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Published in:
Int. J. Med. Inform.

DOI:
10.1016/j.ijmedinf.2019.104013

Publication date:
2020

Document Version:
Proof

Link to publication

Citation for published version (APA):
Muylle, K., Gentens, K., Dupont, A., & Cornu, P. (2020). Evaluation of Context-Specific Alerts for Potassium-Increasing Drug-Drug Interactions: A Pre-Post Study. *Int. J. Med. Inform.*, *133*, [104013]. https://doi.org/10.1016/j.ijmedinf.2019.104013

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Evaluation of context-specific alerts for potassium-increasing drug-drug interactions: a pre-post study

Original paper

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Declarations of interest: none

Word count: 2986

ABSTRACT

Objective: To investigate whether context-specific alerts for potassium-increasing drug-drug interactions (DDIs) in a clinical decision support system reduced the alert burden, increased alert acceptance, and had an effect on the occurrence of hyperkalemia.

Materials and Methods: In the pre-intervention period all alerts for potassium-increasing DDIs were level 1 alerts advising absolute contraindication, while in the post-intervention period the same drug combinations could trigger a level 1 (absolute contraindication), a level 2 (monitor potassium values), or a level 3 alert (informative, not shown to physicians) based on the patient's recent laboratory value of potassium. Alert acceptance was defined as non-prescription or non-administration of the interacting drug combination for level 1 alerts and as monitoring of the potassium levels for level 2 alerts.

Results: The alert burden decreased by 92.8%. The relative risk (RR) for alert acceptance based on prescription rates for level 1 alerts and monitoring rates for level 2 alerts was 15.048 (86.5% vs 5.7%; 95% CI 12.037 – 18.811; P < 0.001). With alert acceptance for level 1 alerts based on actual administration and for level 2 alerts on monitoring rates, the RR was 3.597 (87.6% vs 24.4%; 95% CI 3.192 – 4.053; P < 0.001). In the generalized linear mixed model the effect of the intervention on the occurrence of hyperkalemia was not significant (OR 1.091, 95% CI 0.172 – 6.919).

Conclusion: The proposed strategy seems effective to get a grip on the delicate balance between over- and under alerting.

Keywords:

clinical decision support systems, electronic health records, drug interactions, alert fatigue, hyperkalemia

1. INTRODUCTION

One key cause of preventable adverse drug events (ADEs) are drug-drug interactions (DDIs)[1]. Computerized physician order entry (CPOE) with built-in clinical decision support systems (CDSS) have the potential to prevent medication errors and consecutive ADEs at the very moment of prescribing[2-7]. Yet, the evidence on the impact of CDSS on patient outcomes remains scarce[8, 9]. It is well established that CDSS for DDI checking are often overly sensitive generating excessive alerts with low specificity leading to alert fatigue and high override rates, often exceeding 80%[10-16]. The main problems are the low specificity of the alerts and their perceived lack of clinical importance[4, 12, 16, 17]. This makes it difficult for clinicians to distinguish between clinically significant and insignificant alerts leading to both types of alerts being overridden which compromises the primary objective of patient safety[4, 13, 18, 19]. Integration of patient characteristics in the clinical decision support (CDS) logic was suggested to improve alert specificity [20, 21]. Specifically, linkage and follow-up of laboratory values with the CDS rules was proposed[22-27]. However, just displaying laboratory values in the alert did not significantly improve the alert adherence in high-risk patients[28].

We have encountered the same problem of low specificity and high override rates in our hospital[29, 30]. Of all DDI alerts generated by the CDSS from the 1st of January 2010 till the 30th of June 2011, 72.1% were alerts for the risk of hyperkalemia due to the interaction between potassium-sparing diuretics and potassium supplements, with an override rate of 85.7%[31]. Hyperkalemia is a serious and potentially life-threatening electrolyte disorder caused by an imbalance in potassium homeostasis and is associated with increased mortality and adverse cardiovascular effects such as cardiac arrhythmia and cardiac arrest[32-34]. Uijtendaal et al. found that DDI-induced hyperkalemia occurred in 10% of hospitalized patients who were prescribed at least one potassium increasing drug[24].

Context-specific alerts for potassium-increasing DDIs with patient-specific risk assessments for hyperkalemia were developed as part of our CDSS. Alerts for low-risk patients were not shown to the

physicians to improve the specificity, as suggested by Duke et al.[28]. The main objective of this study was to investigate whether these context-specific alerts reduced the alert burden and had a higher alert acceptance compared to alerts without context-specific rules. Because it is important to improve the efficiency of the DDI alerting system without compromising patient safety, the effect of the optimized CDSS on the patient outcome, occurrence of hyperkalemia, was also examined.

2. MATERIALS AND METHODS

2.1. Design and setting

This pre-post study was conducted at the UZ Brussel, a 721-bed tertiary university hospital in Brussels, Belgium. The in-house developed software system "Primuz" is fully integrated within the workflow and provides different functionalities including CPOE and CDS for DDIs[26, 35, 36]. The knowledge base used for DDI checking is the commercially available DelphiCare® database[37]. The intervention was the hospital wide implementation of a context-specific DDI alerting system, discussed in detail elsewhere[29]. In this study, the focus was on the context-specific alerts for potassium-increasing DDIs. All patients with a DDI for risk of hyperkalemia due to prescription of a potassium-sparing diuretic concomitantly with a potassium supplement were included in this study. The study was approved by the UZ Brussel Medical Ethics Committee with reference BUN 143201421156.

2.2. Intervention

2.2.1. Pre-intervention situation

In the pre-intervention period the DDI between potassium-sparing diuretics and potassium supplements generated an interruptive level 1 alert (Figure 1). A fixed screening interval of 3 days back in the medication history and 2 days ahead in the medication planning was used. The screening interval is the defined interval between the administrations of two interacting drugs for which an alert is triggered. If the interval between two drugs is longer than this specified time period, no alert is triggered[29].

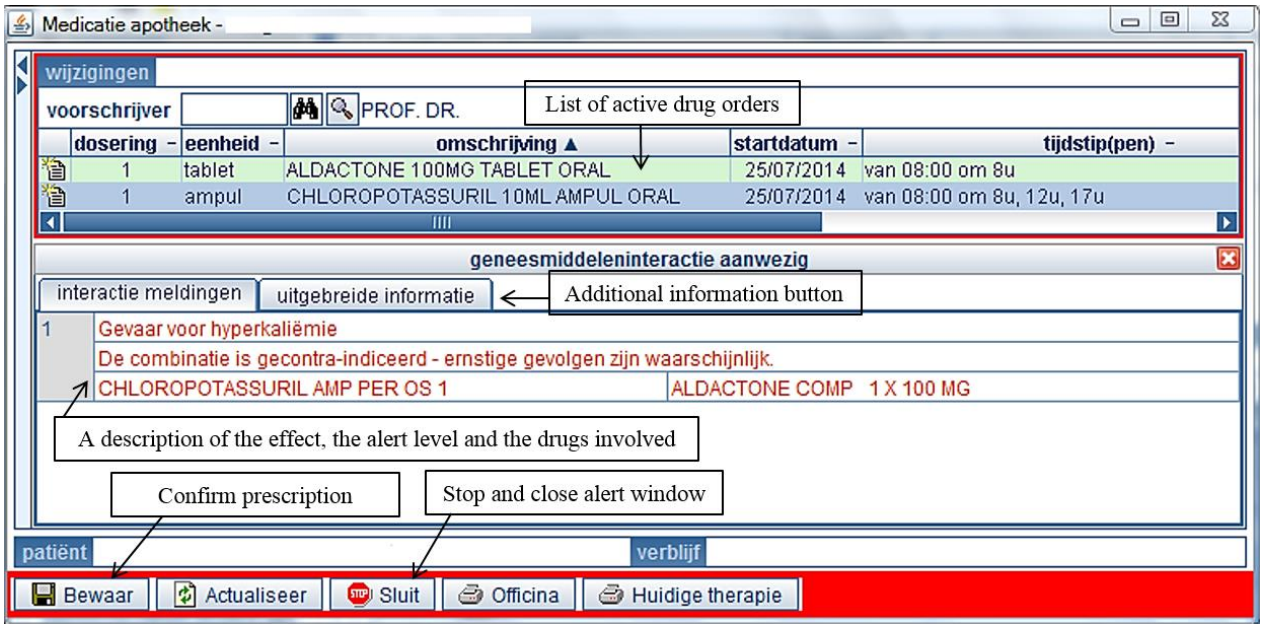


Figure 1: The alert screen in the pre-intervention period for the combination of a potassium-sparing diuretic and a potassium supplement.

2.2.2.Post-intervention situation

In the new CDSS, customization of the commercial Delphicare® database is performed by adding context-specific information and changes to the commercial knowledge base in a so-called shadow table[29]. For the potassium-increasing DDIs, this context-specific information is a recent laboratory value of potassium, which determines the alert level of the DDI. The alert level no longer uniquely depends on the intrinsic risk category of the specific drugs, but also on patient-specific information. When in the last 3 days prior to the DDI a potassium value of ≥ 5 mmol/L is found, an interruptive level 1 alert is generated (Figure 2). The value on which the risk assessment is based, is provided on the alert screen and is directly linked with the laboratory overview screen. By clicking on the value, the laboratory overview screen opens so the physician can evaluate other and older laboratory values. Additionally, in the new system the screening interval between administrations of the two interacting drugs is narrower and set on 24h back in the medication history and 24h ahead in the medication planning.

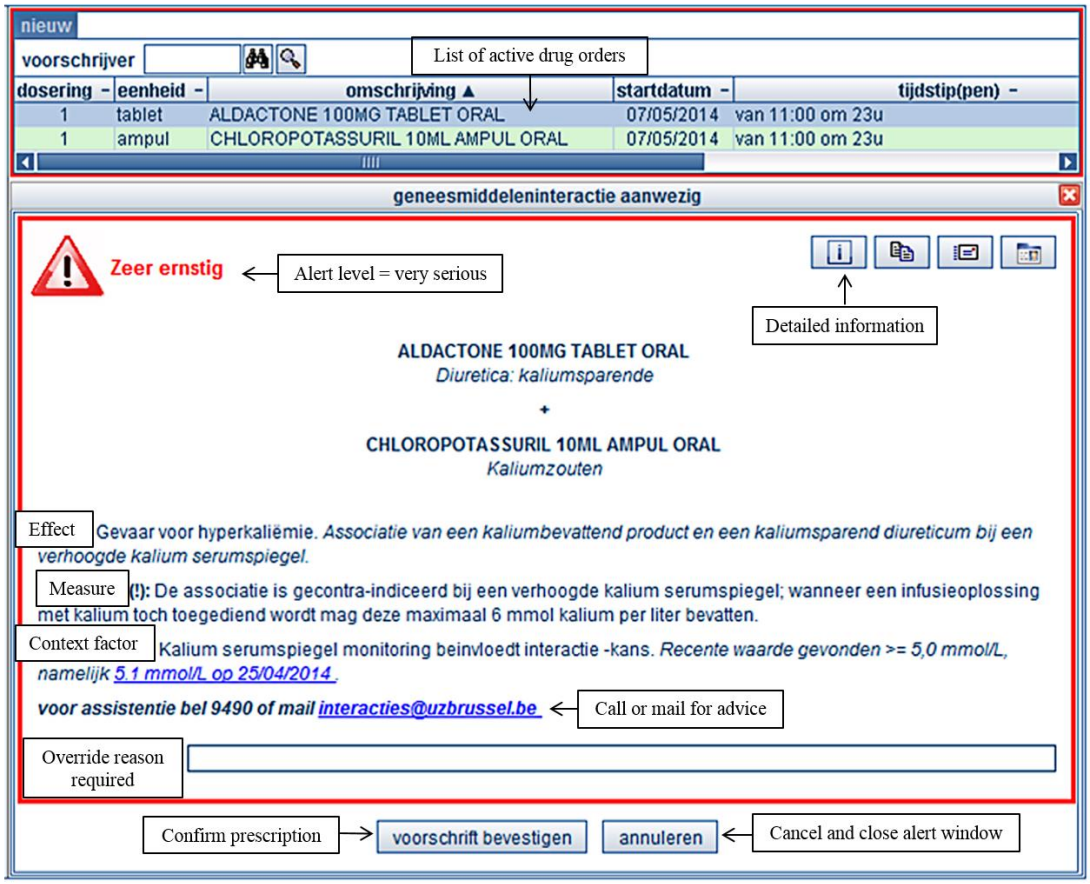


Figure 2: The alert screen from a level 1 alert in the post-intervention period for the combination of a potassium-sparing diuretic and a potassium supplement with a recent potassium value ≥ 5 mmol/L.

When either no recent potassium value or a potassium value with an exception code (e.g. severe hemolysis of the blood sample) is detected, an interruptive level 2 alert which advises monitoring of the potassium levels, is generated (Figure 3). In case a potassium value < 5 mmol/L is identified, a level 3 alert is created, which is informative and not shown to the end users, but which can be consulted by clinical pharmacists.

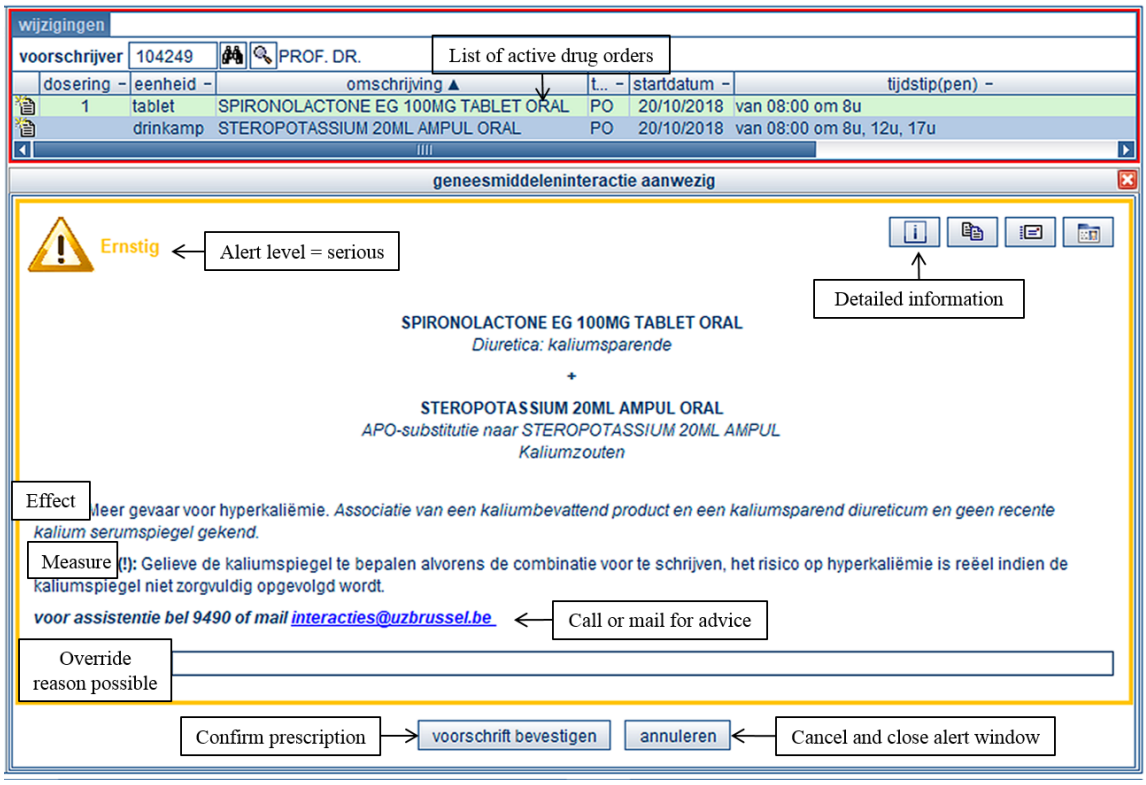


Figure 3: The alert screen from a level 2 alert in the post-intervention period for the combination of a potassium-sparing diuretic and a potassium supplement when either no recent potassium value is available or a potassium value with an exception code is detected.

2.3. Data collection

2.3.1.Study population

Based on an a priori sample size calculation a study period of 1 year in both periods was deemed suitable (Supplementary file 1). The pre-intervention period started on November 18, 2012 and ended on November 18, 2013. Between November 19, 2013 and November 23, 2015, the new CDSS was implemented on all clinical departments of our hospital. Post-intervention data was collected between November 24, 2015 and November 24, 2016. Alert data was acquired from the automatically generated alert reports from the CDSS. All consecutive hospitalized patients for whom an alert for risk of hyperkalemia was triggered were included. Patients having the same DDI alert for the same combination of drugs twice or more on the same day, were included only once to avoid bias in acceptance rates.

2.3.2.Alert acceptance

An alert was considered accepted if the physicians adhered to the proposed measures. Level 1 alerts advised absolute contraindication, so for these alerts, alert acceptance was defined as the discontinuation of the prescription triggering the DDI alert or as the non-administration of the interacting drug combination. Level 2 alerts in the new system don't advise absolute contra-indication but close monitoring of potassium levels. For these alerts, alert acceptance was defined as an available potassium measurement within 24h after the alert was triggered or within 24h after the last simultaneous administration of the interacting drug combination.

Sometimes cancelling a pre-existing order and not the order triggering the alert is the best solution to the DDI, but this is not directly possible from the alert screen. Physicians then frequently opt to override the alert and prescribe the new drug, but then immediately cancel the pre-existing order. Therefore, acceptance rates for level 1 alerts were not only analyzed based on prescription rates, but also based on actual administration of the drug combination. This information was retrieved from the electronic nursing record and categorized as administered when the drug combination was administered either simultaneously or sequentially. When one of the two drugs was not administered, this was classified as no administration. In order to calculate an overall alert acceptance, the alert acceptance was conceptualized as a composite outcome, i.e. as prescription discontinued or non-administration of the drug combination for level 1 alerts or as monitoring of the potassium values for level 2 alerts.

2.3.3.Occurrence of hyperkalemia

The outcome measurement was a serum potassium level within 24h after the last simultaneous administration of the interacting drug combination or within 24h after the DDI alert was triggered in case no simultaneous administration occurred. This post-DDI alert potassium measure was classified as hyperkalemia when it was ≥ 5 mmol/L. Potassium levels from hemolyzed blood samples were excluded for the outcome assessment because these levels could be falsely elevated leading to bias in the occurrence of hyperkalemia. Potential confounders were taken into account in the analysis in order to correct for

factors other than the intervention contributing to the effect size. These potential confounders are risk factors previously described as being associated with hyperkalemia and included the patient's age, sex, BMI, diabetic status, renal function, baseline serum potassium value, serum magnesium value, and the co-administration of potential confounding drugs[24, 38, 39]. The renal function was identified as the most recent estimated glomerular filtration rate (eGFR) of maximum 3 days prior to the DDI alert. The baseline potassium value or the pre-DDI alert potassium value was the most recent potassium value with a maximum of 3 days prior to the DDI alert. In the post-intervention period, the baseline potassium value was the value upon which the risk assessment was based. The magnesium value was the lowest value in the interval between 3 days prior to the DDI alert and the time of the post-DDI alert potassium value. The co-administration of other potential confounding drugs besides the ones triggering the DDI alert within a time window of 24h was also recorded. These drug classes are potassium supplements, potassium-sparing diuretics, NSAIDs, calcineurin inhibitors, systemic corticosteroids, angiotensin II receptor antagonists and ACE inhibitors.

2.4. Data analysis

Descriptive and statistical analyses were performed using IBM SPSS Statistics and the R package lme4[40, 41]. Potassium, magnesium and eGFR measurements were categorized for evaluation of the characteristics. The population characteristics between pre- and post-intervention were compared with the Mann-Whitney U test for continuous variables and with the Pearson Chi-square test for categorical variables. Comparison of the population characteristics between patients having the outcome measurement and those missing the outcome measurement was performed in an analogous way. The Pearson Chi-square test was used to compare the alert acceptance between pre- and post-intervention period. To account for clustering on the level of the patient, a generalized linear mixed model for binary data with patients as random intercept was used to determine the effect of the intervention on the occurrence of hyperkalemia. Backward selection based on the Akaike information criterion value was used

to obtain the final model. All statistical analyses were performed with a 0.05 significance level and 95% CI were calculated for the odds ratios (ORs).

3. RESULTS

3.1. Characteristics of study population

The patient characteristics in the pre- and post-intervention period are provided in Table 1. Significant differences were found for sex ($P = 0.001$), the frequency of diabetes ($P = 0.038$), the distribution of magnesium ($P = 0.018$) and eGFR values ($P = 0.005$), and for the administration of extra potassium supplements ($P < 0.001$), extra potassium-sparing diuretics ($P = 0.011$), NSAIDs ($P < 0.001$), and calcineurin inhibitors ($P = 0.048$). There was also a significant difference for the distribution of pre-DDI alert potassium values ($P < 0.001$). The percentage of missing values was lower in the post-intervention period compared to the pre-intervention period for BMI, pre-DDI alert potassium levels, post-DDI alert potassium levels and magnesium levels. The decrease was highest for the outcome measurement (33.4% to 17.5%).

	Pre-intervention	Post-intervention	*P* value[c]
Number of drug alerts	1461	1237	
Sex			0.001
Male	630 (43.1%)	616 (49.8%)	
Female	831 (56.9%)	621 (50.2%)	
Age (median, range)	73 (28-102)	72 (1-102)	0.192
BMI (median, range)	26.04 (14.65 – 45.85)	26.10 (15.32 – 48.83)	0.817
Missing values	189 (12.9%)	81 (6.5%)	
Diabetes Mellitus			0.038
No diabetes	1081 (74.0%)	871 (70.4%)	
Diabetes	380 (26.0%)	366 (29.6%)	
Pre-DDI alert potassium level (mmol/L)			< 0.001
Normal 3.4-4.9	675 (47.7%)	508 (41.5%)	
Hyperkalemia ≥ 5.0	19 (1.3%)	3 (0.2%)	
Hypokalemia < 3.4	720 (50.9%)	714 (58.3%)	
Missing values	47 (3.2%)	12 (1%)	
Magnesium level (mmol/l)			0.018
Normal 0.66-0.95	594 (66.4%)	519 (60.1%)	
Hypomagnesemia < 0.66	196 (21.9%)	215 (24.9%)	
Hypermagnesemia > 0.95	104 (11.6%)	129 (14.9%)	
Missing values	567 (38.8%)	374 (30.2%)	
eGFR (ml/min/1.73m2)[a]			0.005
Normal ≥ 60	893 (61.7%)	755 (61.6%)	
Moderate impairment 30-59	467 (32.3%)	367 (30.0%)	
Severe impairment 15-29	54 (3.7%)	81 (6.6%)	
ESRD[b] < 15	34 (2.3%)	22 (1.8%)	
Missing values	13 (0.9%)	12 (1.0%)	
Extra potassium supplements			< 0.001
No	920 (63.0%)	564 (45.6%)	
Yes	541 (37.0%)	673 (54.4%)	
Extra potassium-sparing diuretics			0.011
No	1223 (83.7%)	989 (80.0%)	
Yes	238 (16.3%)	248 (20.0%)	
NSAIDs			< 0.001
No	1347 (92.2%)	1194 (96.5%)	
Yes	114 (7.8%)	43 (3.5%)	
Calcineurin inhibitors			0.048
No	1455 (99.6%)	1224 (98.9%)	
Yes	6 (0.4%)	13 (1.1%)	

Systemic corticosteroids			0.315
No	1228 (84.1%)	1057 (8.4%)	
Yes	233 (15.9%)	180 (14.6%)	
Angiotensin II receptor antagonists			0.078
No	1355 (92.7%)	1168 (94.4%)	
Yes	106 (7.3%)	69 (5.6%)	
ACE inhibitors			0.407
No	1000 (68.4%)	865 (69.9%)	
Yes	461 (31.6%)	372 (30.1%)	
Post-DDI alert potassium level (mmol/l)			
No hyperkalemia <5.0	935 (96.1%)	968 (94.9%)	0.200
Hyperkalemia ≥ 5.0	38 (3.9%)	52 (5.1 %)	
Missing values	488 (33.4%)	217 (17.5%)	

Table 1: Patient characteristics in the pre-intervention period versus the post-intervention period.

[a] eGFR = estimated Glomerular Filtration Rate

[b] ESRD = end stage renal disease

[c] Pearson Chi-square test was used for categorical variables and the Mann-Whitney U test for the continuous variables age and BMI

3.2. Number of alerts

In the pre-intervention period 1461 unique alerts and in the post-intervention period 1237 unique alerts were retrieved. In the pre-intervention period, there was only one type of alert for the risk of hyperkalemia, which means all 1461 alerts (100%) were level 1 alerts advising absolute contraindication. In the post-intervention period there were 4 types of alerts for the same combination of drugs, depending on the context factors (Table 2). In the post-intervention period 3 alerts (0.2%) were level 1 alerts advising absolute contraindication and 86 alerts (7.0%) were level 2 alerts advising close monitoring of the potassium values. The remaining 1148 level 3 alerts (92.8%) were not shown to physicians.

	Alert level	Advice	Context factors	Number (%)
Pre-intervention period	1 = very serious	Absolute contraindication	*None*	1461 (100%)
Post-intervention period	1 = very serious	Absolute contraindication	Recent potassium level ≥ 5 mmol/l	3 (0.2%)
	2 = serious	Monitor potassium values	Unknown recent potassium level	28 (2.3%)
	2 = serious	Monitor potassium values	Recent potassium level has been flagged by clinical biologist (hemolysis, extreme low)	58 (4.7%)
	3 = informative	*Not shown to physicians*	Recent potassium level < 5 mmol/l	1148 (92.8%)

Table 2: Types of DDI alerts for the risk of hyperkalemia in the pre-intervention period and post-intervention period with their corresponding levels, advices, context factors taken into account and percentages of the total alert burden within the intervention period.

3.3. Alert acceptance

For level 1 alerts, acceptance rates were measured both on prescription and administration level. For the pre-intervention period the alert acceptance based on prescription rates was 5.7%, but increased to 24.4% when based on actual administration rates. In the post-intervention period only three level 1 alerts were triggered with 66.7% alert acceptance based on prescription rates and 100% acceptance based on administration rates. For level 2 alerts, acceptance was achieved when the potassium levels were monitored, which was the case for 75 of the 86 (87.2%) level 2 alerts. In table 3 the overall alert acceptance with the alert acceptance rates for the pre-intervention period based on either prescription or administration rates and for the post-intervention period as a composite outcome based on prescription or administration rates for level 1 alerts and monitoring rates for level 2 alerts is provided. With the alert acceptance based on prescription rates, the relative risk (RR) for overall acceptance rate was 15.048 (86.5% vs 5.7%; 95% CI 12.037 – 18.811; $P < 0.001$). When the alert acceptance for level 1 alerts was based on actual administration, the RR was 3.597 (87.6% vs 24.4%; 95% CI 3.192 – 4.053, $P < 0.001$).

	Pre-intervention	Post-intervention (level 1 and level 2)	Statistics
Override = Prescription continued (level 1) or no monitoring (level 2)	1377 (94.3%)	12 (13.5%)	*P* = < 0.001 RR = 15.048 (95% CI 12.037 – 18.811)
Acceptance = Prescription discontinued (level 1) or monitoring (level 2)	84 (5.7%)	77 (86.5%)	
Override = DDI administered (level 1) or no monitoring (level 2)	1105 (75.6%)	11 (12.4%)	*P* = < 0.001 RR = 3.597 (95% CI 3.192 – 4.053)
Acceptance = DDI not administered (level 1) or monitoring (level 2)	356 (24.4%)	78 (87.6%)	

Table 3: Overall alert acceptance with a composite outcome based on prescription rates and administration rates for level 1 alerts and based on monitoring rates for level 2 alerts.

3.4. Risk of hyperkalemia

The crude incidence of hyperkalemia after a DDI alert was triggered, was 3.9% in the pre-intervention period and 5.1% in the post-intervention period (P = 0.200, Table 1, RR = 1.305 with 95% CI 0.867 – 1.965). The adjusted OR of the intervention variable was 1.091 (95% CI 0.172 – 6.919, Table 4). The only significant confounder was the pre-DDI alert potassium value with an OR of 5.703 (95% CI 2.569 – 12.657). Other retained confounders were sex, BMI, the use of systemic corticosteroids or ACE inhibitors and the renal function. For this analysis, only patients with an available post-DDI measurement could be included. Of the missing outcomes 69.22% were from patients from the pre-intervention period and high-risk patients were more likely to have a post-DDI alert measurement (Supplementary file 2).

Variable	OR	95% CI
Intervention	1.091	0.172 – 6.919
Sex: female vs male	1.005	0.154 – 6.538
Pre-DDI alert potassium[a]	5.703	2.569 – 12.657
BMI[a]	0.915	0.748 – 1.118
Systemic corticosteroids[b]	1.790	0.484 – 6.620
ACE inhibitors[b]	0.611	0.155 – 2.409
eGFR: impaired vs normal	2.476	0.667 – 9.193

Table 4: Odds ratios and 95% CI for the intervention variable and the confounders of the generalized linear mixed model for binary data with patients as a random intercept variable.

[a] Continuous variable

[b] Dichotomous variable (yes vs no)

4. DISCUSSION

The optimized CDSS which uses context factors for the individual risk assessment of hyperkalemia significantly reduced the alert burden without a significant difference in occurrence of hyperkalemia. The intervention converted 92.8% of the alerts – which would have been fixed level 1 alerts in the old CDSS – into level 3 alerts which are not shown to the physicians. This means a significant reduction of the alert burden, which was our primary purpose. Since most studies only measure alert acceptance based on prescription rates, it is an important strength of the present study to also measure alert acceptance based on actual administration. Indeed, an important difference in alert acceptance was observed when based on administration rates instead of prescription rates (24.4% vs. 5.7% in the pre-intervention period). Nevertheless, a significant difference for the composite outcome of alert acceptance based on both prescription and administration rates for level 1 alerts and monitoring rates for level 2 alerts was observed. The suppressing of the alerts for patients with low risk of hyperkalemia did not have a significant negative effect on the occurrence of hyperkalemia, thus preserving patient safety. This finding is very important in the endeavor to obtain the right balance between over- and under alerting many institutions struggle with. Our results align with the findings of a systematic review by Van de Velde et al. which identified that CDSS might be more effective in terms of adherence and patient outcomes when it is more patient-specific[9]. Several studies have stated that overridden alerts in terms of continuation of prescription still have value if they prompt physicians to monitor more closely, to discuss other treatment options with the patient, or modify the prescription in any other way [13, 15, 20]. However, Slight et al. demonstrated that when physicians said they would monitor the patient as recommended, only 35.5% actually completed the monitoring[42]. In this study, we demonstrate that 87.2% of the patients with a level 2 alert were effectively monitored.

4.1. Limitations

Our study has several limitations. First, since this was a single-center study where the CDSS was implemented in all departments no RCT could be performed. The best alternative design was a pre-post design with multivariable regression analysis for correction for confounding factors. Only adjustments for known and measured confounders could be made so there is still a risk of residual confounding. Second, our study didn't include potassium-increasing DDIs other than the combination of potassium supplements and potassium-sparing diuretics because these DDIs were not yet active in the pre-intervention period. Other studies on DDIs for risk of hyperkalemia also included DDIs with other potassium-increasing drugs such as ACE inhibitors, angiotensin II receptor antagonists, and calcineurin inhibitors but these are intrinsically less serious DDI alerts [23, 24, 37, 39]. Third, only patients with an available post-DDI alert potassium measurement were included in the mixed effect logistic regression. Therefore, the population with an outcome measurement may differ from the population without an outcome measurement causing the results not to be generalizable to a general hospital population.

4.2. Future perspectives

The important differences between alert acceptance rates based on prescription or administration rates indicate that pre-existing orders are frequently changed to act upon the DDI. Therefore, the system should offer the possibility to discontinue pre-existing orders directly from the alert screen as a possible solution for the DDI. A further optimization priority for our CDSS is the activation of asynchronous testing, where alert warnings can be generated in response to changed context factors after the DDI was prescribed. This function was already developed but was activated in 2018 after the post-intervention period evaluated in this study. This may result in a further optimization as Eschmann et al. already showed that continuous monitoring of potassium levels better predicted the risk of hyperkalemia compared to the risk prediction at onset of potassium-increasing DDIs[43].

5. CONCLUSION

In conclusion, we succeeded to reduce the DDI alert burden of physicians without compromising patient safety by reducing the number of alerts shown to the physician by 92.8% without a significant difference in the occurrence of hyperkalemia. This study demonstrates the proposed strategy seems effective to get a grip on the delicate equilibrium between over- and under alerting many institutions struggle with. Further research into the development, optimization and evaluation of context-specific prediction rules for complex DDIs is warranted.

6. SUMMARY TABLE

What was already known on the topic?

- Most CDSS are overly sensitive generating alerts with low specificity leading to high override rates and alert fatigue
- Potassium-increasing DDIs are frequently observed and are of high clinical significance because hyperkalemia can be potentially life-threatening
- Integration of patient characteristics into the CDS logic was suggested to improve alert specificity
- The evidence on the impact of CDSS on patient outcomes remains scarce

What this study added to our knowledge

- The inclusion of context factors into the CDS logic for potassium-increasing DDIs made it possible to suppress alerts for low-risk patients which led to a large reduction in alert burden
- A marked increase in alert acceptance (based on either prescription rates or administration rates) was observed with the patient-specific CDSS
- The suppressing of the alerts for patients with low risk of hyperkalemia did not have a significant negative effect on the occurrence of hyperkalemia, thus preserving patient safety

7. AUTHORS' CONTIBUTIONS AND ACKNOWLEDGEMENTS

PC and AD participated in the design of the study. KM and KG were responsible for the data acquisition. KM and PC performed the data analysis and interpretation. The Interfaculty Center for Data processing and Statistics from the Vrije Universiteit Brussel was consulted for the data analysis. KM drafted the manuscript. All authors critically evaluated the manuscript and gave their final approval before submission. The study was carried out with the support of Wetenschappelijk Fonds Willy Gepts of the UZ Brussel. This funding body had no role in the study design, data collection, analysis or interpretation of data, nor in the writing of the report or the decision to submit the article for publication.

8. CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this study.

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