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ORIGINAL ARTICLE

Adverse drug events caused by three high-risk drug–drug interactions in patients admitted to intensive care units: A multicentre retrospective observational study

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Aims: Knowledge about adverse drug events caused by drug–drug interactions (DDI-ADEs) is limited. We aimed to provide detailed insights about DDI-ADEs related to three frequent, high-risk potential DDIs (pDDIs) in the critical care setting: pDDIs with international normalized ratio increase (INR^{+}) potential, pDDIs with acute kidney injury (AKI) potential, and pDDIs with QTc prolongation potential.

Methods: We extracted routinely collected retrospective data from electronic health records of intensive care units (ICUs) patients (≥18 years), admitted to ten hospitals in the Netherlands between January 2010 and September 2019. We used computerized triggers (e-triggers) to preselect patients with potential DDI-ADEs. Between September 2020 and October 2021, clinical experts conducted a retrospective manual patient chart review on a subset of preselected patients, and assessed causality, severity, preventability, and contribution to ICU length of stay of DDI-ADEs using internationally prevailing standards.

Results: In total 85 422 patients with ≥1 pDDI were included. Of these patients, 32 820 (38.4%) have been exposed to one of the three pDDIs. In the exposed group, 1141 (3.5%) patients were preselected using e-triggers. Of 237 patients (21%) assessed, 155 (65.4%) experienced an actual DDI-ADE; 52.9% had severity level of

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serious or higher, 75.5% were preventable, and 19.3% contributed to a longer ICU length of stay. The positive predictive value was the highest for DDI-INR^{+} e-trigger (0.76), followed by DDI-AKI e-trigger (0.57).

Conclusion: The highly preventable nature and severity of DDI-ADEs, calls for action to optimize ICU patient safety. Use of e-triggers proved to be a promising preselection strategy.

KEYWORDS

adverse drug events, drug–drug interactions, intensive care, patient safety, triggers

1 | INTRODUCTION

In the intensive care unit (ICU), 28–96% of patients are exposed to one or more potential drug–drug interactions (pDDIs).[1] This rate is twice as high compared to patients on general wards,[2] and is due to often present polypharmacy in the ICU patients. A pDDI can be defined as a patient safety incident in which a patient is simultaneously exposed to two drugs known to interact.[3] Such exposure could result in an actual DDI in the body, manifesting itself as drug toxicity or loss of drug effectiveness; i.e. an adverse drug event (ADE). ICU patients are more likely to experience ADEs caused by DDIs (DDI-ADEs) due to frequently decreased organ function and changes in drug pharmacokinetics,[4] and the aforementioned polypharmacy.[5]

To support ICU clinical staff in recognizing and preventing pDDIs, the most common tool used is a computerized decision support system (CDSS).[4] A CDSS integrated with a Computerized Provider Order Entry/electronic prescribing system, produces pDDI alerts during medication prescribing. However, a recent Delphi study showed that of all pDDI alerts in the ICU, 38% was deemed not clinically relevant.[6] Overabundance of not clinically relevant pDDI alerts leads to alert fatigue with override rates as high as 82%, increasing the risk of missing clinically relevant pDDI alerts.[7] To improve CDSS effectiveness, investigating the occurrence of DDI-ADEs has been proposed as essential to determine for which pDDIs alerting is warranted.[2,8] However, to the best of our knowledge, only five single-centre studies investigated DDI-ADE occurrence in ICU patients.[9–13] Three of these specified which pDDIs groups were involved,[11] two assessed the severity of DDI-ADEs[12,13] and none investigated preventability. To be able to determine the impact of pDDIs on patient safety in the ICU, we need more detailed insights into the clinical consequences of pDDIs.

An explanation for the paucity of research on DDI-ADE occurrence is the resource-intensive nature (in terms of time and experts needed) of manual patient chart reviews and formal causality assessments to reliably detect whether actual ADEs have occurred.[14] Therefore, such reviews and assessments should be reserved for records that are highly likely to contain ADEs. The implementation of the electronic health record (EHR) systems in hospitals, makes it possible to apply so called electronic triggers (e-triggers),[15,16] E-triggers point to records containing adverse events (e.g. laboratory abnormalities, antidotes orders, monitoring procedures) that may have been caused by drugs, i.e. records that may contain ADEs. Subsequently, confirmatory reviews of the preselected records are conducted to determine causality between these adverse events and the suspected drugs, making manual patient chart review more efficient. Furthermore, use of e-triggers helps standardizing the ADE detection processes and eliminating reviewer subjectivity and error.[15,17] This methodology has shown to be applicable in the ICU setting.[13,18,19]

Therefore, we conducted a multicentre study in academic and nonacademic ICUs and investigated ADE occurrence, preventability, and severity caused by one of the three pDDI groups: (i) pDDIs with international normalized ratio increase (INR+) potential; (ii) pDDIs with acute kidney injury (AKI) potential; and (iii) pDDIs with QTc prolongation (QTc^{+}) potential. The choice for these three pDDI groups was motivated by their high-frequency in the ICU,[8,20] high-risk to cause ADEs in ICU patients,[9–13,21] and their clinical

What is already known about this subject

- Up to 96% of intensive care patients are exposed to one or more potential drug–drug interactions (pDDIs).
- Knowledge about adverse drug events caused by DDIs (DDI-ADEs) is limited.
- Investigating the occurrence of DDI-ADEs is crucial for enhancing the effectiveness of computerized decision support systems and reducing alert fatigue.

What this study adds

- We applied triggers to electronic health records data to detect DDI-ADEs for three high-risk pDDIs.
- Our findings demonstrate that these pDDIs often result in serious and preventable ADEs.
- Our study emphasizes the need to optimize patient safety in intensive care and encourages trigger use for detecting DDI-ADEs.

manifestation that can be identified via structured and easily to retrieve data in EHR systems. To preselect patients for the manual patient chart review, we applied three e-triggers to the extracted routinely collected retrospective ICU patients' data from EHRs. Since the yield of the triggers is important to determine their value in detecting patients that may have suffered from ADEs, we assessed their positive predictive value (PPV).

2 | METHODS

2.1 | Study design

In this multicentre retrospective observational study, we determined the extent of DDI-ADEs in ICU patients based on routinely collected retrospective data extracted from EHR systems. Therefore, this study is reported according to the Reporting of studies Conducted using Observational Routinely-collected Data statement for pharmacoepidemiology (RECORD-PE).[22] Checklist is included in Data S1.

2.2 | Setting and participants

We included data of all adult patients (≥18 years) admitted to ten ICUs situated in three academic and seven nonacademic hospitals in the Netherlands between January 2010 and September 2019 with at least one pDDI. Per patient, only the first ICU admission was taken into account. Between 2010 and 2019, seven ICUs implemented a CDSS to alert physicians about pDDI during prescribing.

2.3 | Data sources

The data included were extracted from the Patient Data Management System Metavision, a type of EHR system, and from the National Intensive Care Evaluation quality registry.[23]

2.4 | Detection of (potential) DDI-ADEs

First, we designed and retrospectively applied e-triggers to EHR data to preselected patients who may have experienced one of the three DDI-ADEs. For each of the three high-risk pDDIs we designed a specific e-trigger. The main rules of the three e-triggers were: (i) exposure of a patient to a pDDI with vitamin K antagonists and subsequent INR ≥ 5 (DDI-INR$^+$ e-trigger); (ii) exposure of a patient to a pDDI with AKI potential and subsequent AKI stage 2 or 3 (DDI-AKI e-trigger) according to internationally prevailing Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury serum creatinine criteria[24]; and (iii) exposure of a patient to a pDDI with QTc prolongation potential and subsequent ordering of electrocardiogram (ECG), (DDI-QTc$^+$ e-trigger). The choice for the INR ≥ 5 threshold in our DDI-INR$^+$ e-trigger, was motivated by the findings from previous studies in which PPV for INR ≥ 6 varied between 0.38 and 1.0 and for INR ≥ 4 showed 0.11.[16,25,26] We chose a middle ground. For DDI-AKI e-trigger we set the threshold at AKI stage 2 or 3 because according to a guiding reference on drug-induced kidney disease, it is proposed, in order to increase specificity, to meet at minimum KDIGO stage 2 AKI when assessing causality between drugs and kidney disease such like AKI.[27] Regarding the DDI-QTc$^+$ e-triggers it is important to stress that we used ECG orders as a surrogate for QTc prolongation, i.e. the adverse event of our interest. We reasoned that placing an ECG order points to checks of ICU clinical staff for QTc prolongation, and could help identify patients with QTc prolongation. This choice was made because the QTc measurements were not available as structured data within the EHR systems from which we extracted data for this study.

To detect pDDIs, we used a previously described and validated algorithm.[20] This algorithm was based on the pDDI list included in the "G-Standaard". The G-Standaard is the Dutch evidence-based professional drug and drug-safety knowledge database.[28] At the time of this study, the G-Standaard pDDI list included 569 pDDI types (see Appendix S1), of which 74 types were relevant for this study. We did not precode specific timeframes between the first occurrence a pDDI and subsequent adverse event into our e-trigger logic. Instead, the ICU admissions identified using the e-triggers were pre-evaluated on the temporal plausibility by one experienced medication safety expert (J.K.). This is because timeframes differ per type of medication involved in a pDDI. It was agreed with the participating ICUs that for the manual patient chart review a sample of 30–50 ICU patients was feasible to accomplish during the study period. All ICUs participated equally in the manual chart review process. After temporal plausibility check, we consecutively selected for the manual patient chart review a total sample of 30–50 ICU patients having one of the three e-triggers. We started with the most recent admissions first, until the target of 50 was met per ICU or earlier if there were no more cases that met the e-triggers criteria. The logic of each e-trigger is illustrated in detail in Appendix S2.

Second, following internationally prevailing methodology for measuring adverse (drug) events,[23–25] at each ICU, either an ICU physician with clinical pharmacology expertise or a team consisting of an ICU physician and a hospital pharmacist was appointed. Between September 2020 and October 2021, they conducted manual patient chart review of patients with e-triggers to assess whether actual DDI-ADEs occurred. For each selected patient only one e-trigger corresponding to one pDDI was assessed. Of note here are patients with DDI-QTc$^+$ e-triggers. For these patients the clinical experts needed to check if actual QTc prolongation has occurred using data from vital signs monitors. If no QTc prolongation occurred, causal assessment was not applicable because no adverse event has occurred. To ensure comparable assessments three standardization measures were taken: (i) an online ADE causality assessment tutorial was provided; (ii) a standardized electronic case report form (eCRF) designed in the CASTOR Electronic Data Capture system[29] was used to collect findings; and (iii) frequent

1-on-1 online meetings were organized between the medication safety expert (J.K.) and the reviewers of the participating ICUs. Our eCRF was designed according to the World Health Organization–Uppsala Medical Centre (WHO-UMC) causality assessment procedure.[30] To make the WHO-UMC procedure fit for the purpose of DDI-ADE assessment, a few adaptations were made (see Appendix S3). A summary of our approach is illustrated in Figure 1.

2.5 | Outcome definition

A DDI-ADE was defined as any injury resulting from an exposure to a pDDI and assessed as *nearly certain*, *probable* or *possible* DDI-ADE by the expert reviewers. This definition is in line with standard patient safety definition and practice in ADE research.[31,32] Any injury included a dangerously abnormal laboratory value (e.g. INR ≥ 5, AKI stage 2 or 3) or a clinical sign (e.g. bleeding, QTc prolongation, cardiac arrhythmia), again in line with internationally prevailing patient safety definitions.[32,33] The severity of patient harm was scored according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAEv5), which includes 5-points scale of seriousness: mild, moderate, serious, life-threatening, and fatal.[34] See Appendix S3 for more details. Each DDI-ADE was assessed on preventability and on the contribution to length of stay (LOS) in the ICU using a 5-point Likert scale (same as WHO-UMC procedure). Again, only assessments with score of at least *possible* were taken into account.

2.6 | Outcome measures

The primary outcome was the number of DDI-ADEs, their severity and preventability. The secondary outcome was the performance of e-triggers expressed as the PPV of each e-trigger.

2.7 | Statistical analyses

Descriptive statistics were applied for the analysis of ICU patient characteristics, and differences tested according to the distribution of the variables. We estimated the PPV of the e-triggers by dividing the number of true positive (TP) ICU patients by the sum of true positives (TP) and false positives (FP) ICU patients: TP / (TP + FP). TP ICU patients were patients preselected using the e-triggers, presented for review, and assessed by clinical experts as patients *with* an actual DDI-ADEs. FP ICU patients were patients preselected using the e-triggers, presented for review and assessed as patients *without* actual DDI-ADEs. All data analyses were conducted in R (version 4.0.3).[35]

2.8 | Ethics approval and informed consent

The study protocol was reviewed by the Medical Ethics Committee of the Amsterdam Medical Center, the Netherlands. A waiver from formal approval (W16_391 # 17.001) was provided since this study does not fall within the scope of the Dutch Medical Research (Human

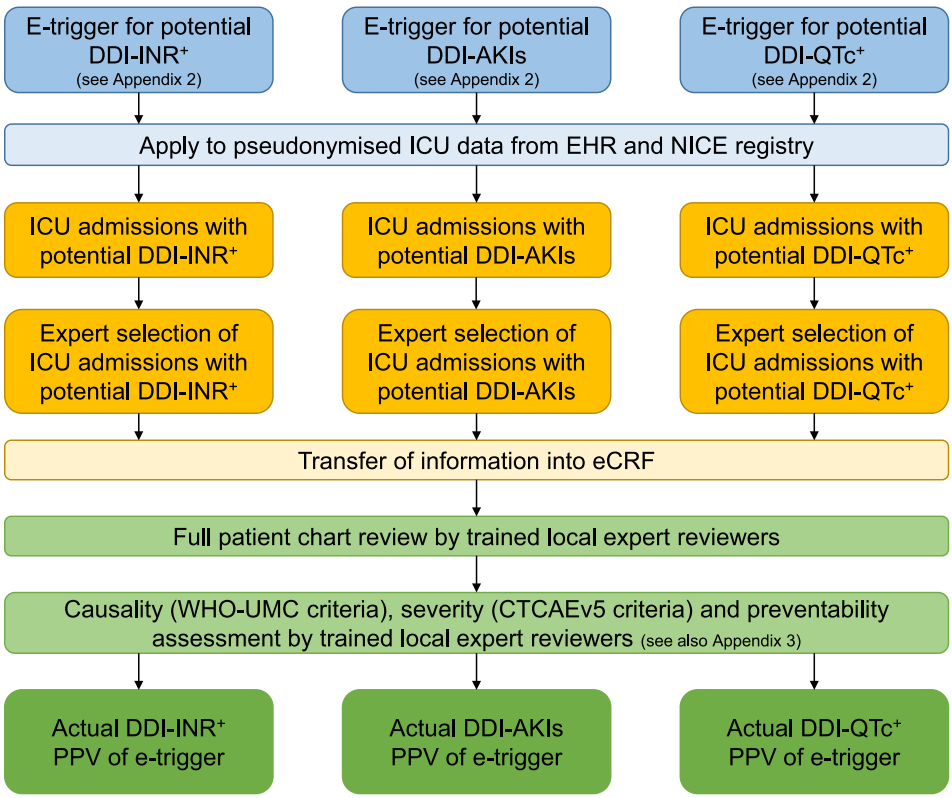

FIGURE 1 Summary of the approach used to identify adverse drug events caused by drug–drug interactions (DDIs) in intensive care patients. CTCAEv5, common terminology criteria for adverse events version 5.0; DDI-AKI, DDI causing acute kidney injury; DDI-INR$^+$, DDI causing supratherapeutic INR; DDI-QTc$^+$, DDI causing QTc prolongation; eCRF, electronic case report form; EHR, electronic health record; ICU, intensive care unit; NICE, National Intensive Care Evaluation; PPV, positive predictive value; WHO-UMC, World Health Organization–Uppsala Medical Center.

Subjects) Act (i.e. non-WMO research). Furthermore, within the Dutch legal framework for non-WMO research with large number of patients (>1000) pseudonymized routinely collected data, exception from patient informed consent applies.

3 | RESULTS

3.1 | Patient characteristics

In total, 85 422 ICU patients with ≥1 pDDI were included. Overall, ICU patients with e-triggers had a higher Acute Physiology and Chronic Health Evaluation (APACHE) IV score and ICU mortality, and a longer ICU LOS than those without e-triggers (see Table 1). The patterns in chronic conditions and diagnosis at ICU admission differed per subgroup mainly due to the e-trigger logic.

3.2 | E-triggers and DDI-ADEs

In total, 32 820 (38.4%) of the included patients were exposed to one of the three pDDIs. Using our e-triggers, 1141 ICU patients (3.5%) were preselected as patients who may have suffered from a DDI-ADE related to one of the three pDDIs. In total 1907 e-triggers were identified in these patients. A selection of 327 patients with an e-trigger (28.4%) was presented for the manual patient chart review by the clinical experts (see Table 2). After patient chart review, the experts conducted causality assessment for 237 (20.8%) patients with e-triggers. The remaining 90 cases not assessed for causality, were patients with DDI-QTc^{+} e-triggers without QTc prolongation. In 155 patients of the 237 assessed patients (65.4%), actual DDI-ADE was confirmed by clinical experts with 17 (7.2%) judged as nearly certain, 45 (19.0%) as probable and 93 (39.2%) as possible DDI-ADEs. See Appendix S4 for more details about drug (groups) pertaining to the pDDIs, e-triggers

TABLE 1 Characteristics of the intensive care patients with ≥1 potential drug–drug interaction(s) and with e-triggers.

Characteristic	With ≥1 pDDI (n = 85 422)	With INR e-trigger (n = 185)	With AKI e-trigger (n = 247)	With QTc e-trigger (n = 709)
Age, median (Q1–Q3)	67 (57–75)	71 (62–77)*	61 (51–68)*	70 (62–77)*
Male, *n* (%)	55 741 (65.3)	133 (71.9)	159 (64.4)	466 (65.8)
Acute Physiology and Chronic Health Evaluation IV score, median (Q1–Q3)	56 (41–77)	70 (57–85)*	72 (58–89)*	68 (52–85)*
Intensive care unit mortality, *n* (%)	8330 (9.8)	28 (15.1)**	99 (40.1)*	81 (11.4)
Hospital mortality, *n* (%)	11 931 (14.0)	41 (22.2)**	112 (45.3)*	126 (17.8)**
Intensive care unit length of stay, median (Q1–Q3)	1.7 (0.9–4.4)	6.8 (3.6–18.4)*	16.3 (8.1–27.0)*	4.3 (2.5–8.6)*
Admission type, *n* (%)				
Medical	32 751 (38.3)	134 (72.4)	143 (57.9)	324 (45.8)
Emergency surgical	11 280 (13.2)	23 (12.6)	62 (25.1)	92 (13.0)
Elective surgical	41 215 (48.2)	26 (14.1)	38 (15.3)	291 (41.2)
Admission type missing	13 (0.0)	NA	NA	NA
Chronic conditions, *n* (%)				
Chronic kidney insufficiency	5475 (6.4)	27 (14.6)*	22 (8.9)	64 (9.0)**
Chronic obstructive pulmonary disease	10 104 (11.8)	36 (19.5)*	33 (13.3)	110 (15.5)**
Diabetes	16 429 (19.2)	40 (21.6)	45 (18.2)	158 (22.3)
Cardiovascular insufficiency	5784 (6.8)	32 (17.3)*	22 (8.9)	41 (5.8)
Hematologic malignancy	1781 (2.1)	1 (0.5)	38 (15.3)*	8 (1.1)
Cirrhosis	1160 (1.4)	1 (0.5)	8 (3.2)**	9 (1.4)
Immunodeficiency	6756 (7.9)	19 (10.3)	85 (34.4)*	53 (7.5)
Diagnosis at admission, *n* (%)				
Acute renal failure	6918 (8.1)	26 (14.1)**	33 (13.4)**	91 (12.8)*
Dysrhythmia	6359 (7.4)	26 (14.1)**	14 (5.7)	69 (9.7)**
Cardiovascular accident	2319 (2.7)	5 (2.7)	5 (2.0)	9 (1.3)**
Gastrointestinal bleeding	1191 (1.4)	3 (1.6)	4 (1.6)	12 (1.7)
Intracranial bleeding	2044 (2.4)	0 (0.0)**	5 (2.0)	3 (0.4)*
Infection	13 377 (15.7)	64 (34.6)*	78 (31.6)*	139 (19.6)**

Note: We tested for differences between admission with ≥1 pDDI and admissions with e-triggers per trigger category.
Abbreviations: AKI, acute kidney injury; INR, international normalized ratio; NA, not applicable; pDDI, potential drug–drug interaction; Q, quartile.
*P < .001, and**P < .05.

TABLE 2 E-triggers and results from patient chart review followed by causality assessment.

	All DDI-ADE e-triggers	DDI-INR$^+$ e-triggers	DDI-AKI e-triggers	DDI-QTc$^+$ e-triggers
Patients with 1 of the 3 pDDIs, *n*	32 820	1776	8121	22 923
Patients with e-triggers, *n* (%)	1141 (3.5)	185 (10.4)	247 (3.0)	709 (3.1)
Patients presented for review, *n* (% of cases with an e-trigger)	327 (28.7)	81 (43.8)	101 (40.8)	145 (20.4)
Patients for which causality was assessed, *n* (% of cases with an e-trigger)	237 (20.8)	81 (43.8)	101 (40.8)	55 (7.7)[a]
Nearly certain[b]	15 (6.3)	9 (11.1)	2 (2.0)	4 (7.3)
Probable[b]	43 (18.1)	15 (18.5)	16 (15.8)	12 (21.8)
Possible[b]	97 (40.9)	36 (44.4)	40 (39.6)	21 (38.2)
Unlikely	75 (31.6)	17 (21.0)	41 (40.6)	17 (30.9)
Unassessable/unclassifiable	7 (3.0)	4 (4.9)	2 (2.0)	1 (1.8)
Patients with DDI-ADEs, *n* (% of cases reviewed)[b]	155 (47.4)	60 (74.1)	58 (57.4)	37 (25.5)
Positive predictive value	0.47	0.74	0.57	0.26

Abbreviations: ADE, adverse drug events; DDI, drug–drug interaction; DDI-ADE, adverse drug event related to DDI; DDI-AKI, DDI causing acute kidney injury; DDI-INR$^+$, DDI causing supratherapeutic INR with and without bleeding; DDI-QTc$^+$, DDI causing QTc prolongation; INR, international normalized ratio; pDDI, potential DDI.

[a]After patient chart review, 90 patients were excluded from subsequent assessment of causality, preventability, severity and contribution to length of stay in the intensive care. These patients did not have an actual QTc prolongation; i.e. the adverse event of our interest. Since the DDI-QTc$^+$ e-triggers preselected patients with electrocardiogram order (as a proxy for QTc prolongation; see Section 2 and Appendix S2), only after patient chart review the experts could confirm if actual QTc prolongation occurred, and followed through with causality assessment of the remaining 55 patients with QTc prolongation.

[b]These causality categories constitute actual DDI-ADEs.

and DDI-ADEs. According to the reviewers, in 117 (75.5%) ICU patients DDI-ADEs were preventable, and in 30 ICU patients (19.3%) DDI-ADEs contributed to a longer ICU LOS (see Table 3). The DDI-INR$^+$ events had the highest preventability proportion (86.7%), while the DDI-AKI events had the highest contribution to a longer LOS in the ICU (37.9%). More than half of DDI-ADEs (52.9%) resulted in severity level of serious or higher, with DDI-QTc$^+$ events having the highest proportion of such events (78.4%). Events with severity level serious or higher included: 23 dialysis events (39.7% of all DDI-AKI cases); three deaths related to AKI (5.2% of all DD-AKI cases); 15 dangerously increased INR > 2.5× baseline events of which three resulted in bleeding (25.0% of all DDI-INR+ cases); 27 dangerously prolonged QTc ≥ 501 ms events (73.0% of all DDI-QTc + cases); one torsade de pointes and one ventricular tachycardia event (5.4% of all DDI-QTc$^+$ events). Appendix S3 provides an explanation of all severity categories. In Table 4, drug pairs involved in at least one DDI-ADE are presented.

3.3 | PPV of the e-triggers

The overall PPV of all three e-triggers was 0.47. The highest PPV was found for the DDI-INR$^+$ e-trigger: 0.74, followed by DDI-AKI e-trigger with PPV of 0.57 (Table 2). The DDI-QTc$^+$ e-trigger had the lowest PPV of 0.26. If QTc measurements would have been available, the PPV of the DDI-QTc$^+$ e-trigger could have been increased to 0.67 (of the 55 cases with QTc prolongation as confirmed by medical experts, 37 were assessed as DDI-QTc$^+$).

4 | DISCUSSION

In this multicentre observational study, we reused routinely collected EHR data of ten ICUs and 85 422 ICU patients. In the sample of 237 patients reviewed and assessed by clinical experts, 155 DDI-ADEs (65%) were identified. In 53% of DDI-ADEs, the severity level of patient harm was assessed as serious or higher, 76% as preventable and 19% as contributing to a longer ICU stay.

Previous research in the ICU setting shows that the proportion of adult ICU patients experiencing DDI-ADE varies between 7% and 64%.[9–13] In our study we found an overall DDI-ADE proportion of 65%, which is at the higher end of that spectrum. Comparing our findings to the previous DDI-ADE studies is hampered by heterogeneity in setting, terminology and methodology,[31] as well as EHR systems used and EHR data quality.[15] However, two aspects of our approach may explain our findings. First, we have focused on three high-risk pDDIs in the ICU setting.[9,11,21,36] Second, we used e-triggers to preselect patient charts for a review by clinical experts. Such approach has shown to capture comparable to higher and more severe number of ADEs in (non) ICU settings, in comparison to patient chart review without use of e-triggers.[19,37,38]

The value of e-triggers to preselect patients for patient chart review depends on their PPV. The higher the PPV, the less time of clinical experts is lost on reviewing charts with no actual (DDI-)ADEs. We found a PPV of 0.74 for our DDI-INR$^+$ e-trigger and 0.57 for our DDI-AKI e-trigger, showing that these e-triggers capture a substantial part of actual DDI-ADEs. One previous study in the ICU setting

TABLE 3 Characteristics of adverse drug events caused by drug–drug interactions.

	All DDI-ADEs $n = 155$	DDI-INR$^+$ $n = 60$	DDI-AKI $n = 58$	DDI-QTc$^+$ $n = 37$
Severity, *n* (%)				
Mild	12 (7.7)	6 (10.0)	NA	6 (16.2)
Moderate	61 (39.4)	39 (65.0)	20 (34.5)	2 (5.4)
Serious	54 (34.8)	15 (25.0)[a]	12 (20.7)	27 (73.0)
Life-threatening	25 (16.1)	NA	23 (39.7)	2 (5.4)[b]
Death	3 (1.9)	NA	3 (5.2)	-
Preventability, *n* (%)				
Nearly certain[c]	4 (2.5)	2 (3.3)	2 (3.4)	0 (0.0)
Probable[c]	30 (19.4)	13 (21.7)	6 (10.3)	11 (29.7)
Possible[c]	83 (53.5)	37 (61.7)	30 (51.7)	16 (43.2)
Unlikely	36 (23.2)	8 (13.)	19 (32.8)	9 (24.3)
Unassessable/unclassifiable	2 (1.3)	0 (0.0)	1 (1.7)	1 (2.7)
Contribution to length of stay in intensive care, *n* (%)				
Nearly certain[d]	7 (4.5)	1 (1.7)	6 (10.3)	0 (0.0)
Probable[d]	12 (7.7)	3 (5.0)	9 (15.5)	0 (0.0)
Possible[d]	11 (7.1)	1 (1.7)	7 (12.1)	3 (8.1)
Unlikely	90 (58.1)	45 (75.0)	14 (24.1)	31 (83.8)
Unassessable/unclassifiable	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.7)
Not applicable because patient died	34 (21.9)	10 (16.7)	22 (37.9)	2 (5.4)

Abbreviations: ADE, adverse drug events; DDI, drug–drug interaction; DDI-AKI, DDI causing acute kidney injury; DDI-INR$^+$, DDI causing supratherapeutic INR with and without bleeding; DDI-QTc$^+$, DDI causing QTc prolongation; INR, international normalized ratio; NA, not applicable; -, not identified.
[a]Three supratherapeutic INR events resulted in a bleeding: 1 haematuria and 2 gastro-intestinal bleedings.
[b]Two life-threatening QTc interval prolongations results in: 1 torsade de pointes, and 1 ventricular tachycardia.
[c]These categories taken together constitute what was defined as preventable.
[d]These categories taken together constitute what was defined as contributed to length of stay in intensive care.

investigated the use of e-triggers to find ADEs caused by DDIs.[13] Their INR e-trigger for pDDIs with warfarin showed a higher PPV of 0.89. We investigated pDDIs with acenocoumarol or phenprocoumon. Differences in pharmacological properties of vitamin K antagonists may explain the difference in PPV, given the differences in interaction potential.[39] Regarding our DDI-QTc$^+$ e-trigger, and given its low PPV of 0.26, an ECG order can be deemed as less appropriate for preselection purposes. A possible explanation here may be that ECG measurements are conducted to monitor patients at risk for QTc prolongation after being exposed to QTc prolonging drugs, as opposed to a procedure conducted to assess ADE occurrence. Therefore, actual QTc prolongation seems a better option as an e-trigger as long as QTc time measurements are available as structured data in EHR systems.

4.1 | Strengths and limitations

This study has several strengths. First, to the best of our knowledge, this is the first multicentre study on DDI-ADEs in academic and nonacademic settings.[1,2,8] Second, we utilized a large dataset with 85 422 ICU patients over a period of 9.5 years. Third, the richness of our dataset enabled us to apply more complex e-trigger logic with satisfactory results for two of the three investigated e-triggers. Fourth, we used a structured and standardized eCRF based on the WHO-UMC causality assessment[30] to guide expert reviewers in the process of patient chart review and causality assessment. The clinical experts assessed not only the causality, but also preventability, severity and contribution to ICU LOS of DDI-ADEs. Lastly, in our study, we have followed international guidelines and procedures regarding ADE definition,[33] ADE severity[34] and ADE causality assessment.[23]

This study also has some limitations. First, the multicentre nature of our study, made the analysis of DDI-ADE inter-rater agreement not feasible with the resources and time available. Such analysis would require clinical experts from one ICU to visit other ICUs to conduct on-site patient chart reviews, as well as anonymization of the entire EHR record of the patient. To ensure the comparability of the DDI-ADE causality, severity and preventability assessments, we implemented three standardization measures as described in Section 2.4. Furthermore, we used the WHO-UMC causality assessment which

TABLE 4 Drug–drug interactions (DDIs) causing adverse drug event.

Adverse drug events	DDIs[a]	*n* (%)
Supratherapeutic international normalized ratio (≥5)	All DDIs with vitamin K antagonists	60
	Acenocoumarol + cephalosporins (2 × ceftriaxone, 2× cefazolin, cefotaxime, 1× cefuroxime)[b]	7 (11.7)
	Acenocoumarol + macrolides (5× erythromycin, 1× azithromycin)[c]	6 (10.0)
	Acenocoumarol + amiodarone	6 (10.0)
	Phenprocoumon + amiodarone	6 (10.0)
	Acenocoumarol + ciprofloxacin	5 (8.3)
	Phenprocoumon + ciprofloxacin	4 (6.7)
	Acenocoumarol + fluconazole	3 (5.0)
	Phenprocoumon + flucloxacillin	2 (3.3)
	Acenocoumarol + esomeprazole	2 (3.3)
	Acenocoumarol + doxycycline	2 (3.3)
	Acenocoumarol + metronidazole	2 (3.3)
	Phenprocoumon + co-trimoxazole	2 (3.3)
	Other DDIs with vitamin K antagonists	13 (21.6)
Acute kidney injury stage 2 or 3	All DDIs with nephrotoxic potential	58
	Furosemide + aminoglycosides (13× gentamicin, 6× tobramycin)[d]	19 (32.8)
	Tacrolimus + triazole derivatives (6× voriconazole, 1× posaconazole, 1× fluconazole)	8 (13.8)
	Tacrolimus + antivirals (4× aciclovir, 3× valaciclovir)	7 (12.1)
	Ciclosporin + co-trimoxazole	5 (8.6)
	Tacrolimus + amiodarone	4 (6.9)
	Tacrolimus + erythromycin	3 (5.2)
	Furosemide + diclofenac	2 (3.4)
	Ciclosporin + amphotericin B (liposomal formulation)	2 (3.4)
	Amlodipine + erythromycin	2 (3.4)
	Other DDIs with nephrotoxic potential	6 (10.3)
QTc prolongation (≥450 ms)	All DDIs between QTc prolonging drugs	37
	Amiodarone + sotalol[e]	11 (29.7)
	Amiodarone + haloperidol[f]	7 (18.9)
	Amiodarone + ciprofloxacin	6 (16.2)
	Amiodarone + erythromycin	4 (10.8)
	Erythromycin + ciprofloxacin	2 (5.4)
	Other DDIs between QTc prolonging drugs	7 (18.9)

[a]Only DDIs with more than 1 adverse drug event are specified.
[b]Two of these DDIs led to gastrointestinal bleeding.
[c]One of these DDIs led to haematuria.
[d]Six of these DDIs (all with gentamicin) were related to dialysis.
[e]One of these DDIs led to QTc prolongation with torsade de pointes.
[f]One of these DDIs led to QTc prolongation with ventricular tachycardia.

showed the highest consistency for causal imputation of ADEs in the inpatient setting,[40] and CTCAEv5 for ADE severity assessment which showed to increase consistency in severity scoring between different reviewers.[14] Also, use of e-triggers has shown to reduce reviewer subjectivity and error.[15,16] Nevertheless a limitation of our study is that we did not assess inter-rated agreement and hence our results should be interpreted with caution, since even with highly trained reviewers and use of trigger tool, the level of agreement between reviewers with regard to the presence of an adverse event is usually only moderate.[41] Second, we could not select patients at random for the manual patient chart review given the need to manually check plausibility of the temporality criterion. This check was, however, done by screening consecutive ICU admissions, starting with the most recent admissions, and moving down in time until the agreed sample of 30–50 cases was

met. Therefore, selection bias based on ADE severity or patient characteristics was avoided. Third, this study was conducted in the Netherlands, which may reduce the generalizability of our findings to other settings. However, our results align broadly with DDI-ADEs results in other settings, our data represent not only academic but also nonacademic ICUs, and variables that were included in the e-trigger logic are very common in most EHR systems. Fourth, during the study period at various time points, seven (70%) participating ICUs implemented CDSS containing pDDI alerts. This may have prevented prescription of potentially interacting drugs and therefore DDI-ADEs that may arise from them. Consequently, the true potential of pDDIs to cause DDI-ADEs may have been underestimated. However, since CDSS is becoming a common and desirable practice,[42] research without CDSS in place may be unethical from patient safety perspective. Lastly, we did not assess the negative predictive value of our e-triggers in this study because our primary goal was to identify DDI-ADEs, and not to validate e-triggers. Evaluating negative predictive value would require examining patients without e-triggers, which was beyond the time of clinical experts involved and resources for this study. However, since the results of two out of our three e-triggers are promising, investing limited time of clinical experts and often limited research resources to further refine and validate these two e-triggers in the near future is justified.

4.2 | Implications for practice and future research

Our study is a direct answer to the call of the international research community for studies that go further than just measuring pDDIs.[2,8,43,44] Based on the extent and type of DDI-ADEs in a specific patient population, it could be decided for which pDDIs, alerts via CDSS are warranted and how these pDDI alerts should be presented to prescribers of medication (e.g. as on-demand, interrupting, or in-line alerts).[2,45] We have shown that the exposure to three high-risk pDDI categories often leads to DDI-ADEs, justifying the use of pDDI alerts via CDSS for these three high-risk pDDIs. At the same time, the detected DDI-ADEs occurred despite CDSS being in place in the majority of our participating ICUs. This urges further improvement of the logic-based rules behind pDDI alerts to make them fit better to a specific clinical context and/or patient factors.[6,46,47] Given the high variety of pDDIs in the ICU,[1,8] more research is needed to investigate ADE potential of a broader sample of pDDIs, as a way to optimize CDSS effectiveness. Prioritizing which pDDIs to focus on in future research, should be done with the input of ICU clinical staff.

This study also underlines the multifactorial nature of adverse (drug) events in ICU patients.[48] This multifactorial nature explains why only a small proportion of DDI-ADEs in our study (6%) was assessed as having a nearly certain causality. Furthermore, possibly due to resilience of ICU care, of all 155 DDI-ADEs identified, the majority (81.9%) resulted in abnormal laboratory findings/QTc prolongation, and smaller fractions of 18.0 and 1.9% resulted in clinically symptomatic events (dialyses, bleeding, arrhythmias), and DDI-ADE related deaths, respectively. However, since the majority of DDI-ADEs was deemed as preventable, putting medication including pDDIs on the differential diagnoses list when confronted with an adverse event (abnormal laboratory findings or clinically symptomatic findings), could preclude further patient harm. This can be even the case in situations where causality is less certain or the adverse event mild or moderate. As proposed by Jerry Avorn, a professor of medicine at Harvard Medical School: 'Discovering that a symptom is caused by a drug presents an uncommon opportunity to effect a total "cure" by stopping the offending prescription or lowering the dose.'[49]

The best prevention measure for DDI-INR+ in patients taking vitamin K antagonists in the ICU is to avoid prescribing or continuing vitamin K antagonists and instead choose alternative drugs with a limited potential for pDDIs.[43] Over the past decade, there has been a trend in the Netherlands of initiating or switching patients from vitamin K antagonists to direct oral anticoagulants.[44] Consequently, the number of ICU patients on vitamin K antagonists upon admission is decreasing. However, vitamin K antagonists remain the second most commonly used oral anticoagulant in the Netherlands, where INR monitoring in patients taking these medications is closely supervised by thrombosis clinics.[44] If alternatives are not appropriate, daily monitoring of INR should be part of anticoagulation monitoring in patients taking vitamin K antagonists to detect unintended INR increases early on. Vitamin K antagonist interactions with antibiotics were the most frequent DDI-INR$^+$ category in our study. Although most antibiotics do not exhibit direct effect on the metabolism of vitamin K antagonists, their use can be an indication that the INR is or is being disrupted.[28] Enhanced monitoring should also be considered in situations where refraining from concomitant use of two or more nephrotoxic drugs or QTc prolonging drugs is not possible. Here one could increase the frequency of serum creatinine, QTc and electrolytes checks. Of note is the high frequency of aminoglycosides and furosemide combinations in the group of DDI-AKI. In the G-Standaard, this combination is earmarked as having insufficient evidence-base and therefore no alerting is indicated.[28] However, since both drug (groups) have nephrotoxic potential and use of diuretics has been identified as a risk-factor for aminoglycoside-induced nephrotoxicity, caution is advisable when they are administered at the same time.[45–47]

The PPV findings for our DDI-AKI and DDI-INR$^+$ e-triggers are encouraging. Use of e-triggers can largely automate the process of ADE detection, and save substantial time for patient chart review by clinical experts.[15,16,50] Such automation is urgently needed to build ADE monitoring systems capable of continuous and hospital-wide ADE detection.[51] This, especially since the workforce in healthcare is shrinking and at the same time the complexity of patients admitted to hospitals (in terms of multimorbidity and polypharmacy) is increasing. Such ADE monitoring system could help in enlarging the evidence-base about patient harm caused by pDDI, be used to optimize pDDI alerting via CDSS, and provide insights in patient outcomes when measuring CDSS effectiveness.

5 | CONCLUSION

Potential DDIs with vitamin K antagonists, between nephrotoxic drugs and between QTc prolonging drugs, frequently result in actual serious and often preventable DDI-ADEs in the ICU patients. These findings call for action to optimize patient safety in the ICU. This could be accomplished by refraining from prescribing of certain high-risk drug combinations, increasing patient monitoring when refraining is not possible and/or improving clinical relevance of pDDI alerts in CDSS. Use of the INR and AKI e-triggers proved to be a promising and feasible preselection strategy to study the occurrence of DDI-ADEs in ICU patients, and their further optimization and application should be intensified.

AUTHOR CONTRIBUTIONS

Joanna E. Klopotowska: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; validation; visualization; writing—original draft; writing—review and editing. **Jan-Hendrik Leopold**: Methodology; software; writing—review and editing. **Tinka Bakker**: Data curation; methodology; software; writing—review and editing. **Izak Yasrebi-de Kom**: Data curation; methodology; software; writing—review and editing. **Frouke M. Engelaer**: Investigation; validation; writing—review and editing. **Evert de Jonge**: Funding acquisition; resources; writing—review and editing. **Esther K. Haspels-Hogervorst**: Investigation; validation; writing—review and editing. **Walter M. van den Bergh**: Resources; writing—review and editing. **Maurits H. Renes**: Resources; writing—review and editing. **Bas T. Jong**: Investigation; validation; writing—review and editing. **Hans Kieft**: Resources; writing—review and editing. **Andre Wieringa**: Investigation; validation; writing—review and editing. **Stefaan Hendriks**: Investigation; resources; validation; writing—review and editing. **Cedric Lau**: Investigation; validation; writing—review and editing. **Sjoerd H.W. van Bree**: Investigation; resources; validation; writing—review and editing. **Hendrick J.W. Lammers**: Investigation; validation; writing—review and editing. **Peter C. Wierenga**: Resources; writing—review and editing. **Rob J. Bosman**: Funding acquisition; investigation; resources; validation; writing—review and editing. **Eric J.F. Franssen**: Investigation; validation; writing—review and editing. **Wytze J. Vermeijden**: Investigation; resources; validation; writing—review and editing. **Joost Masselink**: Investigation; validation; writing—review and editing. **Ilse M. Purmer**: Investigation; resources; validation; writing—review and editing. **Liesbeth E. Bosma**: Investigation; validation; writing—review and editing. **Martin Hoeksema**: Investigation; resources; validation; writing—review and editing. **Elsbeth Wesselink**: Investigation; validation; writing—review and editing. **Dylan W. de Lange**: Funding acquisition; investigation; resources; validation; writing—review and editing. **Nicolette F. de Keizer**: Conceptualization; funding acquisition; methodology; resources; writing—review and editing. **Dave A. Dongelmans**: Conceptualization; funding acquisition; methodology; resources; writing—review and editing. **Ameen Abu-Hanna**: Conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; verification; writing—review and editing. All authors gave final approval of the submitted version.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The pDDI and e-trigger algorithms are available upon request with the corresponding author. Due to the sensitive nature of our dataset and the data sharing agreements with the participating ICUs data can only be shared after explicit consent of the participating ICUs per request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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