and Intensive Care, Branch Cardiovascular and Thoracic Anesthesia	PI: Angel Manuel Candela Toha Eli Claros Pilar Cobeta Pascual Crespo Trini Dorado Elena Elías Javier Felices Diego Gil María Gómez Nuria Mané María Martín Adolfo Martínez Lucía Pereira Alberto Balvis Noemí Samaranch Ana Serrano Carlos Tiscar Judith VillaHoz	Research Ethics Committee of the University Hospital Ramón y Cajal
Barcelona, Spain University Hospital Vall d'Hebron, Department of Anesthesiology and Critical Care	PI: Patricia Galán Menéndez Elena Cardona Anna Conesa Veronica Estepa Patricia Galán Laura Llinares Espí Yuri Loaiza Aldeán Susana Manrique	Research Ethics Committee of the University Hospital Vall d'Hebron

	Víctor Morales Ariza Laura Villarino Villa	
SUDAN		
Omdurman, Sudan Shargh Alneel Hospital, Military Hospital Omdurman, Department of Anesthesia	PI: Elfayadh Saidahmed Mohamed Amed Suliman Hytham Hamid	Committee of the Sharg Alneel Hospital
Al-Qadarif, Sudan Gadarif Teaching Hospital, Department of Anesthesia	PI: Ahmed Mohamed Ibrahim Modather Mohamed Saeed	Medical Research Ethics Committee of the University of Gadarif
TURKEY		
Istanbul, Turkey Istanbul University, Istanbul Faculty of Medicine, Department of Anesthesiology	PI: Orhan Sungur Mukadder Demet Altun Nur Canbolat Müşerref Beril Dinçer Tulay Özkan Seyhan	Ethics Committee of the University of Istanbul (Nationwide approval)
Istanbul, Turkey Acıbadem Altunizade Hospital, Department of Anesthesiology	PI: Serap Aktaş Yıldırım	Ethics Committee of the University of Istanbul
Istanbul, Turkey Acibadem Atakent Hospital, Department of Anesthesiology	PI: Müzeyyen İyigün	Ethics Committee of the University of Istanbul
Mersin University, School of Medicine, Department of Anesthesiology and Intensive Care	PI: Davut Yapıcı Levent Özdemir Aslinur Sagun	Ethics Committee of the University of Istanbul
Antalya, Turkey University Hospital Akdeniz, Department of Anesthesiology	PI: Neval Boztug Yesim Cetintas Bora Dinc Emel Gündüz	Ethics Committee of the University of Istanbul
Adana, Turkey Çukurova University, Department of Anesthesiology	PI: Hakkı Ünlügenç Demet Lafli Tunay	Ethics Committee of the University of Istanbul
Samsun, Turkey Mayıs University, Department of Anesthesiology	PI: Deniz Karakaya Burhan Dost Ozgur Komurcu	Ethics Committee of the University of Istanbul
Istanbul, Turkey Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Anesthesiology and Intensive Care Medicine	PI: Özlem Korkmaz Dilmen Eren Fatma Akcil Özlem Korkmaz Dilmen Yusuf Tunali	Ethics Committee of the University of Istanbul
Manisa, Turkey Manisa Celal Bayar University, Medical Faculty, Department of Anesthesiology and Reanimation	PI: Gülay Ok Eda Tok Alsina Özge Hakli	Ethics Committee of the University of Istanbul
Istanbul, Turkey Prof. Dr. Cemil Tascioglu City Hospital, Department of Anesthesiology	PI: Cengiz Polat Namigar Turgut	Ethics Committee of the University of Istanbul
Istanbul, Turkey Yeditepe University, Faculty of Medicine	PI: Nurcan Kızılcık Özge Köner	Ethics Committee of the University of Istanbul

Istanbul, Turkey Haseki Sultangazi Research and Training Hospital, Department of Anesthesiology and Intensive Care	PI: Öznur Şen Nurdan Aydin Burcu Basaran Emre Sertac Bingul	Ethics Committee of the University of Istanbul
Istanbul, Turkey University Hospital Koç, Department of Anesthesiology and Reanimation	PI: Yavuz Gürkan Kamil Darcin Semra Ugur	Ethics Committee of the University of Istanbul
Istanbul, Turkey Health Sciences University Kartal Dr. Lutfi Kirdar Training and Research Hospital, Department of Anesthesiology and Intensive Care	PI: Kemal Tolga Saracoglu	Ethics Committee of the University of Istanbul
Ankara, Turkey Ankara City Hospital, Department of Anesthesiology	PI: Asli Demir Özgök Aysegül Eda Balci Behic Girgin Aygun Guler Ümit Karadeniz Nihal Özaslan Yigit Özay Hülya Namik Ozcan Aysun Postaci Mehmet Sahap Nevriye Salman	Ethics Committee of the University of Istanbul
Balikesir, Turkey Balikesir University, Department of Anesthesiology and Intensive Care	PI: Özlem Sağır Bulent Atik Murat Bicakcioglu Hafize Fisun Demir Ugün Fatih Nazan Kocaoglu	Ethics Committee of the University of Istanbul
Malatya, Turkey University Hospital Inonu, Department of Anaesthesiology and Reanimation	PI: Hüseyin ilksen Toprak Duygu Demiröz Aslan Yusuf Ziya Colak	Ethics Committee of the University of Istanbul
Isparta, Turkey Suleyman Demirel University School of Medicine, Department: Anesthesiology and Reanimation	PI: Mustafa Soner Ozcan	Ethics Committee of the University of Istanbul
Department of Anesthesiology and Reanimation, Health Sciences University Medical School, Derince, Kocaeli, Turkey	PI: Mehmet Yilmaz	Ethics Committee of the University of Istanbul
Bursa, Turkey University of Health Sciences Turkey, Yuksek Ihtisas Training and Research Hospital, Department of Anesthesiology and Reanimation	PI: Umran Karaca	Ethics Committee of the University of Istanbul
Edirne, Turkey Trakya University, Faculty of Medicine Department of Anesthesiology and Reanimation	PI: Sevtap Hekimoglu Sahin	Ethics Committee of the University of Istanbul
Düzce, Turkey Düzce University, Department of Anesthesiology and Reanimation	PI: Özlem Ersoy Karka Gizem Demir Şenoğlu	Ethics Committee of the University of Istanbul

Ankara, Turkey Ankara University School of Medicine, İbni Sina Hospital	PI: Süheyla Erkoç Karadağ Neslihan Alkis	Ethics Committee of the University of Istanbul
Ankara, Turkey Ankara University School of Medicine, Cebeci Hospital	PI: Volkan Baytaş	Ethics Committee of the University of Istanbul
Trabzon, Turkey Karadeniz Technical University, Faculty of Medicine, Department of Anesthesiology and Intensive Care	PI: Engin Erturk Ali Akdogan Ahmet Besir Engin Erturk Dilek Kutanis Sedat Saylan Ersagun Tugcugil	Ethics Committee of the University of Istanbul
Izmir, Turkey Izmir Democracy University School of Medicine, Department of Anesthesiology and Reanimation Department	PI: Pinar Ayvat	Ethics Committee of the University of Istanbul
Ankara, Turkey Gazi University School of Medicine, Department of Anesthesiology	PI: Berrin Günaydın Beyza Mehri Büyükgebiz	Ethics Committee of the University of Istanbul
Kahramanmaraş, Turkey Kahramanmaras Sutcu Imam University Faculty of Medicine, Department of Anesthesiology and Reanimation	PI: Omer Faruk Boran Feyza Calisir Yavuz Orak	Ethics Committee of the University of Istanbul
Izmir, Turkey Dokuz Eylül Üniversitesi, Department of Anesthesiology and Reanimation	PI: Bahar Kuvaki Balkan Bahar Kuvaki Balkan Sibel Büyükcoban Erol Gökel Sakize Ferim Günenc Sule Özbilgin	Ethics Committee of the University of Istanbul
Bursa, Turkey Bursa Uludag University, Medical Faculty Department of Anaesthesiology and Reanimation	PI: Suna Göre Selcan Akesen Seda Cansabuncu	Ethics Committee of the University of Istanbul
UKRAINE		
Zaporizhzhia, Ukraine Zaporizhzhia State Medical University Hospital, Department of Anesthesiology and Intensive Care	PI: Natalia Momot Anna Panchenko	Bioethics Commission of Zaporizhzhia State Medical University
UNITED STATES		
Birmingham, USA University of Alabama, Department of Anesthesiology and Perioperative Medicine	PI: Jean-Francois Pittet Kristen Rutledge	Office of the Institutional Review Board for Human Use, University of Alabama at Birmingham