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A B S T R A C T

Purpose: Potential drug-drug interactions (pDDIs) may harm patients admitted to the Intensive Care Unit (ICU). Due to the patient's critical condition and continuous monitoring on the ICU, not all pDDIs are clinically relevant. Clinical decision support systems (CDSSs) warning for irrelevant pDDIs could result in alert fatigue and overlooking important signals. Therefore, our aim was to describe the frequency of clinically relevant pDDIs (crpDDIs) to enable tailoring of CDSSs to the ICU setting.

Materials & methods: In this multicenter retrospective observational study, we used medication administration data to identify pDDIs in ICU admissions from 13 ICUs. Clinical relevance was based on a Delphi study in which intensivists and hospital pharmacists assessed the clinical relevance of pDDIs for the ICU setting.

Results: The mean number of pDDIs per 1000 medication administrations was 70.1, dropping to 31.0 when considering only crpDDIs. Of 103,871 ICU patients, 38% was exposed to a crpDDI. The most frequently occurring crpDDIs involve QT-prolonging agents, digoxin, or NSAIDs.

Conclusions: Considering clinical relevance of pDDIs in the ICU setting is important, as only half of the detected pDDIs were crpDDIs. Therefore, tailoring CDSSs to the ICU may reduce alert fatigue and improve medication safety in ICU patients.

1. Introduction

A recent systematic review estimated that 58% of the Intensive Care Unit (ICU) patients are exposed to a potential drug-drug interaction (pDDI) [1]. This is twice as much as in general wards [2]. A pDDI is defined as two drugs administered concomitantly, potentially interacting through pharmacokinetic or pharmacodynamic mechanisms [2]. pDDIs may lead to actual DDIs and result in Adverse Drug Events (ADE), causing higher mortality and morbidity, prolonged length of stay (LOS), and increased hospital costs [3]. On average, 30 different medications are administered to ICU patients during ICU stay and each intravenous medication administered increases the ADE risk by 3% [1,4]. Besides polypharmacy, ICU patients often suffer from impaired kidney and hepatic function, exposing them to increased risks of drug toxicity [5].

The condition of ICU patients may require administration of potentially interacting medications. Furthermore, ICU patients are continuously monitored, enabling timely detection and risk management of potential adverse effects. Therefore, ICU patients may encounter a high number of pDDIs, but not all pDDIs are clinically relevant. As Fitzmaurice et al. stated [1], pDDI frequency is not always indicative of clinical relevance, and more research is needed to understand the clinical relevance of pDDIs in the ICU.

Yet, most studies assessing clinical relevance of pDDIs in the ICU based their clinical relevance definition on severity categories from interaction databases [1]. Since interaction databases are not tailored to the ICU setting, their severity categories are less appropriate for the ICU. Additionally, the majority were single-center studies with relatively small samples, limiting generalizability [1].

To address these limitations, we previously conducted a Delphi study with an expert panel of 27 hospital pharmacists and intensivists from 14 different ICUs to assess the clinical relevance of 148 pDDI types for ICU patients, of which 86 pDDI types were considered clinically relevant [6].

The aim of this large multicenter study was to describe the frequency and type of clinically relevant pDDIs (crpDDIs) in the ICU. This will improve our understanding of the extent and risks of crpDDI exposure in ICU patients, and may inform the development of appropriate clinical decision support systems (CDSS).

2. Materials and methods

2.1. Study design

In this multicenter retrospective observational study, we determined the frequency and type of crpDDIs on the ICU, based on routinely-collected medication administration data. This study is reported according to the RECORD-PE statement [7] (Supplementary file 1).

2.2. ICU and patient inclusion

All fifteen Dutch ICUs using the commercial patient data management system (PDMS) Metavision© at the time of the study were invited. Thirteen ICUs agreed to participate, two declined because they were migrating to another PDMS. Adult patients (18 years and older) admitted to the ICU within the study period with at least two administered medications were included. No further exclusion criteria were used. All admission days were included.

The study period lasted from January 2010 until July 2017 (7.5 years). Four ICUs implemented Metavision© after January 2010 or migrated to another PDMS before July 2017 reducing their study period by one to four years. During the study period, seven ICUs implemented a CDSS warning prescribers through pDDI alerts during order entry. The other six ICUs did not have a CDSS in place. The seven ICUs that implemented a CDSS during the study period did not show a qualitative change in (cr) pDDIs after CDSS implementation.

At the thirteen study sites, hospital pharmacists provided centralized clinical pharmacy services on prescribing, consisting of daily on-call availability for medication-related problems. Hospital pharmacists had no access to the CDSS alerts.

2.3. Data sources

All medication administration data were extracted from the PDMS using validated queries. Medication administration data included name, dose, administration route, and start and stop date and time per administration of each medication during admission. If the time interval between administrations of the same medication did not exceed 24 h, the separate administrations were merged into one medication administration record. The resulting record was given the start time of the first administration and the stop time of the last administration.

To characterize the study population, the medication administration dataset was enriched by linking it with the National Intensive Care Evaluation (NICE) quality registry in which all Dutch ICUs participate [8]. The following characteristics were included: ICU LOS, admission type, admission diagnosis, presence of chronic conditions, ICU mortality, hospital mortality, and expected mortality. ICU admissions that could not be linked with the NICE database were excluded.

2.4. pDDI detection

To detect pDDIs in the medication administration data, we used the G-standard drug database [9]. The G-standard is an evidence-based professional drug database, used in electronic prescribing systems in Dutch hospitals [2]. Medications are represented by a generic product code

(GPK in Dutch). Each pDDI type is enlisted by various pairs of GPKs. For example, the pDDI type NSAIDs + corticosteroids is represented by 14,190 GPK combinations of medication subtypes, such as ibuprofen + dexamethasone. The G-standard provides a summary of mechanism(s) and potential risk(s) of each pDDI, and recommendations to handle the pDDI [9]. We used the February 2017 G-standard version, including 557 pDDIs (see Supplementary file 2). To detect pDDIs using the G-standard, we mapped all medication names in the medication administration data to GPK codes.

For this study, we developed a computerized algorithm to detect pDDIs, incorporating information from the G-standard. The algorithm defines a pDDI as the administration of two potentially interacting medications within a time interval of 24 h maximum. For example, if medication A interacts with medication B, and the time interval between the stop time of A and the start time of B is 24 h or less, it was considered a pDDI. The pDDI start was defined as the start time of A and the pDDI stop as the stop time of B. The pDDI duration is the time difference between the pDDI start and the pDDI stop.

Per pDDI type, each combination of interacting medications was counted separately. For example, if a patient received NSAIDs and two corticosteroids both interacting with NSAIDs, these interactions were counted separately. If a pDDI occurred more than once, all occurrences were counted if the time interval between the occurrences was more than 24 h. Two developers validated the algorithm through unit testing [10].

Clinical relevance of a pDDI in the ICU was based on a previous study [6]. Supplementary file 3 lists the 86 crpDDI types.

2.5. Outcome measures

The primary outcome was the number of crpDDIs per 1000 medication administrations. This contrasts some previous studies using patient days to express pDDI rate [1]. Expressing a crpDDI rate per 1000 administrations seems more appropriate since not all admission days hold the same risk for crpDDIs. Patients with a longer LOS are more at risk in the first admission days. To enable comparison to other studies, we also report secondary outcome measures used in other studies [1], including the number of crpDDIs per ICU admission, the proportion of ICU admissions with at least one crpDDI, and the distribution of crpDDIs over admission days.

To improve our understanding of potential risks of crpDDIs, we categorized crpDDI types according to its potential clinical consequences and monitoring strategy following the example of Uijtendaal et al. [2]. Furthermore, the fifteen most frequently occurring crpDDI types will be presented.

Additionally, crpDDI duration and pDDIs at ICU discharge will be described. crpDDI duration is important since pharmacokinetic/pharmacodynamic mechanisms are often time-dependent, e.g. for crpDDIs with an underlying liver metabolism induction mechanism, it takes several days to produce an induction effect on the enzymes involved [11]. Knowing which pDDIs are present at ICU discharge could help intensivists guide transfers to non-ICU wards with less frequent monitoring. This estimate included all pDDIs, independent of clinical relevance.

2.6. Statistical analysis

Count and continuous variables are characterized by mean with standard deviation, or median with interquartile range, depending on their distribution.

Aside from the crpDDI set, all primary and secondary outcomes were calculated on the complete set of pDDIs. Furthermore, a subgroup analysis of crpDDIs was performed for patients with a minimum LOS of 24 h, enabling comparison to other studies.

All data analyses and development of the detection algorithm were performed in the R statistical environment (3.5.3) [12].

3. Results

All 13 ICUs were mixed medical-surgical closed format ICUs situated in academic hospitals ($n = 2$), teaching hospitals ($n = 7$) and general hospitals ($n = 4$) in the Netherlands. Together they represent 278 beds (mean: 21.4; SD: 13.4). The ICUs were geographically distributed over the Netherlands. Fig. 1 shows the inclusion and data linkage process. The resulting study population included 103,871 ICU admissions corresponding to 2,282,974 administrated medications. Table 1 displays the patient characteristics. The median LOS was 1.03 days (IQR: 2.2; Q1: 0.8; Q3:3.0), totaling 364,855 ICU days. The median age was 66 (IQR: 19; Q1: 55; Q3: 74) and 61.4% were male. Most admissions were medical (42.2%) or elective surgery (44.2%), and 47.1% of the admissions had a cardiovascular admission diagnosis.

3.1. pDDI frequency

In 103,871 ICU admissions, 228,489 pDDIs were detected, corresponding to 270 of 557 (48.5%) pDDI types. The mean number of pDDIs per 1000 medication administrations was 70.1 (SD: 90.5) and the mean number of pDDIs per admission was 2.2 (SD: 4.1). Of the 103,871 admissions, 56,561 (54.5%) had at least one pDDI.

3.2. crpDDI frequency

Of the 228,489 detected pDDIs, 226,740 (99.2%) correspond to pDDI types that were assessed for clinical relevance in the previous Delphi study. Of those 226,740 pDDIs, 107,908 were crpDDIs (47.2% of all pDDIs), corresponding to 85 crpDDI types, while 112,086 (49.0% of all pDDIs) were not clinically relevant, corresponding to 53 pDDI types. The remaining 6746 pDDIs (3.0% of all detected pDDIs), corresponding to 9 pDDI types, were assessed but agreement regarding the clinical relevance was not reached in the Delphi study. The mean number of crpDDIs per 1000 medication administrations was 31.0 (SD: 53.7), and the mean number of crpDDIs per admission was 1.0 (SD: 2.3). Of the 103,871 admissions, 39,661 (38.2%) had at least one crpDDI. Fig. 2a displays the number and percentage of admissions with 0 to 7 or more crpDDIs.

Table 2 shows the 15 most frequently occurring crpDDIs types. crpDDIs that might potentially lead to cardiac arrhythmias were most frequent, including interactions with QT-prolonging agents and interactions with digoxin. These accounted for 80,631 (74.7%) of the detected crpDDIs. Another frequent type was NSAIDs interactions, potentially resulting in gastrointestinal bleeding (18.6%). Supplementary file 4 shows the top 15 of all pDDI types.

Supplementary file 5 summarizes the post-hoc analysis of patients with a minimum LOS of 24 h. This subgroup had a higher frequency of crpDDIs compared to the whole group. Subgroup patients were on average exposed to 1.7 crpDDIs compared to 1.0, and 53.8% was exposed to a crpDDI, compared to 38.2%.

3.3. crpDDI timing

Fig. 2b shows the number of crpDDIs per admission day for day 1 to day 15. crpDDIs mostly occurred on the first day while the following days the risk decreased gradually. To obtain these results, the number of crpDDIs on an admission day was divided by the number of admissions on that day, correcting for differences in LOS. Supplementary file 4 shows the number of all pDDIs per admission day.
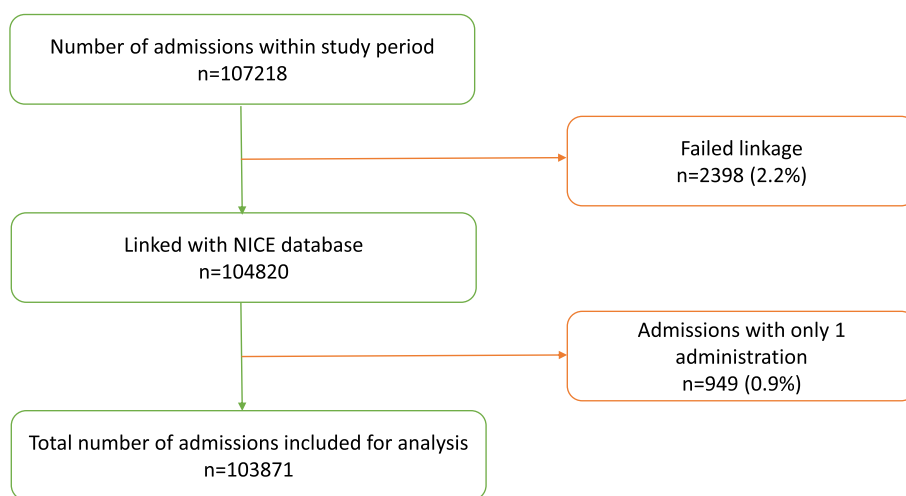
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┌─────────────────────────────────────────┐
│ Number of admissions within study period │
│              n=107218                     │
└─────────────────────────────────────────┘
                    │
                    │              ┌──────────────────────┐
                    ├─────────────▶│   Failed linkage     │
                    │              │    n=2398 (2.2%)      │
                    ▼              └──────────────────────┘
┌─────────────────────────────────────────┐
│       Linked with NICE database          │
│              n=104820                     │
└─────────────────────────────────────────┘
                    │
                    │              ┌──────────────────────┐
                    ├─────────────▶│ Admissions with only 1│
                    │              │    administration     │
                    ▼              │    n=949 (0.9%)       │
┌─────────────────────────────────────────┐└──────────────────────┘
│ Total number of admissions included for  │
│           analysis  n=103871              │
└─────────────────────────────────────────┘
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Fig. 1. Overview of data inclusion and linkage process.

3.4. Potential clinical consequences & monitoring strategies

Most crpDDIs increased the potential risk of side effects (96.6%) (Table 3). Within this category, potential risk of cardiac arrhythmias occurred most often (75.9%), followed by risk of bleeding (18.7%) and risk of neurologic disturbances (4.5%). Clinical monitoring (78.6%), ECG monitoring (74.5%) and avoiding the combination (76.9%) were the most frequent monitoring strategies to reduce the risk of DDI-related ADEs.

3.5. crpDDI duration & pDDIs at discharge

The median duration of a crpDDI was 1.2 days (IQR: 1.9; Q1: 0.9; Q3: 2.8). At ICU discharge, 44,366 admissions (42.7%) had at least one pDDI.

Table 2 shows the top 15 pDDIs at discharge. Interactions with QT-prolonging agents occurred most frequently, followed by pDDIs potentially leading to blood pressure disturbances (pDDI #3, #6, #8, #13), potassium disturbances (pDDI #4, #10, #15) or glucose disturbances (pDDI #2, #7).

4. Discussion

Our study shows the mean number of pDDIs per 1000 medication administrations was 70.1, dropping to 31.0 when considering only crpDDIs. In total, 53.8% of the ICU patients was exposed to a pDDI and 38.2% to a crpDDI. On average patients were exposed to 2 pDDIs, of which one clinically relevant. crpDDIs mostly occurred on the first admission day and lasted approximately one day. The most frequent crpDDIs were interactions with QT-prolonging agents, digoxin, and NSAIDs, increasing the potential risk of cardiac arrhythmia and bleeding. Accordingly, ECG monitoring, clinical monitoring and adding gastric protection are commonly advised monitoring strategies. Around 42% of the patients is discharged with a pDDI, of which the majority potentially leads to disturbances in blood pressure, potassium or glucose.

Other studies report one to five pDDIs per admission, and overall 58.0% of ICU patients have a pDDI [1]. Consistently, we found on average 2 pDDIs per admission and 53.8% of all patients having a pDDI. Regarding crpDDIs, we found on average 1.0 crpDDIs per admission and 38.2% of the patients have a crpDDI. We identified one study similar to ours, using a Delphi procedure to establish crpDDIs in the ICU [13]. This single-center study by Askari et al. identified on average 1.7 crpDDIs per admission, slightly higher compared to our findings. Differences in clinical relevance definition and detection methods may explain this. Another possible explanation may be the longer median LOS in their study population (1.7 days vs 1.0 days). The high percentage of elective surgery admissions may explain the relatively short LOS in our study population.

Table 1
Patient characteristics of included admissions ($n = 103,871$).

Characteristics	n (%)
Age	
median (Q1– Q3)	66 (55–74)
Gender (male)	63,726 (61.4%)
APACHE IV predicted mortality[a]	
median (Q1– Q3)	15 (11–21)
ICU mortality	8784 (8.5%)
Hospital mortality	12,955 (12.5%)
ICU Length of stay	
median (Q1-Q3)	1.0 (0.8–3.0)
Admission type	
Medical	43,788 (42.2%)
Emergency surgical	13,299 (12.8%)
Elective surgical	45,895 (44.2%)
Admission type missing	889 (0.8%)
Chronic conditions	
Chronic kidney failure	5222 (5.0%)
COPD	12,966 (12.5%)
Respiratory failure	3867 (3.7%)
Cardiovascular disease	5752 (5.5%)
Cirrhosis	1132 (1.1%)
Hematological malignancy	1673 (1.6%)
AIDS	205 (0.2%)
Immunodeficiency	9982 (9.6%)
Admission diagnosis type category	
Cardiovascular	48,922 (47.1%)
Gastrointestinal	14,087 (13.6%)
Genitourinary	3937 (3.8%)
Hematology	352 (0.3%)
Metabolic/Endocrine	1803 (1.7%)
Musculoskeletal_skin	1546 (1.5%)
Neurologic	11,346 (10.9%)
Respiratory	16,137 (15.5%)
Transplant	469 (0.5%)
Trauma	4051 (3.9%)
Admission diagnosis missing	1221 (1.2%)

[a] Calculated within the first 24 h of ICU admission using the APACHE IV model APACHE = Acute Physiology And Chronic Health Evaluation, ICU = Intensive Care Unit, COPD = Chronic Obstructive Pulmonary Disease, AIDS = Acquired Immune Deficiency Syndrome.
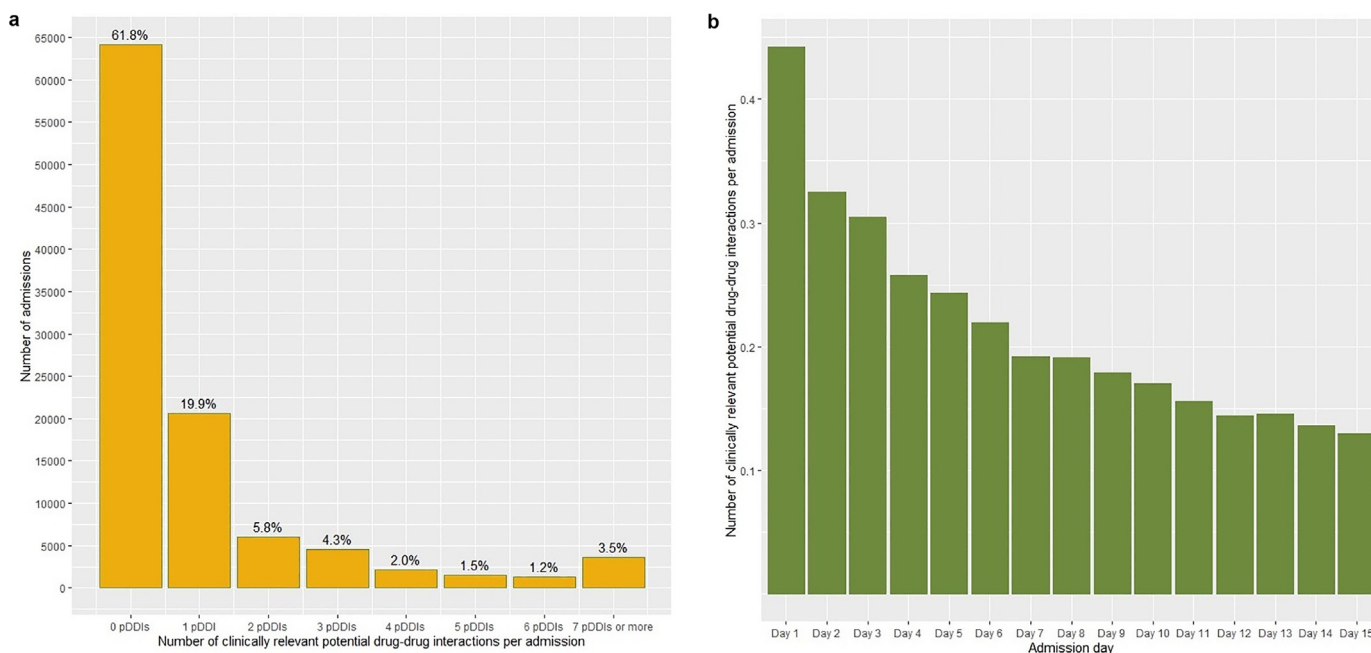
Fig. 2. a Number and percentage of clinically relevant potential drug-drug interactions per admission. b Number of clinically relevant potential drug-drug interactions per admission for each admission day.

Table 2
Top 15 most frequently occurring clinically relevant potential drug-drug interactions and top 15 most frequent potential drug-drug interactions at discharge.

Top 15 most frequent clinically relevant potential drug-drug interactions

	crpDDI	Number of crpDDIs (%)[a]	Admissions with crpDDI (%)[b]
1	QT-PROLONGING AGENTS[c] + QT-PROLONGING AGENTS[c]	77,883 (72.2)	29,323 (28.2)
2	NSAIDs + CORTICOSTEROIDS	18,132 (16.8)	14,206 (13.7)
3	DIGOXIN + AMIODARON	1945 (1.8)	1512 (1.5)
4	NSAIDs + SEROTONERGIC AGENTS	1198 (1.1)	1066 (1.0)
5	DIGOXIN + ERYTHROMYCIN/CLARITHROMYCIN/ROXITHROMYCIN/AZITHROMYCIN	803 (0.7)	716 (0.7)
6	SALICYLIC ACID IN ANTITHRMBOTIC DOSE (UP TO 100 MG) + NSAIDs	719 (0.7)	686 (0.7)
7	HALOPERIDOL + INDUCERS	666 (0.6)	525 (0.5)
8	BETA-LACTAM ANTIBACTERIALS + TETRACYCLINES	561 (0.5)	456 (0.4)
9	THYROID HORMONES + ANTACIDS/CALCIUM PREPARATIONS	512 (0.5)	467 (0.4)
10	PHENYTOIN + VARIOUS INHIBITORS	439 (0.4)	390 (0.4)
11	THEOPHYLLINE + CYP1A2-INHIBITORS	436 (0.4)	413 (0.4)
12	PHENYTOIN + VALPROIC ACID	430 (0.4)	357 (0.3)
13	TACROLIMUS + CYP3A4-INHIBITORS	401 (0.4)	303 (0.3)
14	THEOPHYLLINE + ERYTHROMYCIN	321 (0.3)	286 (0.3)
15	DOPAMINERGIC AGENTS + ANTIPSYCHOTICS	207 (0.2)	157 (0.2)

Top 15 most frequent potential drug-drug interactions at intensive care unit discharge

	pDDI	Number of pDDIs (%)[d]	Number of admissions with this pDDI at discharge (%)[b]
1	QT-PROLONGING AGENTS[c] + QT-PROLONGING AGENTS[c]	18,635 (20.2)	13,548 (13.0)
2	BETA BLOCKING AGENTS (SELECTIVE) + INSULINS	11,960 (13.0)	11,227 (10.8)
3	RAAS-INHIBITORS + DIURETICS	8914 (9.7)	8206 (7.9)
4	RAAS-INHIBITORS + POTSASSIUM-SPARING AGENTS	8654 (9.4)	6861 (6.6)
5	NSAIDs + CORTICOSTEROIDS	8569 (9.3)	7928 (7.6)
6	BETA BLOCKING AGENTS (NON-SELECTIVE) + BETA AGONISTS	4727 (5.1)	4610 (4.4)
7	BETA BLOCKING AGENTS (NON-SELECTIVE) + INSULINS	4017 (4.4)	3930 (3.8)
8	BETA BLOCKING AGENTS + NSAIDs	2594 (2.8)	2500 (2.4)
9	CLOPIDOGREL + OMEPRAZOLE/ESOMEPRAZOLE	2036 (2.2)	2034 (2.0)
10	POTASSIUM + POTASSIUM SPARING AGENTS	1591 (1.7)	1300 (1.3)
11	SIMVASTATIN/ATORVASTATIN + CYP3A4-INHIBITORS	1504 (1.6)	1386 (1.3)
12	MIDAZOLAM/ALPRAZOLAM + CYP3A4-INHIBITORS	1411 (1.5)	1309 (1.3)
13	ALPHA BLOCKING AGENTS (NON-SELECTIVE) + BETA BLOCKING AGENTS/CALCIUM CHANNEL BLOCKERS	1296 (1.4)	737 (0.7)
14	VITAMIN K ANTAGONISTS + ANTIBIOTICS[e]	1215 (1.3)	834 (0.8)
15	ACETAZOLAMIDE + DIURETICS (EXCL. POTASSIUM SPARING AGENTS)	1177 (1.3)	1040 (1.0)

NSAIDs = nonsteroidal anti-inflammatory drugs; RAAS = renin-angiotensin-aldosterone system; (cr)pDDI = (clinicaly relevant) potential drug-drug interaction.
[a] % of all clinically relevant potential drug-drug interactions.
[b] % of admissions with this (clinically relevant) potential drug-drug interaction.
[c] QT-prolonging agents with high risk for torsade de pointes.
[d] % of all potential drug-drug interactions at ICU discharge.
[e] Excluding sulfamethoxazole and trimethoprim/metronidazole/cefamandole.

Table 3
Frequency of clinically relevant potential drug-drug interaction categorized by type of increased potential risk and monitoring strategy.

Increased potential risk	Number and percentage (%)[a]
Increased potential risk of side effects/toxicity	**104,202 (96.6%)**
Cardiac arrhythmias (including QT prolongation)	81,870 (75.9%)
Bleeding risk (including gastrointestinal ulcer risk)	20,128 (18.7%)
Neurologic disturbances	4802 (4.5%)
Nephrotoxicity	754 (0.7%)
Other	206 (0.2%)
Hypotension or hypertension	112 (0.1%)
Myopathy	152 (0.1%)
Hematologic disturbances	74 (0.07%)
Serotonergic syndrome	0 (0%)
Masking hypoglycemia	0 (0%)
Electrolyte disturbance	0 (0%)
Potential risk of decreased efficacy	**3706 (3.4%)**
Antipsychotics (incl. haloperidol)	965 (0.9%)
Absorption (various drugs)	922 (0.9%)
Antibiotics	603 (0.6%)
Antiepileptics	639 (0.6%)
Other	208 (0.2%)
Antihypertensive drugs	131 (0.1%)
Benzodiazepines/opioids	116 (0.1%)
Antimycotics	100 (0.09%)
Immunomodulators	22 (0.02%)
Antithrombotics	0 (0%)
Lipid-modifying agents	0 (0%)
Monitoring strategy	**Number and percentage (%)[a]**
Clinical monitoring	**84,768 (78.6%)**
Avoid combination	**82,987 (76.9%)**
ECG monitoring	**80,400 (74.5%)**
Risk-modifying strategy	**21,053 (19.5%)**
Add gastric protection (proton pump inhibitor)	20,074 (18.6%)
Separate moments of oral administration	922 (0.9%)
Other	57 (0.05%)
Potassium or potassium-sparing diuretic	0 (0%)
Monitoring of laboratory values	**5107 (4.7%)**
Drugs (therapeutic drug monitoring)	4874 (4.5%)
Kidney_function (serum creatinine)	284 (0.3%)
Liver function	154 (0.1%)
Blood clotting time (international normalized ratio)	79 (0.07%)
Other	33 (0.03%)
Sodium	0 (0%)
Glucose	0 (0%)
Potassium	0 (0%)
Adjust/titrate dose slowly	**2513 (2.3%)**
Other	**492 (0.5%)**
Blood pressure monitoring	**101 (0.09%)**

100% since clinically relevant potential drug-drug interactions may fall in multiple categories.
ECG = electrocardiogram.
[a] Numbers may not add up to 107,908 and percentages may not add up to.

Our study shows that by considering clinical relevance for the ICU setting, the frequency of pDDIs drops by 47%. Despite the decrease, risks for ICU patients remain substantial. Adjusted for clinical relevance, ICU patients are still frequently exposed to increased risks of ADEs such as QT-prolongation, bleeding and neurological disturbances. Although research on DDI-related ADEs in the ICU is limited, QT-prolongation, bleeding and neurological disturbances are mentioned as DDI-related ADEs [14-17]. Edrees et al. [15] investigated overridden pDDI alerts and associated ADEs. Seven of 78 ICU patients with an inappropriately overridden severe alert experienced a QT-prolongation ADE. Armahizer et al. [14] investigated DDI-related QT-prolongation in ICU patients with a QTc ≥ 500 ms. They found that 187 (37%) ICU patients experienced QT-prolongation, with a DDI being the probable cause in 30 patients. Patients with QT-prolongation have a higher mortality rate and prolonged ICU stay [18]. Increasing awareness of pDDI risks could focus on crpDDIs. Our results provide clues on how to improve DDI intervention strategies such as CDSSs.

4.1. Tailoring CDSSs to the ICU

Warning prescribers only for crpDDIs could decrease alert fatigue, reducing the risk of overriding relevant alerts and eventually improve medication safety [19]. Considering crpDDI duration could further decrease alert fatigue, since most crpDDIs lasted 1 day [20]. For many crpDDIs, this is too short to exert pharmacokinetic/pharmacodynamic actions and cause harmful effects. Furthermore, initiating monitoring actions directly from within the alert could help mitigate crpDDI risks [21]. Moreover, for frequent crpDDIs such as NSAIDs + corticosteroids, alerts could only be triggered when specific risk factors are present. Also, as 42.7% of the patients are discharged with a pDDI, alerts could be triggered upon ICU discharge to help physicians on non-ICU wards to take appropriate monitoring actions. Lastly, most crpDDIs were related to QT-prolonging agents. This may be explained by the wide variation of often prescribed medications causing this crpDDI, including cardiovascular medication, psychomodulating medication, antibiotics and antiemetics. Not prescribing QT-prolonging agents often is impossible, but ICU patients routinely undergo ECG monitoring. ECG monitoring for QT-prolongation, however, could be further personalized by considering risk factors for QT-prolongation and potential arrhythmias including older age, female gender, heart disease history, electrolyte abnormalities, and factors influencing the drug concentration, such as infusion rate and impaired kidney function. This contextual information could be considered by a CDSS, or presented within the DDI alert [22].

Additionally, many crpDDIs involved NSAIDs. Some ICUs refrain from prescribing NSAIDs at all, preventing these crpDDIs. Instead of following the sequence of the WHO pain treatment steps [23] they skip the NSAIDs and prescribe opioids. CDSSs providing safer treatment options effectively reduce prescription of potentially inappropriate medications [24].

This study has several strengths. First, to our knowledge this is the first multicenter study on the frequency of (cr)pDDIs in the ICU. Our study sample represents several ICU types and a large, heterogeneous ICU patient population. Second, our clinical relevance definition was based on a Delphi procedure where clinical relevance for the ICU was assessed by a multidisciplinary expert panel. Third, we used medication administrations instead of prescriptions to detect pDDIs, ensuring patients received the medication. This study also has some limitations. First, we used only one database (G-standard) to identify pDDIs and possibly missed pDDIs not included in this database [17]. However, commonly prescribed medication in the ICU does not differ from other countries. The top 10 medications implicated in pDDIs by Fitzmaurice et al. [1] compares to our results. Second, since the G-standard is not tailored to the ICU setting, the monitoring strategies not always apply to the ICU, e.g. monitoring Hb is not included in the G-standard, while ICUs use this strategy to monitor the risk of bleeding. Third, our detection algorithm did not consider the half-life of medications. Instead, pDDIs were defined as the administration of two interacting medications within a 24 h period. This might lead to an overestimation of pDDIs involving medications with a short half-life and an underestimation of pDDIs involving medications with a long half-life. However, to our knowledge no other pDDI study considered half-life, therefore our results are comparable to other studies [1]. Fourth, measuring crpDDI frequency does not gauge how much patient harm is caused.

5. Conclusions

In line with other studies, we showed that pDDIs frequently occur in ICU patients. Our study shows the importance of considering clinical relevance of pDDIs, as only 47.2% of the detected pDDIs are clinically relevant in the ICU setting. The most frequent risks related to crpDDIs are cardiac arrhythmia and bleeding. Aside from clinical relevance, pDDI duration and timing, as well as contextual information, are important to consider when tailoring CDSSs to the ICU setting. To further optimize

prevention strategies, future studies should assess actual harm resulting from pDDIs.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.11.020.

Compliance with ethical standards

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

Authors' contribution

AA, DD, JK, NK and TB conceptualized and designed the study. DL, JV and RB contributed substantially to the acquisition of data. AA, DD, DL, JK, JV, NK, RB and TB (all authors) have drafted or revised the manuscript critically. All authors gave final approval of the submitted version. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; all authors agreed to be accountable for aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data, material and code

The detection algorithm will be 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.

Conflicts of interest and source of funding

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