Clinical Kidney Journal, 2023, vol. 16, no. 12, 2549–2558

https://doi.org/10.1093/ckj/sfad160
Advance Access Publication Date: 5 July 2023
Original Article

ORIGINAL ARTICLE

Acute kidney injury associated with nephrotoxic drugs in critically ill patients: a multicenter cohort study using electronic health record data

Izak A.R. Yasrebi-de Kom [1,2], Dave A. Dongelmans[2,3], Ameen Abu-Hanna[1,2], Martijn C. Schut[1,2,4], Dylan W. de Lange[5], Eric N. van Roon[6], Evert de Jonge[7], Catherine S.C. Bouman[3,8], Nicolette F. de Keizer[1,2], Kitty J. Jager [1,2] and Joanna E. Klopotowska[1,2]; on behalf of the RESCUE Study Group*

[1]Amsterdam UMC location University of Amsterdam, Department of Medical Informatics, Amsterdam, The Netherlands, [2]Amsterdam Public Health, Amsterdam, The Netherlands, [3]Amsterdam UMC location University of Amsterdam, Department of Intensive Care Medicine, Amsterdam, The Netherlands, [4]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Laboratory Medicine, Amsterdam, The Netherlands, [5]Department of Intensive Care and Dutch Poison Information Center, University Medical Center Utrecht, Utrecht, The Netherlands, [6]Department of Clinical Pharmacy and Pharmacology, Medical Center Leeuwarden, Leeuwarden, The Netherlands, [7]Department of Intensive Care, Leiden University Medical Center, Leiden, The Netherlands and [8]Amsterdam Institute for Infection and Immunity, Amsterdam, The Netherlands

*Members of the RESCUE Study Group are listed in the Appendix.
Correspondence to: Izak A.R. Yasrebi-de Kom; E-mail: i.a.r.dekom@amsterdamumc.nl

ABSTRACT

Background. Nephrotoxic drugs frequently cause acute kidney injury (AKI) in adult intensive care unit (ICU) patients. However, there is a lack of large pharmaco-epidemiological studies investigating the associations between drugs and AKI. Importantly, AKI risk factors may also be indications or contraindications for drugs and thereby confound the associations. Here, we aimed to estimate the associations between commonly administered (potentially) nephrotoxic drug groups and AKI in adult ICU patients whilst adjusting for confounding.

Methods. In this multicenter retrospective observational study, we included adult ICU admissions to 13 Dutch ICUs. We measured exposure to 44 predefined (potentially) nephrotoxic drug groups. The outcome was AKI during ICU admission. The association between each drug group and AKI was estimated using etiological cause-specific Cox proportional hazard models and adjusted for confounding. To facilitate an (independent) informed assessment of residual confounding, we manually identified drug group-specific confounders using a large drug knowledge database and existing literature.

Results. We included 92 616 ICU admissions, of which 13 492 developed AKI (15%). We found 14 drug groups to be associated with a higher hazard of AKI after adjustment for confounding. These groups included established (e.g. aminoglycosides), less well established (e.g. opioids) and controversial (e.g. sympathomimetics with α- and β-effect) drugs.

Received: 13.12.2022; Editorial decision: 18.6.2023

Conclusions. The results confirm existing insights and provide new ones regarding drug associated AKI in adult ICU patients. These insights warrant caution and extra monitoring when prescribing nephrotoxic drugs in the ICU and indicate which drug groups require further investigation.

LAY SUMMARY

Acute kidney injury (AKI) is a common problem in adult intensive care unit (ICU) patients and is often caused by nephrotoxic drugs. However, due to a lack of large pharmaco-epidemiological studies investigating the associations between drugs and AKI, our knowledge on the nephrotoxicity of drugs is limited. This hampers our ability to improve medication safety in the ICU. Using real-world data from 13 ICUs on 92 616 ICU admissions, we estimated the associations between 44 (potentially) nephrotoxic drug groups and AKI whilst adjusting for confounding. In total, 14 groups were associated with a higher hazard of AKI. Our approach confirms existing knowledge and provides new insights and directions for current ICU practice and follow-up research regarding AKI associated with drugs.

Keywords: acute kidney injury, adverse drug events, confounding, drugs, intensive care units

INTRODUCTION

Acute kidney injury (AKI) is a clinically relevant problem in intensive care unit (ICU) patients. AKI is associated with prolonged hospital stays and increased morbidity and mortality [1]. Drugs often play a causal role in the development of AKI and have been deemed as one of the few preventable causes [2, 3]. Which drugs may cause AKI and the strength of the relationships are the subject of debate [4]. Randomized controlled trials provide limited insights regarding drug side-effects as they primarily focus on drug efficacy [5]. We therefore need large pharmaco-epidemiological studies using observational data to gain insights into the nephrotoxicity of drugs [4, 5]. Current pharmaco-epidemiological research concerning drug-induced AKI has been limited in several ways [6–8]. First, sample size was often limited, which hindered the identification of (weaker) associations. Second, data often lacked appropriate detail, limiting the adjustment for confounding. Third, known confounders (according to etiological information in, e.g. existing literature) were often not identified and reported, which precluded an (independent) informed assessment and discussion of potential residual confounding. Fourth, aggregation of all or most (potentially) nephrotoxic drugs into one variable, possibly due to limited numbers of exposed patients, hindered the identification of drug or drug group-specific associations.

The paucity of large pharmaco-epidemiological studies that did address the above limitations has led to an expert opinion–based ranking of the nephrotoxic potential of 167 drugs in the ICU setting in a recent study by Gray *et al.* [4]. The authors of this study re-iterated the need for large pharmaco-epidemiological studies to investigate the nephrotoxicity of drugs. In our study we aimed to help meet this need and attempted to address the above-mentioned four limitations. We re-used detailed routinely collected data from electronic health record (EHR) systems of ICUs located in 13 Dutch hospitals, and investigated the associations between 44 commonly administered (potentially) nephrotoxic drug groups and AKI whilst adjusting for confounding.

MATERIALS AND METHODS

This study was part of the project "Towards a leaRning mEdication Safety system in a national network of intensive Care Units—timely detection of adverse drug Events" (RESCUE). We report our findings according to the REporting of studies Conducted using Observational Routinely collected health Data for pharmacoepidemiology (RECORD-PE) guideline (Supplementary data, S1) [9].

Data sources

We re-used retrospectively collected pseudonimized EHR data from consecutive admissions to 13 Dutch ICUs from 1 January 2010 to 31 December 2019. The data contained serum creatinine (SCr) levels, drug administrations, arterial blood pressure measurements and kidney replacement therapy (KRT) treatments. We enriched these EHR data with controlled and curated admission characteristics previously collected from the 13 ICUs via the Dutch National Intensive Care Evaluation quality registry (NICE) [10]. For this purpose we used the pseudonymized minimal dataset (MDS) of the NICE registry containing admission characteristics, (chronic) comorbidities, physiology measurements and the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) ICU admission diagnoses and scores.

Patient inclusion

All adult patients with at least two SCr samples during ICU admission were included: one SCr sample within 24 h of admission and at least one subsequent SCr sample within 7 days to allow for a diagnosis of AKI. We excluded admissions with an APACHE IV acute renal failure admission diagnosis, admissions with pre-ICU chronic KRT, admissions with KRT during the admission but without preceding AKI and readmissions to the ICU. Furthermore, we excluded admissions with a missing APACHE IV admission diagnosis or admission type, length, weight, age, sex or AKI risk factors.

Identification of (potentially) nephrotoxic drugs

We used information available in the online Drug Knowledge Database (https://kennisbank.knmp.nl/) of the Royal Dutch Pharmacists Association [Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), in Dutch, https://www.knmp.nl/] to identify (potentially) nephrotoxic drugs to investigate [11]. The KNMP Drug Knowledge Database (KNMP-DKD) offers comprehensive and up-to-date drug information. Using the Medical Dictionary for Regulatory Activities (MedDRA) acute renal failure Standardized MedDRA Query (SMQ) terms [12] translated to Dutch and complemented with acute renal

failure terms typically used in Dutch, the side-effects sections in the KNMP-DKD were searched to identify drugs with AKI as a potential side-effect (Supplementary data, S2). We aggregated the identified drugs to drug groups defined by the KNMP-DKD.

To guide the interpretation of our results, we categorized each drug group as "confirmatory" or "exploratory" by utilizing the recently published consensus rating regarding the nephrotoxic potential of drugs commonly administered in the ICU [4]. Drug groups containing at least one member drug with a nonzero nephrotoxic potential rating were categorized as "confirmatory" and the remaining groups as "exploratory".

Exposure to (potentially) nephrotoxic drug groups

We recorded systemic exposures (e.g. parenteral or oral) to the identified drug groups from ICU admission until ICU discharge, AKI diagnosis or death, whichever occurred first. Exposure to a drug group was defined as the administration of at least one of the group's individual drugs. We coded the exposure variable for each group as time-varying, with time up to initiation as unexposed and from initiation to the outcome as exposed. We deliberately did not investigate dose-response relationships because our aim was to uncover associations between drug groups and AKI after adjusting for confounding, regardless of dose and duration of use. We included drug groups with at least one member drug to which a minimum of 1% of all admissions was exposed.

Acute kidney injury

The outcome of interest was AKI during ICU admission according to the SCr criteria in the KDIGO Clinical Practice Guideline for Acute Kidney Injury [13] (https://kdigo.org/guidelines/acute-kidney-injury/). Since SCr baselines from before ICU admission were not available, we used the first measured SCr within 24 h of the ICU admission as the baseline. For AKI staging we applied the SCr and KRT criteria.

Identification of group-specific confounders through existing knowledge

We collected known risk factors for AKI from the literature [13–16] and attempted to find suitable variables or variable constructs to represent these factors using our data (Supplementary data, S3). To identify confounding factors by indication and contraindication we manually recorded the AKI risk factors that were also indications or contraindications for each individual drug using the KNMP-DKD [11]. The acute AKI risk factors that were side-effects of a drug were labeled as mediators if the side-effect frequency was at least 0.1% (Supplementary data, Fig. S4.1). We aggregated the collected confounders per drug to the drug groups: if an AKI risk factor was a confounder in any of the drug group's members, it was labeled as a confounder for that group. If an acute AKI risk factor was a mediator for one of the group's members, but a confounder for another, we labeled the AKI risk factor as a mediator for that group (Supplementary data, Fig. S4.2).

Statistical analysis

We investigated the associations between exposure to each (potentially) nephrotoxic drug group and AKI using etiological cause-specific Cox proportional hazard (CSPH) models [17]. We censored ICU admissions when discharge or death occurred, as these were censoring and competing risk events, respectively. Potential clustering of data within ICUs was addressed by adding a cluster term in all models. For each drug group we fitted three CSPH models: (i) unadjusted, (ii) adjusted and (iii) adjusted, but with "shifted" outcome timestamps. We fitted the latter models as a secondary analysis to assess the impact of two important notions. First, SCr is a lagged indicator of renal function [18], which may lead to protopathic bias. Second, one should consider a plausible time-to-onset of at least 24 h between a drug exposure initiation and AKI diagnosis for there to be a potential causal relationship [3]. For this secondary analysis we therefore re-calculated the outcome timestamps by subtracting 24 h and re-fitted the adjusted CSPH models. This way, we assumed that an SCr-based AKI diagnosis occurring at a specific time point was the result of an injury occurring 24 h earlier, and ignored any (un)exposed time after this injury during the analysis. We excluded admissions that experienced the outcome within the first 24 h of ICU admission, as these admissions would have experienced their hypothetical "shifted" outcome before ICU admission.

In the adjusted analyses we adjusted for age, sex, the SCr baseline, the APACHE IV predicted mortality probability and all AKI risk factors except the identified group-specific mediators. We additionally adjusted for exposure to nephrotoxic comedication groups, as defined by the included groups categorized as "confirmatory". Our approach is illustrated in Fig. 1.

Sensitivity analyses

Recent research suggested several criteria to recognize drug-induced AKI in clinical practice, including reaching AKI stage 2 or 3 [3]. We therefore investigated the associations between the included drug groups and AKI stage 2 or 3. In addition, we combined the latter analysis with our secondary analysis.

P-values were adjusted for multiple testing using the Benjamini–Hochberg procedure [19]. All data analyses were performed in R version 4.0.3 [20].

RESULTS

We included 92 616 admissions from the 13 ICUs (Fig. 2). The characteristics of the included admissions are presented in Table 1 (see Supplementary data, S6 for more details).

AKI incidence and selected drug groups

Of the 92 616 included admissions, 13 492 admissions developed AKI (15%). We included 44 (potentially) nephrotoxic drug groups in our analyses. The identified confounders and mediators per drug can be found in Supplementary data, S7. For groups with only one or two member drugs we specify the drug members at first mention. For a full overview of the drugs per group we refer to Supplementary data, S7.

Associations between drug groups and AKI

The results of the CSPH models are presented in Table 2 (this table only includes the drug groups associated with a higher hazard of AKI in the adjusted models, see Supplementary data, S8 for the results of all 44 groups). We categorized 19 and 25 drug group analyses as "confirmatory" and "exploratory," respectively. In the unadjusted models, 23 of the 44 investigated groups were associated with higher hazard of AKI. However, only 14 of these 23 groups were associated with a higher hazard of AKI in the

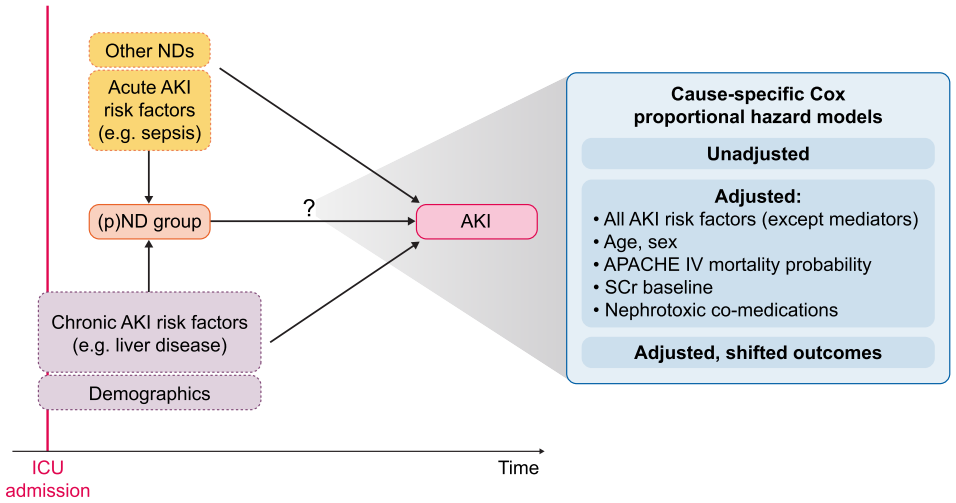

Figure 1: Illustration of our approach to investigate the association between each (potentially) nephrotoxic drug group and AKI. The crude association between a drug group and AKI can be confounded. A confounder is a factor that both (indirectly) affects the administration of the group under investigation and (indirectly) affects AKI risk. The collection of all confounders may include (1) acute AKI risk factors (e.g. sepsis), (2) chronic AKI risk factors (e.g. liver disease), (3) demographics (e.g. sex) and (4) other nephrotoxic drugs, illustrated by the boxes with dotted outlines. For each investigated drug group, we identified the group-specific confounders. In addition, we identified age, sex, the SCr baseline, the APACHE IV predicted mortality probability and known nephrotoxic drugs as confounders for all groups. We measured exposure to each drug group from ICU admission until the outcome (i.e. AKI, discharge or death) and estimated the association between each group and AKI independent of the confounders using cause-specific Cox proportional hazard models. See Supplementary data, Fig. S4.1 for group-specific examples of confounding by indication and confounding by contraindication. (p)ND: (potentially) nephrotoxic drug.

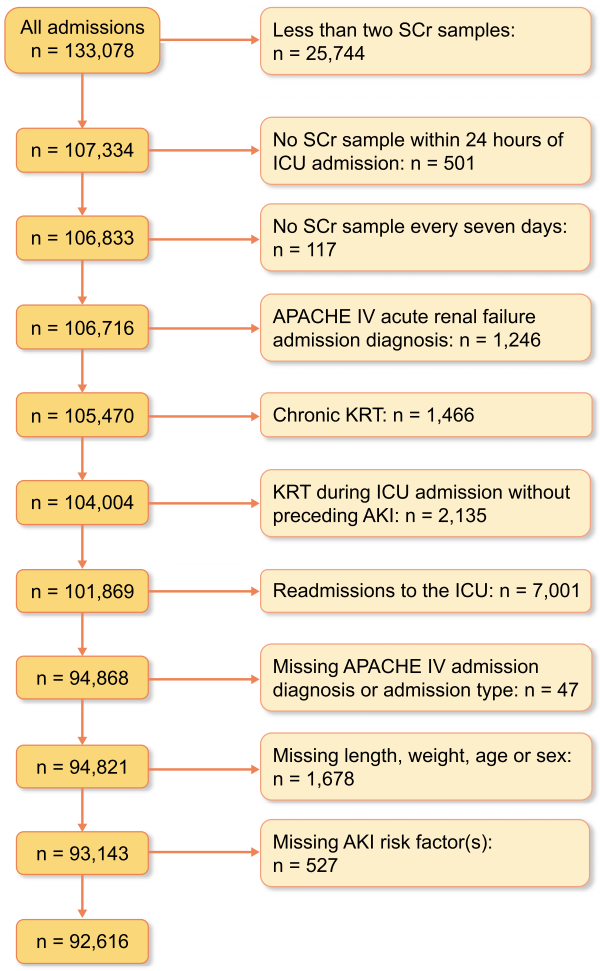

Figure 2: Overview of included and excluded admissions with corresponding exclusion criteria.

adjusted models. In the "confirmatory" category, 8 of the 19 (42%) groups were associated with a higher hazard of AKI, while in the "exploratory" category, 6 of the 25 (24%) groups were associated with a higher hazard of AKI. The three drug groups with the highest hazard ratios (HRs) in the adjusted models were phosphodiesterase inhibitors [enoximone and milrinone, 1.75, 95% confidence interval (CI) 1.50–2.03, $P < .001$], loop diuretics (furosemide and bumetanide, 1.73, 95% CI 1.52–1.96, $P < .001$) and immunosuppressants (1.67, 95% CI 1.44–1.95, $P < .001$).

The HRs in the adjusted models were often similar to the HRs in the secondary analysis in which we "shifted" the outcome timestamps by subtracting 24 h. Notable exceptions were opioids, blood and plasma products (albumin), and antihypertensives (ketanserin; changing from a higher hazard to no association), other systemic anesthetics (propofol), other analgesics (paracetamol) and carbapenems (meropenem and ertapenem; changing from no association to a lower hazard) and angiotensin-converting enzyme (ACE) inhibitors (changing from a lower hazard to a higher hazard) (Table 2, Supplementary data, S8).

The sensitivity analysis investigating AKI stage 2 or 3 as the outcome showed similar results compared with our main analysis. Notable exceptions were antimycotic antibiotics (amphotericin B) and antihypertensives (changing from a higher hazard to no association), calcium antagonists (nifedipine and verapamil; changing from no association to a higher hazard) and ACE inhibitors (showing a stronger association with a lower hazard) (Supplementary data, S9).

The second sensitivity analysis combined the AKI stage 2 or 3 outcome with the secondary analysis ("shifted" outcomes). The results showed a high impact on the HRs of phosphodiesterase inhibitors and sympathomimetics with α- and β-effect, both no longer associated with a higher hazard of AKI. Furthermore, other systemic anesthetics, other analgesics, carbapenems and cephalosporins changed from no association to a lower hazard of AKI (Supplementary data, S9).

Table 1: Characteristics of the included ICU admissions.

Characteristic	All admissions ($n = 92\,616$)	Admissions with AKI ($n = 13\,492$)	Admissions without AKI ($n = 79\,124$)
Age (years), median (Q1–Q3)	66.0 (56.0–74.0)	68.0 (59.0–76.0)	65.0 (55.0–74.0)
Male sex, No. (%)	58 106 (62.7)	8909 (66.0)	49 197 (62.2)
Planned admission, No. (%)	41 830 (45.2)	3645 (27.0)	38 185 (48.3)
Admission type, No. (%)			
Medical	36 151 (39.0)	7053 (52.3)	29 098 (36.8)
Emergency surgical	11 754 (12.7)	2488 (18.4)	9266 (11.7)
Elective surgical	44 711 (48.3)	3951 (29.3)	40 760 (51.5)
Length of stay (days), median (Q1–Q3)	1.5 (0.9–3.5)	5.2 (2.2–12.2)	1.1 (0.9–2.7)
APACHE IV score, median (Q1–Q3)	41.0 (30.0–59.0)	65.0 (50.0–88.0)	38.0 (28.0–53.0)
ICU mortality, No. (%)	7309 (7.9)	3712 (27.5)	3597 (4.5)
Hospital mortality, No. (%)	10 770 (11.6)	4634 (34.3)	6136 (7.8)
SCr baseline (mg/dL), median (Q1–Q3)	0.9 (0.7–1.2)	1.3 (0.9–1.8)	0.9 (0.7–1.1)
KRT during admission, No. (%)	2734 (3.0)	2734 (20.3)	0 (0.0)
AKI stages, No. (%)			
Stage 1	8449 (62.6)	8449 (62.6)	
Stage 2	1242 (9.2)	1242 (9.2)	
Stage 3	3801 (28.2)	3801 (28.2)	
Time between ICU admission and AKI (h), median (Q1–Q3)	24.3 (13.6–41.4)	24.3 (13.6–41.4)	
Acute AKI risk factors, No. (%)			
Acute heart failure	9879 (10.7)	2782 (20.6)	7097 (9.0)
Burns	41 (0.0)	5 (0.0)	36 (0.0)
Graft or transplant surgery	19 938 (21.5)	1964 (14.6)	17 974 (22.7)
Hypotension	25 464 (27.5)	5117 (37.9)	20 347 (25.7)
Hypovolemia	2209 (2.4)	465 (3.4)	1744 (2.2)
Major surgery	55 226 (59.6)	6181 (45.8)	49 045 (62.0)
Mechanical ventilation	61 425 (66.3)	10 812 (80.1)	50 613 (64.0)
Sepsis	15 324 (16.5)	3984 (29.5)	11 340 (14.3)
Trauma	4351 (4.7)	456 (3.4)	3895 (4.9)
Chronic AKI risk factors, No. (%)			
Alcohol abuse	9981 (10.8)	2469 (18.3)	7512 (9.5)
Cardiovascular disease	28 923 (31.2)	3716 (27.5)	25 207 (31.9)
Chronic kidney disease	3365 (3.6)	1397 (10.4)	1968 (2.5)
Chronic pulmonary disease	12 172 (13.1)	2045 (15.2)	10 127 (12.8)
Diabetes mellitus	15 593 (16.8)	2850 (21.1)	12 743 (16.1)
Liver disease	1189 (1.3)	330 (2.4)	859 (1.1)
Malignancy	12 894 (13.9)	1493 (11.1)	11 401 (14.4)
Obesity	18 503 (20.0)	3189 (23.6)	15 314 (19.4)

See Supplementary data, S6 for more details.

Finally, of all 44 investigated drug groups, 7 groups consistently showed an association with a higher hazard of AKI across all our analyses: glycopeptide antibiotics (vancomycin and teicoplanin), sulfonamides (co-trimoxazole), aminoglycosides, penicillins, antiarrhythmics, loop diuretics and immunosuppressants. All of the latter seven groups, except the antiarrhythmics, were categorized as "confirmatory" (Supplementary data, S8 and S9).

DISCUSSION

We sought to investigate the associations between commonly administered (potentially) nephrotoxic drug groups and AKI in adult ICU patients whilst adjusting for confounding. Using existing etiological knowledge obtained from literature and a drug knowledge database, we identified group-specific confounders to aid the (independent) informed assessment of our results. Of the 44 investigated drug groups, 14 were associated with a higher hazard of AKI in our main adjusted analysis. Seven of the latter groups remained associated with a higher hazard of AKI across the secondary and sensitivity analyses. Below, we discuss our main findings.

Drug groups associated with a higher hazard of AKI

Most of the identified drug groups associated with higher hazard of AKI are in line with previous research [3, 14, 21–28] and the recent consensus-based list of nephrotoxins [4]. While the relationship between some of these drugs and AKI has been studied extensively (e.g. aminoglycosides, antimycotic antibiotics and immunosuppressants), data on other drugs are scarce (e.g. opioids). Surprisingly, phosphodiesterase inhibitors and sympathomimetics with α- and β-effect were relatively strongly associated with a higher hazard of AKI in our main analysis. Yet, at present, no clear empiric evidence of harm from the use of these drugs in the ICU setting with respect to AKI is available. Previous reports have presented potential mechanisms by which AKI may occur due to these drug groups, including hypotension and

Table 2: Unadjusted, adjusted, and adjusted, shifted outcomes HRs and 95% CIs for the included drug groups that were associated with a higher hazard of AKI after adjustment.

Drug group	Fraction admissions exposed	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted, shifted outcomes ($n = 49\,933$) HR (95% CI)	Analysis category
Opioids	0.64	1.57 (1.31–1.89)***	1.40 (1.24–1.57)***	1.23 (1.02–1.48)	C
Glycopeptide antibiotics[a]	0.04	2.03 (1.74–2.36)***	1.55 (1.34–1.79)***	1.50 (1.28–1.77)***	C
Sulfonamides[b]	0.02	1.86 (1.67–2.08)***	1.48 (1.35–1.63)***	1.86 (1.72–2.01)***	C
Aminoglycosides	0.06	1.93 (1.63–2.29)***	1.46 (1.32–1.61)***	1.38 (1.18–1.63)***	C
Antimycotic antibiotics[c]	0.01	2.11 (1.80–2.47)***	1.31 (1.24–1.39)***	1.48 (1.30–1.68)***	C
Penicillins	0.06	1.63 (1.46–1.82)***	1.28 (1.11–1.47)**	1.35 (1.14–1.61)**	C
Phosphodiesterase inhibitors[d]	0.16	2.28 (1.86–2.80)***	1.75 (1.50–2.03)***	1.47 (1.17–1.84)**	E
Antiarrhythmics	0.09	2.60 (2.30–2.93)***	1.64 (1.47–1.84)***	1.69 (1.51–1.88)***	E
Loop diuretics[e]	0.24	1.94 (1.69–2.22)***	1.73 (1.52–1.96)***	1.38 (1.24–1.53)***	C
Sympathomimetics with α- and β-effect	0.59	2.49 (2.06–3.01)***	1.66 (1.42–1.93)***	1.23 (1.05–1.44)*	E
Blood and plasma products[f]	0.08	1.87 (1.21–2.89)**	1.38 (1.09–1.75)*	1.24 (0.97–1.57)	E
Antihypertensives[g]	0.02	1.77 (1.44–2.17)***	1.26 (1.13–1.39)***	1.13 (0.98–1.30)	E
Plasma replacement products[h]	0.07	1.60 (1.38–1.85)***	1.26 (1.12–1.42)***	1.32 (1.18–1.48)***	E
Immunosuppressants[i]	0.01	3.02 (2.72–3.36)***	1.67 (1.44–1.95)***	1.91 (1.66–2.21)***	C

The table is sorted on the adjusted HRs within related drug group collections separated by dashed lines. The last column depicts the analysis category (i.e. confirmatory or exploratory). See Supplementary data, S8 for the results of all 44 included drug groups.
*$P < .05$, **$P < .01$, ***$P < .001$ (P-values adjusted for multiple testing).
[a]Vancomycin and teicoplanin.
[b]Sulfamethoxazole in combination with trimethoprim (co-trimoxazole).
[c]Amphotericin B.
[d]Enoximone and milrinone.
[e]Furosemide and bumetanide.
[f]Albumin.
[g]Ketanserin.
[h]Hydroxyethylstarch.
[i]Excluding corticosteroids.
C: confirmatory; E: exploratory.

excessive accumulation of metabolites for phosphodiesterase inhibitors [29, 30] and renal vasoconstriction and decreased perfusion for sympathomimetics with α- and β-effect [14, 31]. However, improved renal outcomes have also been described [32–34]. Our estimates for sympathomimetics with α- and β-effect may have been biased by unmeasured hypotension events before ICU admission, leading to confounding by indication. Furthermore, both drug groups showed lower HRs in our secondary analysis ("shifted" outcomes) and no longer showed an association after combining the latter analysis with the AKI stage 2 or 3 outcome. Note however, that these findings are compatible with both protopathic bias and a very rapid rise in SCr.

Drug groups not associated with AKI

Our results provided new insights for several highly debated drug groups: iodinated contrast media and proton pump inhibitors. This study supports previous findings showing no higher hazard of AKI with these groups in our analyses [35, 36]. The nonsteroidal anti-inflammatory drug (NSAID) excluding salicylates group was not associated with a higher hazard of AKI, which is surprising as increased risk of AKI with NSAID use is well documented [37]. Previous research found a lower odds of AKI with NSAID use in ICU patients between 16–25 years old and suggested this to be caused by confounding by contraindication [38]. We observed a higher HR for this drug group after adjustment, which suggests that confounding by contraindication indeed plays a role. Residual confounding by contraindication through chronic hypertension and smoking—two AKI risk factors which were not available in our data—might provide further explanations for our findings.

Drug groups associated with a lower hazard of AKI

Several of the investigated drug groups were associated with lower hazard of AKI, including other blood glucose–lowering agents, ACE inhibitors and anti-epileptics. Metformin (other blood glucose–lowering agent) has recently been associated with several pleiotropic effects, including a renoprotective effect [39]. Although this is in line with our main analysis, the protective association was not confirmed in the secondary and sensitivity analyses. Our main analysis showed that ACE inhibitors were associated with a lower hazard of AKI. While our "shifted" outcomes analysis showed a higher hazard of AKI for ACE inhibitors, the association disappeared when combining this analysis with AKI stage 2 or 3 as the outcome. As noted above, we were unable to adjust for chronic hypertension, which may have resulted in an overestimation of the HR for this group due to residual confounding by indication. ACE inhibitors are widely regarded as agents that can cause AKI [25], as also identified in the recent consensus-based list of nephrotoxins [4]. Yet, the current evidence for the prevention of AKI by stopping ACE inhibitors is limited and may be confounded [40]. Previous literature suggests that ACE inhibitors may cause a transient and relatively small rise in SCr without causing an injury to the kidneys, and may even be renoprotective [40–42]. We hypothesized that a reversible fall in glomerular filtration rate due to ACE inhibitors through their effects on intrarenal hemodynamics (auto-regulation) may be less of an issue in ICU patients.

This because the hemodynamic support in the ICU is well maintained making low intraglomerular pressure uncommon. Lastly, anti-epileptics were consistently associated with a lower hazard of AKI across all our analyses. Interestingly, the second most frequently administered anti-epileptic in our database, valproic acid, has recently been shown to protect against AKI in animal models of polytrauma and hemorrhagic shock [43]. However, it is not yet clear whether valproic acid may have caused positive renal responses through improved hemodynamics or direct protection against kidney injury [44].

It is important to note that the estimated associations after adjustment for confounding reflect the average situation in clinical practice rather than the average intrinsic nephrotoxicity in the ICU population. The associations are an aggregate of the intrinsic nephrotoxicity combined with potential (post-administration) mitigations of nephrotoxicity in clinical practice. Mitigations may for example include dosage adjustments, therapeutic drug monitoring or better hemodynamic monitoring and support. This way, AKI due to known nephrotoxic drugs might be prevented in clinical practice and thus not be reflected in the estimated associations. Investigations of such mitigations may uncover reasons why a known nephrotoxic drug is infrequently causing AKI, but will not change the average association that may correctly reflect the average causal effect in clinical practice.

Strengths and limitations

This study has several strengths. We investigated a large collection of 44 drug groups, including groups that are perceived as having an established (categorized as "confirmatory"), less established or even controversial (categorized as "exploratory") nephrotoxic effect. We systematically identified group-specific confounders by leveraging existing knowledge from the literature and a comprehensive drug knowledge database that is up-to-date and in accordance with clinical practice policies. This enabled us to identify confounders and potential residual confounding in a group-specific manner. Obtaining insight into HRs for drug groups containing pharmacologically similar drugs is an important step forward to support decision-making at the bedside when ICU physicians need to take into account risks of many drugs simultaneously. Furthermore, we re-used routinely collected data from EHR systems enriched by quality registry data of almost 100 000 admissions to 13 ICUs over 10 years. This allowed us to capture relatively weak associations in the adult ICU population. Our results contribute to much needed evidence for associations between drugs and AKI [4, 41].

This study also has limitations. First, we did not include the urine output (UO) KDIGO AKI criterion, which may explain the relatively low AKI incidence of 15% [45]. In line with many previous experiences, the registered UO data were incomplete, highly heterogeneous and missed the required resolution to be re-used in our study [45–47]. Yet, drug-induced AKI is often non-oliguric (e.g. for aminoglycosides) [48, 49]. Utilization of the UO criterion may therefore not be self-evident in the study of drug-induced AKI, as it could lead to a major "dilution" of the association between a drug and AKI or even a failure to identify the association. Promising additional markers exist to detect AKI, such as cystatin C [50]. Observational studies using EHR data like ours are—however—limited by the content registered in EHR systems as a reflection of current practice. This is well illustrated by the availability of the cystatin C marker in only three patients of only one of the included ICUs' EHR database in our study. Therefore, we prioritized the consensus based definition of AKI as provided in the KDIGO AKI guideline. SCr-based AKI detection currently presents the most suitable method for the application in large retrospective EHR databases [51]. Second, no pre-ICU SCr data were available, which hindered the assessment of baseline kidney function and precluded investigating stage worsening of pre-existing AKIs during ICU stay. Given that no gold standard exists to impute baseline SCr [52], we used the first SCr at ICU admission as our baseline. Ideally, we would have used historical SCr values to estimate baselines. However, linking data from multiple and diverse EHR systems of general practitioners and hospitals is very complex from interoperability, privacy and legal perspectives [53–55]. Acquiring pre-admission SCr data and linking it to our ICU dataset would therefore have required time and financial resources that would be disproportionate to the funding of our project. Although the first SCr value at admission can be elevated and may therefore lead to missing AKIs, this may not necessarily be the case given the time lag between kidney function and SCr, especially in acute settings [46]. Recommendations from a recent review on the definitions of kidney function measures in observational studies using routine healthcare data amounted to the clear reporting of the approach, including the AKI definition and baseline SCr definition [46]. Third, EHR data are primarily collected for clinical and billing purposes, and using such data for research may introduce important limitations [56]. However, most of the AKI risk factor variables were obtained via the NICE MDS registry database which is under strict data quality control [10]. Furthermore, the variables collected directly via machines or other systems (e.g. blood pressure measurements or SCr laboratory measurements) are less prone to quality issues. Fourth, some of our data on acute AKI risk factors were limited to data collected on the ICU admission day and lacked an exact timestamp (e.g. for acute heart failure and hypovolemia). This limited our ability to adjust for acute AKI risk factors that developed after the day of admission. We attempted to mitigate the lack of an exact timestamp by identifying group-specific mediators through existing knowledge and not adjusting for these factors in the respective models. Fifth, our data on drug administrations did not contain pre-ICU exposures, which prevented us from adjusting for pre-ICU nephrotoxin exposures. Lastly, as in any observational study investigating potential causal relationships, unknown confounders may have biased our estimates. We urge readers to place the estimated associations in the context of existing knowledge regarding nephrotoxicity (e.g. the "confirmatory" or "exploratory" categorization), our ability to adjust for the identified group-specific confounders and the limitations of the EHR database available to our study.

Implications for clinical practice

For many drug groups the nephrotoxicity has been firmly established and is in line with our results. For these groups ICUs should implement strategies to prevent or at least reduce severity of AKI due to nephrotoxicity. Clinical decision support systems [57], implementation of clinical pathways [58] and nephrotoxin stewardship [59] have all shown promising results to attain such improvements in kidney safety in ICU patients.

Implications for future research

Future research may focus on investigations of individual drugs within the drug groups that were associated with higher hazard of AKI in our study. These investigations could encompass the adjustment for potential time-varying confounding effects and the assessment of potential effect modifiers such as chronic

kidney disease. Furthermore, the study of dose-response relationships may uncover whether the associations found in our study are dose-dependent. Ultimately, approaches utilizing the target trial emulation framework are warranted as these may provide stronger evidence for the presence or absence of causal relationships [60]. Such research can aid the development of novel treatment policies which may minimize drug-induced AKI risk. Importantly, as evident from our discussed limitations, more detailed and accurate EHR data are needed to facilitate the optimal adjustment for confounding and measurement of AKI.

CONCLUSION

In conclusion, we identified 14 drug groups associated with a higher hazard of AKI in the ICU after adjusting for confounding. To the best of our knowledge, we provide the first estimations after systematic identification and reporting of group-specific confounders identified through existing knowledge. Our results provide important clinical implications and stimulate researchers to further investigate potential causal relationships between drugs and AKI in ICU patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

We would like to thank the participating ICUs for making this study possible, especially the ICU data managers for their help in acquiring and understanding the data. We would also like to acknowledge the EHR data extraction support by Johan Vogelaar from Itémedical, and the data pre-processing support by Tinka Bakker. In addition, we thank Atty Hielema and the KNMP for their information regarding the KNMP-DKD.

FUNDING

This study was funded by The Netherlands Organization for Health Research and Development (ZonMw project number: 848 018 004). The funder had no role in the design of the study, the collection, analysis and interpretation of the data, or in writing the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

The RESCUE project was exempted from requiring ethics approval (waiver W19_433 # 19.499) on 14 November 2019 by the Medical Ethics Committee of the Amsterdam University Medical Centers, location University of Amsterdam, The Netherlands, as it did not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO).

CONSENT TO PARTICIPATE AND CONSENT FOR PUBLICATION

In The Netherlands, there is no need to obtain consent to make use of registries that do not include patient-identifying information. The NICE initiative is officially registered according to the Dutch Personal Data Protection Act. The data directly collected from EHR systems were pseudonymized by a trusted third party, assuring that patient-identifying information was removed. The Dutch legal framework for non-WMO research with care data allows working with pseudonymized routinely collected data without patient informed consent under specific conditions, for example when datasets consist of a very large number of patients (>1000 patients). In such cases, approaching the group of participants would require an unreasonable effort.

DATA AVAILABILITY STATEMENT

The datasets collected and analyzed in this study are not publicly available due to the data sharing agreements with the participating ICUs. The access to the data might only be provided after explicit consent from each separate participating ICU.

AUTHORS' CONTRIBUTIONS

Concept and design: I.A.R.Y., D.A.D., A.A., M.C.S., N.F.K., K.J.J., J.E.K. Acquisition of data: J.E.K., N.F.K., D.A.D. Analysis of data: I.A.R.Y. Interpretation of data: all authors. Drafting the manuscript: I.A.R.Y., J.E.K. Critically revising the manuscript: all authors. All authors approved the submitted manuscript.

APPENDIX

Members of the RESCUE Study Group:

J. ten Cate and P.F. Schutte, Department of Intensive Care, The Netherlands Cancer Institute, Amsterdam, The Netherlands
D. van Balen, Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
S. Hendriks, Department of Intensive Care, Albert Schweitzer Ziekenhuis, Dordrecht, The Netherlands
C. Lau, Department of Hospital Pharmacy, Albert Schweitzer Ziekenhuis, Dordrecht, The Netherlands
W.J. Vermeijden and A. Beishuizen, Department of Intensive Care, Medisch Spectrum Twente, Enschede, The Netherlands
J.B. Masselink, Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede, The Netherlands
P.E. Spronk, Department of Intensive Care Medicine, Gelre Hospitals, Apeldoorn, The Netherlands
H.J.M. van Kan, Department of Clinical Pharmacy, Gelre Hospitals, Apeldoorn, The Netherlands
W.M. van den Bergh and M.H. Renes, Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
W. Bult, Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
M. Hoeksema, Department of Anesthesiology, Intensive Care and Painmanagement, Zaans Medisch Centrum, Zaandam, The Netherlands
E. Wesselink, Department of Clinical Pharmacy, Zaans Medisch Centrum, Zaandam, The Netherlands
I.M. Purmer, Department of Intensive Care, Haga Hospital, The Hague, The Netherlands
B.E. Bosma, Department of Hospital Pharmacy, Haga Hospital, The Hague, The Netherlands

S.H.W. van Bree, Department of Intensive Care, Ziekenhuis Gelderse Vallei, Ede, The Netherlands
P.C. Wierenga, Department of Hospital Pharmacy, Ziekenhuis Gelderse Vallei, Ede, The Netherlands
R.J. Bosman, Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
E.J.F. Franssen, Department of Clinical Pharmacy, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
A. Karakus and M. Sigtermans, Department of Intensive Care, Diakonessenhuis Utrecht, Utrecht, The Netherlands
E.M. Kuck, Department of Hospital Pharmacy, Diakonessenhuis Utrecht, Utrecht, The Netherlands

REFERENCES

1. Negi S, Koreeda D, Kobayashi S *et al.* Acute kidney injury: epidemiology, outcomes, complications, and therapeutic strategies. *Semin Dial* 2018;**31**:519–27. https://doi.org/10.1111/sdi.12705
2. Awdishu L. Drug-induced kidney disease in the ICU: mechanisms, susceptibility, diagnosis and management strategies. *Curr Opin Crit Care* 2017;**23**:484–90. https://doi.org/10.1097/MCC.0000000000000453
3. Mehta RL, Awdishu L, Davenport A *et al.* Phenotype standardization for drug-induced kidney disease. *Kidney Int* 2015;**88**:226–34. https://doi.org/10.1038/ki.2015.115
4. Gray MP, Barreto EF, Schreier DJ *et al.* Consensus obtained for the nephrotoxic potential of 167 drugs in adult critically ill patients using a modified Delphi method. *Drug Saf* 2022;**45**:389–98. https://doi.org/10.1007/s40264-022-01173-4
5. Bosdriesz JR, Stel VS, van Diepen M *et al.* Evidence-based medicine-when observational studies are better than randomized controlled trials. *Nephrology* 2020;**25**:737–43. https://doi.org/10.1111/nep.13742
6. Soares DB, Mambrini JVM, Botelho GR *et al.* Drug therapy and other factors associated with the development of acute kidney injury in critically ill patients: a cross-sectional study. *PeerJ* 2018;**6**:e5405. https://doi.org/10.7717/peerj.5405
7. Ehrmann S, Badin J, Savath L *et al.* acute kidney injury in the critically ill: is iodinated contrast medium really harmful? *Crit Care Med* 2013;**41**:1017–26. https://doi.org/10.1097/CCM.0b013e318275871a
8. Ehrmann S, Helms J, Joret A *et al.* Nephrotoxic drug burden among 1001 critically ill patients: impact on acute kidney injury. *Ann Intensive Care* 2019;**9**:106. https://doi.org/10.1186/s13613-019-0580-1
9. Langan SM, Schmidt SA, Wing K *et al.* The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ* 2018;**363**:k3532. https://doi.org/10.1136/bmj.k3532
10. van de Klundert N, Holman R, Dongelmans DA *et al.* Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. *Int J Epidemiol* 2015;**44**:1850–1850h. https://doi.org/10.1093/ije/dyv291
11. KNMP Kennisbank. 2021. https://kennisbank.knmp.nl/ (December 2021, date last accessed).
12. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;**20**:109–17. https://doi.org/10.2165/00002018-199920020-00002
13. Kellum JA, Lameire N, Aspelin P *et al.*; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;**2**:1–138
14. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. *Kidney Int* 2012;**81**:1172–8. https://doi.org/10.1038/ki.2010.475
15. Cartin-Ceba R, Kashiouris M, Plataki M *et al.* Risk factors for development of acute kidney injury in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit Care Res Pract* 2012;**2012**:691013.
16. Neugarten J, Golestaneh L. Female sex reduces the risk of hospital-associated acute kidney injury: a meta-analysis. *BMC Nephrol* 2018;**19**:314. https://doi.org/10.1186/s12882-018-1122-z
17. Noordzij M, Leffondre K, van Stralen KJ *et al.* When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant* 2013;**28**:2670–7. https://doi.org/10.1093/ndt/gft355
18. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol* 2009;**20**:672–9. https://doi.org/10.1681/ASN.2008070669
19. Yekutieli D, Benjamini Y. Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics. *J Stat Plan Inference* 1999;**82**:171–96. https://doi.org/10.1016/S0378-3758(99)00041-5
20. R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2013
21. Frenette AJ, Bouchard J, Bernier P *et al.* Albumin administration is associated with acute kidney injury in cardiac surgery: a propensity score analysis. *Crit Care* 2014;**18**:602. https://doi.org/10.1186/s13054-014-0602-1
22. Shaw AD, Kellum JA. The risk of AKI in patients treated with intravenous solutions containing hydroxyethyl starch. *Clin J Am Soc Nephrol* 2013;**8**:497–503. https://doi.org/10.2215/CJN.10921012
23. Fraser TN, Avellaneda AA, Graviss EA *et al.* Acute kidney injury associated with trimethoprim/sulfamethoxazole. *J Antimicrob Chemother* 2012;**67**:1271–7. https://doi.org/10.1093/jac/dks030
24. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. *Ther Adv Endocrinol Metab* 2016;**7**:136–47. https://doi.org/10.1177/2042018816638223
25. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. *Crit Care Med* 2008;**36**:S216–23. https://doi.org/10.1097/CCM.0b013e318168e375
26. Nussbaum EZ, Perazella MA. Diagnosing acute interstitial nephritis: considerations for clinicians. *Clin Kidney J* 2019;**12**:808–13.
27. Mallappallil M, Sabu J, Friedman EA *et al.* What do we know about opioids and the kidney? *Int J Mol Sci* 2017;**18**:223. https://doi.org/10.3390/ijms18010223
28. Bosi A, Xu Y, Gasparini A *et al.* Use of nephrotoxic medications in adults with chronic kidney disease in Swedish and US routine care. *Clin Kidney J* 2022;**15**:442–51. https://doi.org/10.1093/ckj/sfab210
29. Smith NA, Kates RE, Lebsack C *et al.* Clinical pharmacology of intravenous enoximone: pharmacodynamics and pharmacokinetics in patients with heart failure. *Am Heart J* 1991;**122**:755–63. https://doi.org/10.1016/0002-8703(91)90522-J
30. Aronson JK. Milrinone. In: Aronson JK, ed. *Meyler's Side Effects of Drugs*. Sixteenth Edition. Oxford: Elsevier, 2016, 1038–40. https://doi.org/10.1016/B978-0-444-53717-1.01087-8

31. Scholz H, Boivin FJ, Schmidt-Ott KM *et al*. Kidney physiology and susceptibility to acute kidney injury: implications for renoprotection. *Nat Rev Nephrol* 2021;**17**:335–49. https://doi.org/10.1038/s41581-021-00394-7.
32. Zima E, Farmakis D, Pollesello P *et al*. Differential effects of inotropes and inodilators on renal function in acute cardiac care. *Eur Heart J Suppl* 2020;**22**:D12–9. https://doi.org/10.1093/eurheartj/suaa091
33. Bellomo R, Giantomasso DD. Noradrenaline and the kidney: friends or foes? *Crit Care* 2001;**5**:294–8. https://doi.org/10.1186/cc1052
34. Lannemyr L, Bragadottir G, Redfors B *et al*. Effects of milrinone on renal perfusion, filtration and oxygenation in patients with acute heart failure and low cardiac output early after cardiac surgery. *J Crit Care* 2020;**57**:225–30. https://doi.org/10.1016/j.jcrc.2019.12.022
35. Lee J, Mark RG, Celi LA *et al*. Proton pump inhibitors are not associated with acute kidney injury in critical illness. *J Clin Pharmacol* 2016;**56**:1500–6. https://doi.org/10.1002/jcph.805
36. Ehrmann S, Quartin A, Hobbs BP *et al*. Contrast-associated acute kidney injury in the critically ill: systematic review and Bayesian meta-analysis. *Intensive Care Med* 2017;**43**:785–94. https://doi.org/10.1007/s00134-017-4700-9
37. Bentley ML, Corwin HL, Dasta J. Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies. *Crit Care Med* 2010;**38**:S169–74. https://doi.org/10.1097/CCM.0b013e3181de0c60
38. Fuhrman DY, Kane-Gill S, Goldstein SL *et al*. Acute kidney injury epidemiology, risk factors, and outcomes in critically ill patients 16-25 years of age treated in an adult intensive care unit. *Ann Intensive Care* 2018;**8**:26. https://doi.org/10.1186/s13613-018-0373-y
39. Corremans R, Vervaet BA, D'Haese PC *et al*. Metformin: a candidate drug for renal diseases. *Int J Mol Sci* 2019;**20**:42. https://doi.org/10.3390/ijms20010042
40. Tomson C, Tomlinson LA. Stopping RAS inhibitors to minimize AKI more harm than good? *Clin J Am Soc Nephrol* 2019;**14**:617–9. https://doi.org/10.2215/CJN.14021118
41. Ostermann M, Bellomo R, Burdmann EA *et al*. Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney Int* 2020;**98**:294–309. https://doi.org/10.1016/j.kint.2020.04.020
42. Wagner F, Yeter R, Bisson S *et al*. Beneficial hemodynamic and renal effects of intravenous enalaprilat following coronary artery bypass surgery complicated by left ventricular dysfunction. *Crit Care Med* 2003;**31**:1421–8. https://doi.org/10.1097/01.CCM.0000063050.66813.39
43. Biesterveld BE, Siddiqui AZ, O'Connell RL *et al*. Valproic acid protects against acute kidney injury in hemorrhage and trauma. *J Surg Res* 2021;**266**:222–9. https://doi.org/10.1016/j.jss.2021.04.014
44. Licon DA, Xiang L. Letter regarding: Valproic acid protects against acute kidney injury in hemorrhage and trauma. *J Surg Res* 2022;**270**:530–1. https://doi.org/10.1016/j.jss.2021.09.044
45. Koeze J, Keus F, Dieperink W *et al*. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. *BMC Nephrol* 2017;**18**:1–9. https://doi.org/10.1186/s12882-017-0487-8
46. Carrero JJ, Fu EL, Vestergaard SV *et al*. Defining measures of kidney function in observational studies using routine health care data: methodological and reporting considerations. *Kidney Int* 2023;**103**:53–69. https://doi.org/10.1016/j.kint.2022.09.020
47. Wilson FP, Martin M, Yamamoto Y *et al*. Electronic health record alerts for acute kidney injury: multicenter, randomized clinical trial. *BMJ* 2021;**372**:m4786. https://doi.org/10.1136/bmj.m4786
48. Schetz M, Dasta J, Goldstein S *et al*. Drug-induced acute kidney injury. *Curr Opin Crit Care* 2005;**11**:555–65. https://doi.org/10.1097/01.ccx.0000184300.68383.95
49. Perazella MA, Rosner MH. Drug-induced acute kidney injury. *Clin J Am Soc Nephrol* 2022;**17**:1220–33. https://doi.org/10.2215/CJN.11290821
50. Ostermann M, Joannidis M. Acutekidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016;**20**:299. https://doi.org/10.1186/s13054-016-1478-z
51. Sawhney S, Fraser SD. Epidemiology of AKI: utilizing large databases to determine the burden of AKI. *Adv Chronic Kidney Dis* 2017;**24**:194–204. https://doi.org/10.1053/j.ackd.2017.05.001
52. Siew ED, Matheny ME, Ikizler TA *et al*. Commonly used surrogates for baseline renal function can impact acute kidney injury classification and prognosis. *Kidney Int* 2010;**77**:536–42. https://doi.org/10.1038/ki.2009.479
53. Martinez-Costa C, Kalra D, Schulz S. Improving EHR semantic interoperability: future vision and challenges. *Stud Health Technol Inform* 2014;**205**:589–93.
54. Loukides G, Liagouris J, Gkoulalas-Divanis A *et al*. Disassociation for electronic health record privacy. *J Biomed Inform* 2014;**50**:46–61. https://doi.org/10.1016/j.jbi.2014.05.009
55. Dusetzina SB, Tyree S, Meyer A-M *et al*. Linkage feasibility—to link or not to link. In: Dusetzina SB, Tyree S Meyer A-M *et al*., eds. *Linking Data for Health Services Research: A Framework and Instructional Guide*. Rockville: Agency for Healthcare Research and Quality (US), 2014, 21–27.
56. Kohane IS, Aronow BJ, Avillach P *et al*. What every reader should know about studies using electronic health record data but may be afraid to ask. *J Med Internet Res* 2021;**23**:e22219. https://doi.org/10.2196/22219.
57. Czock D, Konias M, Seidling HM *et al*. Tailoring of alerts substantially reduces the alert burden in computerized clinical decision support for drugs that should be avoided in patients with renal disease. *J Am Med Inform Assoc* 2015;**22**:881–7. https://doi.org/10.1093/jamia/ocv027
58. Algaze CA, Margetson TD, Sutherland SM *et al*. Impact of a clinical pathway on acute kidney injury in patients undergoing heart transplant. *Pediatr Transplant* 2021;**26**:e14166
59. Kane-Gill SL. Nephrotoxin stewardship. *Crit Care Clin* 2021;**37**:303–20. https://doi.org/10.1016/j.ccc.2020.11.002
60. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016;**183**:758–64. https://doi.org/10.1093/aje/kwv254

Received: 13.12.2022; Editorial decision: 18.6.2023