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Original Article

ORIGINAL ARTICLE

Drug use and acute kidney injury: a Drug-Wide Association Study (DWAS) in Denmark and Sweden

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ABSTRACT

Background. Knowledge of which medications may lead to acute kidney injury (AKI) is limited, relying mostly on spontaneous reporting in pharmacovigilance systems. We here conducted an exploratory drug-wide association study (DWAS) to screen for associations between dispensed drugs and AKI risk.

Methods. Using two large Danish and Swedish data linkages, we identified AKI hospitalizations occurring between April 1997 and December 2021 in Denmark and between March 2007 and December 2021 in Sweden. We used a case-time control design comparing drug dispensing in the 3 months prior to the AKI with earlier periods for the same patient. Odds ratios (ORs) for the association between each drug and AKI were estimated using conditional logistic regression and adjusting for the presence of comorbidities. We sought replication of signals in both health systems and explored the plausibility of findings through pharmacovigilance system analysis in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, appearance in the RESCUE list of medications that report AKI as a side effect, PubMed evidence review and causality assessment through direct acyclic graphs.

Results. We included 20 622 adults in Denmark and 13 852 in Sweden hospitalized for AKI. In total, 16 unique medications were identified in both cohorts as associated to increased AKI occurrence. Of these, 10 medications had higher reporting ORs in the FAERS database, 9 were listed by RESCUE, and 7 appearing in PubMed. This analysis identified some medications with known AKI risks (i.e. likely true positives such as furosemide, penicillin, spironolactone and omeprazole), medications that may have initiated in response to conditions that lead to AKI (i.e. false positives like metoclopramide provided to treat nausea/vomiting) and other candidates (e.g. opioids) that warrant further evaluation in subsequent studies.

Conclusions. This hypothesis-generating study identifies medications with potential involvement in AKI that require confirmation and validation.

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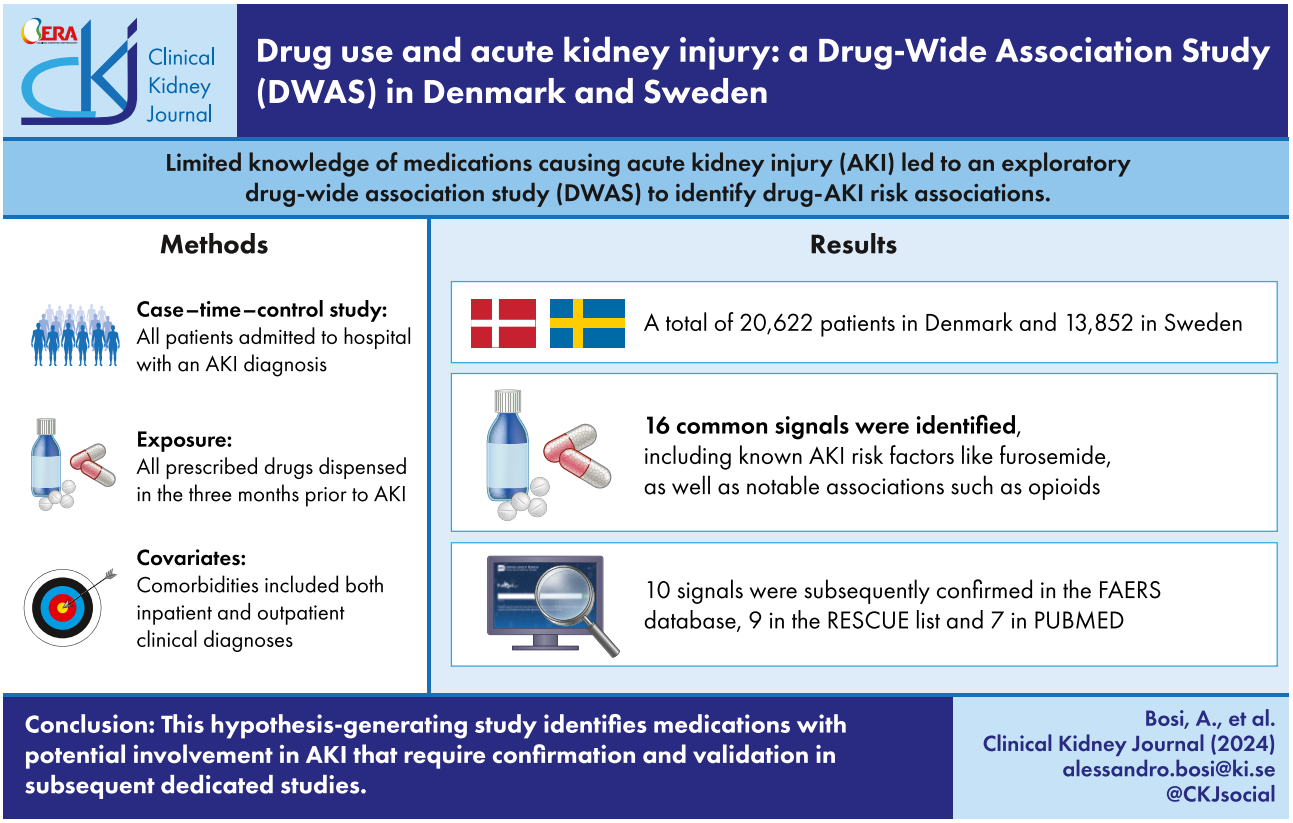
GRAPHICAL ABSTRACT



Keywords: AKI, directed acyclic graphs, drug-wide association study, nephrotoxicity, pharmacovigilance

KEY LEARNING POINTS

What was known:

- Drugs are an important factor in the development of acute kidney injury (AKI).
- Sometimes drugs can be directly toxic to the kidney in the absence of acute illness (e.g. proton pump inhibitors, anti-cancer drugs); in other instances, drugs used in chronic disease can complicate acute illness (e.g. diuretics).
- Knowledge of drugs associated with AKI is reliant on spontaneous reporting within pharmacovigilance systems.

This study adds:

- We performed untargeted 'drug-wide association study' in two large Scandinavian electronic health record databases.
- We identified a list of 16 unique medications that associated with AKI in both cohorts, and provide hypothesis-generating information on possible AKI-inducing agents that require evaluation in future studies.

Potential impact:

- This study identifies drugs associated with AKI for further evaluation in causal studies.

INTRODUCTION

Acute kidney injury (AKI), a sudden deterioration in kidney function over hours or days, is a potentially life-threatening condition of high societal and patient burden: AKI-related mortality is higher than pathologies such as breast cancer, heart failure or diabetes [1], and leads to excess healthcare costs [2, 3]. AKI often occurs as a complication of acute illness (e.g. infection, heart failure), due to the interaction between the illness and drugs (either pre-existing chronic medication or new medication to treat the illness), or due to treatment for the acute illness alone (e.g. antibiotics or diuretics). Sometimes, medications can trigger AKI in the absence of acute illness through direct toxicity (e.g. proton-pump inhibitors, anti-cancer drugs).

Studies evaluating AKI events with pharmacist review suggest that 19%–26% of AKI events in adults are attributable to medications [4–6]. However, knowledge of which medications may lead to AKI can be limited, given that acute nephrotoxicity is not often an adverse event characterized in clinical trials, or trials are not large enough to detect this rare

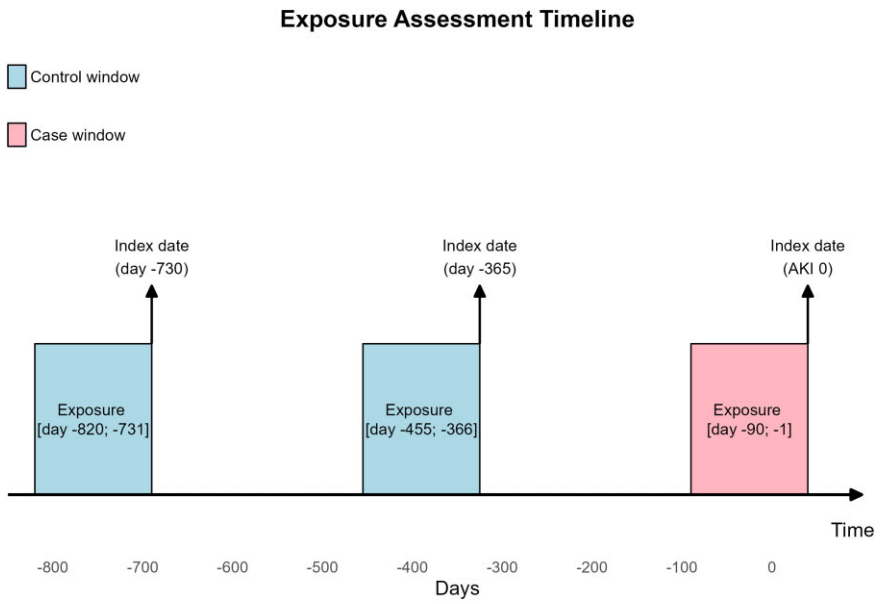


Figure 1: Schematic representation of case-time-control design.

event [7–10]. Furthermore, AKI was not well-defined and/or acknowledged in clinical practice until recent years [11, 12], and no formal AKI risk evaluation has been made for many of the traditional medications available nowadays. Identification of AKI as an adverse drug event often originates from pharmacovigilance systems, which rely heavily on the voluntary reporting of cases by patients and healthcare professionals. Fewer than 1% of adverse drug reactions are reported through these methods [13], which may be influenced by external factors such as media interest or safety alerts. Individual patient chart review by pharmacists is a more comprehensive method to identify adverse drug reactions; however, this approach is prohibitively expensive and time-consuming for research and/or administrative use.

Routinely collected healthcare data from registries, electronic health records and claims databases are increasingly used for research purposes. Classically, historical observational cohort studies focus on one single drug or on the confirmation of refute of one safety signal (i.e. does initiation of drug A compared with B associate with a higher rate of AKI?). However, these targeted approaches cannot embark all possible adverse effects of the >1500 active ingredients currently commercialized. Using an approach based on genome- and phenome-wide association studies, we performed a hypothesis-generating untargeted 'drug-wide association study' (DWAS), in which drugs dispensed up to an AKI event are compared with the use of the same drug in preceding periods for the same patient. We applied this case-time control series design to minimize confounding and sought replication of signals in two healthcare settings in Denmark and Sweden. Finally, we explored the plausibility of these findings through evidence review and pharmacovigilance system analysis, and discussed the challenges and opportunities of DWAS.

MATERIALS AND METHODS

Data sources

This study includes two different data sources. The first data source contains all Danish citizens who redeemed at least one prescription at a community pharmacy during the period 1995 to 2022. Using Danish population-based registries [14], we obtained complete information on demographics, vital status, redeemed prescription drugs [15] and hospital diagnoses [16] during the entire study period. The second data source is the Stockholm CREAtinine Measurements (SCREAM) project [17, 18], which collects healthcare data of all citizens in the region of Stockholm during 2006–22. Through the linkage with Swedish population-based registries [19, 20], complete information on demographics, vital status, redeemed prescription drugs and hospital diagnoses was similarly available during the entire study period. In both data sources, the loss of follow-up is considered minimal or virtually none.

Study population

We used a design where each individual served as his/her own control. In both data sources, cases were all patients admitted to hospital with an AKI diagnosis [International Classification of Diseases (ICD)-10 code 'N17'] attributed as the primary cause of hospitalization between 1 April 1997 and 31 December 2021, in the Danish cohort, and between 31 March 2007 and 31 December 2021, in SCREAM. We defined the index date as the date of AKI diagnosis. Controls were the same individuals as the cases evaluated 1 year and 2 years prior to the AKI diagnosis. The exclusion criteria were age below 18 years, non-residency in Stockholm or Denmark, respectively, as well ongoing kidney replacement therapy (kidney transplantation and/or dialysis).

Exposure

The study exposures were all prescribed drugs dispensed in the 3 months prior to the AKI hospitalization or in the 3 months preceding the control dates 1 and 2 years prior to the AKI event Fig. 1. We evaluated single drugs according to the fifth level of the Anatomical Therapeutic Chemical (ATC) coding system (e.g. N02AA05, oxycodone).

Table 1: Baseline characteristics of the cohort from Denmark.

	AKI cases ($n = 20\,622$)	Control 1 year prior ($n = 20\,622$)	Control 2 years prior ($n = 20\,622$)	SMD
Age in years, median (IQR)	74 (64, 82)	73 (63, 81)	72 (62, 80)	0.088
Female (sex)	8557 (42)	8557 (42)	8557 (42)	<0.001
Diagnosed CKD	3008 (14.6)	853 (4.1)	590 (2.9)	0.259
Diagnosed hypertension	3554 (17.2)	2076 (10.1)	1846 (9.0)	0.165
Diabetes mellitus	3077 (14.9)	2057 (10.0)	1763 (8.5)	0.133
Acute coronary syndrome	703 (3.4)	337 (1.6)	233 (1.1)	0.103
Ischaemic heart disease	1780 (8.6)	1135 (5.5)	963 (4.7)	0.107
Heart failure	2241 (10.9)	1134 (5.5)	836 (4.1)	0.175
Stroke	1013 (4.9)	590 (2.9)	499 (2.4)	0.089
Cerebrovascular disease	670 (3.2)	427 (2.1)	339 (1.6)	0.070
Atrial fibrillation	2347 (11.4)	1291 (6.3)	1075 (5.2)	0.150
Arrhythmia	634 (3.1)	396 (1.9)	311 (1.5)	0.070
Peripheral vascular disease	831 (4.0)	485 (2.4)	436 (2.1)	0.074
Liver disease	538 (2.6)	242 (1.2)	192 (0.9)	0.086
Cancer	2730 (13.2)	1410 (6.8)	1048 (5.1)	0.191
Alcoholism	786 (3.8)	544 (2.6)	475 (2.3)	0.059
Psychiatric disease	1507 (7.3)	1003 (4.9)	899 (4.4)	0.084
Rheumatoid arthritis	480 (2.3)	334 (1.6)	286 (1.4)	0.047
History of fractures	1349 (6.5)	747 (3.6)	708 (3.4)	0.096

SMD, standardized mean difference; CKD, chronic kidney disease

Covariates

Because each case acts as its own control, confounding such as age, sex, lifestyle habits or socioeconomic status are already accounted for on the assumption that they are similar within 1- or 2-year difference. However, we adjusted for the presence of comorbidities that may have appeared between the control window and AKI date and that may be the indication for new treatments. These included in- and outpatient clinical diagnoses for chronic kidney disease, hypertension, diabetes mellitus, acute coronary syndrome, ischaemic heart disease, heart failure, stroke, other cerebrovascular disease, atrial fibrillation, arrhythmia, peripheral vascular disease, liver disease, cancer, alcoholism, psychiatric disorder, rheumatoid arthritis and fractures.

Statistical analyses

We used all the medications dispensed in the 3 months prior as the independent variables in a conditional logistic regression model with informal Bayesian correction for multiple testing, obtaining the odds ratio (OR) and 95% confidence intervals (CIs) of AKI associated with each medication. In the conditional logistic regression model, we treated the exposure as the dependent variable and the outcome as the independent variable, instead of the other way around, which is often referred to as a 'case-time control analysis' [21, 22]. Due to the symmetry of the OR, this 'trick' does not change the interpretation of the estimated exposure effect; however, it enables adjustment for time-varying confounders that are monotonically increasing with time, e.g. age. We present such OR in each cohort grouped by drug classes to explore similarities and differences at a drug-family level. Lastly, we reported discordant cases as number of cases with discordant medication at time of AKI vs at preceding times. Notably, only discordant cases provide relevant information in a case-time control analysis, as these cases constitute the study population for a given drug.

We next explored consistency behind the identified signals, searching for quantitative detection of signals to supplement our study findings. We decided *a priori* to focus on those medications for which a statistically significant association was found in both data sources. We recognize however that differences in sample size, prescription patterns, reimbursement policies and drug availability in Denmark or Sweden can affect the likelihood of replication. As a sensitivity analysis, we explored medication associations within a shorter ascertainment window, considering only dispenses in the 30 days prior to the AKI or case-time control.

Drug associations that were found in both data sources were explored in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, an online database maintained by the US Food and Drug Administration that collects every adverse drug reaction (ADR) report submitted in the US territory and every serious ADR report filed in over 150 countries participating in the World Health Organization's Program for International Drug Monitoring (PIDM). Cases were defined as all Individual Case Safety Reports (ICSRs) where a drug of interest was reported as a primary or secondary suspect. We then used the standardized Medical Dictionary for Regulatory Activities (MedDRA) lower-level term 'acute kidney injury' to identify ICSRs of interest. To identify signals of disproportionate reporting (SDR) for AKI in association with drugs of interest, we used the reporting odds ratio (ROR) as a measure of disproportional reporting, which estimates the frequency of an AKI with the tested drugs compared with all other drugs in the FAERS database. SDRs were detected when the number of reports was higher than three and the lower bound of the 95% CI was greater than one. This approach aligns with the guidelines provided in the 'READUS-PV' framework, ensuring a robust and transparent analysis of drug safety [23].

Next, we contrasted identified medications against the list of commercially available drugs that mention AKI as a potential side-effect recently published by the "Towards a leaRning mEdication Safety system in a national network of intensive Care Units—timely detection of adverse drug Events" (RESCUE) study group [24] based on the online Drug Knowledge Database (https://kennisbank.knmp.nl/) of the Royal Dutch

Table 2: Baseline characteristics of the cohort from SCREAM.

	Case ($n = 13\,852$)	Control 1 year prior ($n = 13\,852$)	Control 2 years prior ($n = 13\,852$)	SMD
Age, median (IQR)	76.00 [67,85]	75.00 [66, 84]	74.00 [65, 83]	0.087
Female (sex)	5897 (42.6)	5897 (42.6)	5897 (42.6)	<0.001
CKD	3399 (24.5)	1804 (13.0)	1401 (10.1)	0.259
Hypertension	7948 (57.4)	6525 (47.1)	6212 (44.8)	0.168
Diabetes	4025 (29.1)	3643 (26.3)	3461 (25.0)	0.061
Acute coronary syndrome	606 (4.4)	273 (2.0)	232 (1.7)	0.106
Ischaemic heart disease	2132 (15.4)	1517 (11.0)	1317 (9.5)	0.119
Heart failure	3739 (27.0)	2345 (16.9)	1834 (13.2)	0.232
Stroke	1185 (8.6)	810 (5.8)	715 (5.2)	0.090
Cerebrovascular disease	1097 (7.9)	790 (5.7)	672 (4.9)	0.084
Atrial fibrillation	3696 (26.7)	2699 (19.5)	2272 (16.4)	0.168
Arrhytmia	901 (6.5)	614 (4.4)	600 (4.3)	0.064
Pheripheral vascular disease	696 (5.0)	469 (3.4)	401 (2.9)	0.073
Liver disease	591 (4.3)	350 (2.5)	308 (2.2)	0.077
Cancer	2676 (19.3)	1751 (12.6)	1515 (10.9)	0.157
Alcoholism	775 (5.6)	573 (4.1)	537 (3.9)	0.054
Psychiatric	2982 (21.5)	2293 (16.6)	2072 (15.0)	0.114
Rheumatoid arthritis	762 (5.5)	577 (4.2)	499 (3.6)	0.061
Fractures	1392 (10.0)	878 (6.3)	777 (5.6)	0.111

SMD, standardized mean difference; CKD, chronic kidney disease

Pharmacists Association. We also performed literature searches in PubMed to identify existing publications suggesting a link between the identified medication and the risk of AKI. The PubMed search strategy, utilizing the MEDLINE database, is detailed in Supplementary data, Table S3. Finally, for selected candidates, directed acyclic graphs (DAGs) were drawn to evaluate plausibility and suggest considerations for the design of pharmacoepidemiological studies to address them.

RESULTS

After applying inclusion and exclusion criteria, we identified 20 622 patients with an AKI diagnosis in Denmark. Their median age was 74 years [interquartile range (IQR) 64–82 years] and 42% were women. Similarly, we identified 13 852 patients with an AKI diagnosis in SCREAM. Their median age was 76 years (IQR 67–85 years) and 43% were women. Tables 1 and 2 describe the general characteristics of these populations.

The total number of unique drugs considered in the Danish analyses was 564. In SCREAM, there were 842 unique drugs. We identified 16 signals that were present in both cohorts (Table 3). These 16 medications were more commonly dispensed at the time of AKI (shows by ORs >1 and statistically significant *P*-value) compared with 1 and 2 years before by the same individual (i.e. two self-controls per case). The drug classes that contained more than one replication across cohorts were antibacterial agents for systemic use and diuretics, with two single replicates in each. In a sensitivity analysis restricting to medications dispensed in the 30 days prior to the AKI, 9 of these signals were still observed (Supplementary data, Table S2). In Supplementary data, Table S1 we described all signals identified in both cohorts, grouped by drug family classes. For example, there were 294 participants in the SCREAM cohort in whom metoclopramide was dispensed prior to the AKI date, but not prior to the 1- or 2-year reference windows. These are referred to as 294 discordant AKI cases. Similarly, there were 1594 discordant AKI cases in the Danish cohort. These cases, in both cohorts, represent a specific discordant exposure pattern, where individuals were 'exposed' at the time of AKI and 'unexposed' in the preceding periods. Metoclopramide is an antiemetic and within the class of antiemetics. Domperidone also was associated with AKI in the Danish cohort (Supplementary data, Table S1) but was not commercialized in Sweden.

For these 16 replicates, we explored the SDR in FAERS (Table 4). SDR were observed for 10 of our replicates, with the strongest signals for spironolactone, furosemide, and pivmecillinam (ROR above 14.00). We then conducted PubMed searches and compared our findings with the RESCUE list, identifying a total of nine preceding links with AKI in the RESCUE list and seven in PubMed (Table 4). Finally, we evaluated the biological plausibility of these associations through DAGs. Considerations about metoclopramide causing AKI are shown in Fig. 2, and other cases are presented in the supplemental materials of this manuscript (Appendix 1).

DISCUSSION

Our understanding on the effect of drugs on the occurrence of AKI is based primarily on voluntary reporting of adverse effects. Healthcare databases can be used to systematically and proactively explore untargeted safety signals. Using a case-time control analysis in two distinct and geographically diverse health systems, we evaluated associations between dispensed drugs and AKI though an untargeted hypothesis-generating approach. We identify a number of medications known to cause AKI, others that may have been given to treat conditions that lead to AKI, and some key suspects that deserve further evaluation and confirmation.

We identified 16 drugs that were associated with AKI in both cohorts. Ten of them had significant ROR in FAERS, and nine were mentioned in the RESCUE list [24], suggesting potential validity of findings. Some of the signals identified are known to possibly cause AKI, such i.e. furosemide, penicillin, spironolactone or omeprazole [25–27], so we take these as positive control

Table 3: Drug signals that associate with AKI in both cohorts, grouped by drug class.

Drug family	Single drug	ATC	Discordant cases in the Danish cohort	Adjusted OR (95% CI) in the Danish cohort	Discordant cases in SCREAM	Adjusted OR (95% CI) in SCREAM
Antiemetic						
	Metoclopramide	A03FA01	1574	6.95 (5.04–9.59)	294	3.11 (1.57–6.13)
Iron						
	Ferrous sulfate	B03AA07	977	1.68 (1.24–2.28)	382	1.98 (1.18–3.32)
Antipropulsive						
	Loperamide	A07DA03	633	2.97 (1.95–4.51)	341	1.95 (1.13–3.41)
Diuretics						
	Furosemide	C03CA01	5685	1.84 (1.63–2.08)	1918	1.64 (1.26–2.14)
	Spironolactone	C03DA01	2360	1.70 (1.40–2.06)	700	2.02 (1.35–3.03)
Antibiotics						
	Ciprofloxacin	J01MA02	1442	2.92 (2.20–3.86)	556	2.61 (1.70–4.03)
	Pivmecillinam	J01CA08	3076	2.65 (2.21–3.19)	377	3.49 (2.11–5.79)
	Flucloxacillin	J01CF05	240	2.39 (1.27–4.50)	490	1.81 (1.89–2.75)
	Phenoxymethylpenicillin	J01CE02	3871	1.93 (1.67–2.24)	391	1.66 (1.06–2.61)
Mineral supplement						
	Potassium chloride	A12BA01	4956	1.64 (1.44–1.87)	517	1.74 (1.09–2.79)
Analgesia (opioid)						
	Oxycodone	N02AA05	1133	2.46 (1.79–3.37)	790	1.54 (1.05–2.26)
	Codeine plus paracetamol	N02AJ06	422	1.73 (1.12–2.68)	490	1.73 (1.13–2.64)
	Paracetamol	N02BE01	6384	1.68 (1.50–1.88)	2193	1.41 (1.13–1.75)
Proton pump inhibitor						
	Omeprazole	A02BC01	1044	1.70 (1.30–2.23)	1387	1.71 (1.29–2.25)
Corticosteroid						
	Prednisolone	H02AB06	1840	1.65 (1.33–2.05)	528	1.69 (1.09–2.62)
Laxative						
	Macrogol, combinations	A06AD65	1284	1.69 (1.26–2.26)	886	1.71 (1.24–2.37)

outcomes. Furthermore, our study identified other drugs whose role in leading to AKI is unlikely when causality was theorized through DAGs. For example, AKI may be the consequence of acute systemic illnesses, like infection or vomiting, which result in impairment of renal perfusion. These causes of AKI may then prompt the prescription of antiemetics, and it then becomes a challenge to disentangle whether a consequent AKI was due to the drug, the indication for the drug, or an interaction of the two. Metoclopramide is a treatment for nausea and vomiting which appeared strongly associated with AKI in our analysis. Our DAG evaluation suggests that the indication for this treatment (vomiting and subsequent dehydration) rather than the treatment may be the cause of AKI. This hypothesis is supported by our findings of a 'drug-class' effect, as there was also a positive association between domperidone (another anti-emetic with a different mechanism of action) and AKI in the Danish cohort. Because this drug was not commercialized in Sweden, we could not replicate it. We note that in the DWAS analysis from Ryan *et al.* [28] hydrochlorothiazide, another diuretic, also yielded the strongest associations with AKI after correction for multiple comparisons, and the authors also argued this to be a false-positive due to confounding by indication.

More intriguing relationships were also identified by our analysis. For instance, among analgesic drugs, associations with AKI were found for codeine, paracetamol and oxycodone, but not for other agents. A recent Dutch study compared the use of 44 drugs potentially associated nephrotoxicity among intensive care unit admissions that experienced or not AKI [24]. The authors also observed strong associations between opioid use ad without yet clear empiric evidence of harm from the use of these drugs with respect to AKI. Many causes of pain are also associated with AKI, leading to confounding by indication, and therefore we hope our observations stimulate subsequent dedicated studies, potentially using a new-user design with an active comparator to quantify effect sizes with adequate control of confounding.

The term 'agnostic drug-wide association studies' was originally proposed by Ryan and colleagues [28], although foundations in this methodology date back to the early 1980s [29–32]. To date, DWAS approaches have primarily been explored in the field of cancer [33, 34]. While this approach is useful for identifying potential associations that warrant further consideration, there are limitations in providing definitive evidence of causal effects because of confounding by indication, temporality of events, and issues related to dose-response and non-exchangeability [35]. In our study, we attempted to address residual confounding and non-exchangeability with the use of case-time control analysis. Specifically, the original formulation of the case-time control method proposed by from Suissa *et al.* [21] and later generalized by Allison [36] does not necessarily

Table 4: Plausibility for the observed signals based on appearance of case-reports for AKI in FAERS (with analysis of RORs) and evaluation of previous literature in PubMed.

Drug family	Single drug	ATC	Number of AKI case reports/total number of AKI reports	ROR (95% CI)	Listed in the RESCUE AKI drug list[a] or in PubMed
Antiemetic					
	Metoclopramide	A03FA01	13 out of 20 217 (0.1%)	0.1 (0.06–0.17)	Not found
Iron					
	Ferrous sulfate	B03AA07	2 out of 1517 (0.1%)	0.21 (0.05–0.82)	Not found
Antipropulsive					
	Loperamide	A07DA03	63 out of 14 311 (0.4%)	0.69 (0.54–0.88)	Listed by RESCUE; PMID: 31417926
Diuretics					
	Furosemide	C03CA01	1944 out of 12 988 (15.0%)	28.00 (26.67–29.40)	Listed by RESCUE; PMID: 20085566
	Spironolactone	C03DA01	464 out of 5292 (8.8%)	14.99 (13.63–16.50)	Listed by RESCUE; PMID: 36127547
Antibiotics					
	Ciprofloxacin	J01MA02	358 out of 25 471 (1.4%)	2.22 (2.00–2.46)	Listed by RESCUE; PMID: 36127547
	Pivmecillinam	J01CA08	5 out of 48 (10.4%)	18.04 (7.14–45.54)	Not found
	Flucloxacillin	J01CF05	32 out of 739 (4.3%)	7.02 (4.93–10.01)	Listed by RESCUE; PMID: 33841856
	Phenoxymethylpenicillin	J01CE02	2 out of 67 (3.0%)	4.77 (1.17–19.49)	Listed by RESCUE
Mineral supplement					
	Potassium chloride	A12BA01	29 out of 5566 (0.5%)	0.81 (0.56–1.17)	Not found
Analgesia (opioid)					
	Oxycodone	N02AA05	178 out of 143 893 (0.1%)	0.19 (0.16–0.22)	Not found
	Codeine plus paracetamol	N02AJ06	118 out of 19 200 (0.6%)	Not found	Not found
	Paracetamol	N02BE01	1020 out of 122 636 (0.8%)	1.31 (1.23–1.39)	Listed by RESCUE; PMID: 35681183
Proton pump inhibitor					
	Omeprazole	A02BC01	1437 out of 22 209 (6.5%)	10.9 (10.35–11.53)	Listed by RESCUE; PMID: 32092686, PMID: 36127547
Corticosteroid					
	Prednisolone	H02AB06	189 out of 22 315 (0.9%)	1.33 (1.15–1.53)	Not found
Laxative					
	Macrogol, combinations	A06AD65	9 out of 146 (6.2%)	10.2 (5.19–20.00)	Listed by RESCUE

[a]The RESCUE study group list of medications that mention AKI as a side effect is published in [24].

include time controls, as in our case. Because each patient is compared with him/herself at a time prior, this analysis automatically controls for confounding factors that are constant within that time-window (such as genetic predisposition to AKI, lifestyle habits and chronic diseases). However, it does not account for time-varying confounding that may have occurred in between the time-series. To minimize this risk of time-varying confounding we chose short time-windows of 1 and 2 years, and assumed that not many new diseases (and thus indications for medications) are identified within a short time-frame. This may introduce specific challenges to AKI identification and raise the issue of temporality, that is, the time between medication start and AKI diagnosis. In this case, we believe that our design is helpful in identifying medications that lead to AKI shortly after its initiation, but perhaps less useful in identifying AKIs that occur after months or years of treatment. For example, some medications of chronic use such as renin–angiotensin system inhibitors (RASi) are known to increase the risk of AKI [37, 38]. The risk of AKI attributed to RASi is not confined to the initial months of therapy and can also occur after years of use or when an additional medication is introduced (drug–drug interaction) or an additional health event happens (dehydration due to illness). Our design would not capture this, given that it is

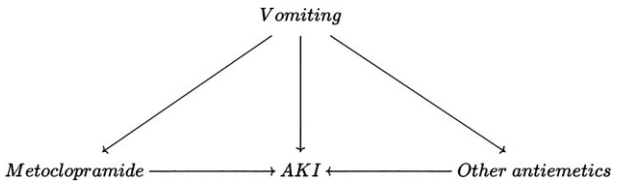


Figure 2: DAG exploring the plausibility of metoclopramide causing AKI. Metoclopramide is a treatment for nausea and vomiting and so it is plausible that AKI is caused by vomiting (confounding by indication). This explanation would be supported by the positive association found between domperidone and AKI in the Danish cohort (this drug was not commercialized in Sweden). Further investigation of data is needed from healthcare systems where other antiemetics (e.g. cyclizine, ondansetron) are commonly used.

only based on the discordance of medication use within a short time-frame. Another limitation of our study is that we evaluated single medications, where the AKI event may be result of drug–drug interactions. This would be the focus of our future analyses while trying to develop the methodology. We lacked data on administrative ICD or procedural codes for volume depletion, dehydration or oliguria, which may serve as important confounding factors, and our ascertainment of AKI events is based on clinical diagnoses. We are not aware of validation of these diagnostic codes in Swedish or Danish healthcare settings, highlighting the need for further research in this area. Finally, we based our signal validity and generalizability of results on replication across two distinct health systems [39]. As alluded to earlier, replication may be by differences in medication preferences/reimbursement across systems or availability of different commercial formulations across countries.

In summary, this untargeted DWAS provides some hypothesis-generating observations on drugs that can potentially cause AKI and that deserve further study and validation. Until validation ensues, our results should not influence clinical decision-making.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

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