Developing strategies for predicting hyperkalemia in potassium-increasing drug-drug interactions

Eschmann, Emmanuel; Beeler, Patrick Emanuel; Schneemann, Markus; Blaser, Jürg

Abstract: OBJECTIVE: To compare different strategies predicting hyperkalemia (serum potassium level ≥ 5.5 mEq/l) in hospitalized patients for whom medications triggering potassium-increasing drug-drug interactions (DDIs) were ordered. MATERIALS AND METHODS: We investigated 5 strategies that combined prediction triggered at onset of DDI versus continuous monitoring and taking into account an increasing number of patient parameters. The considered patient parameters were identified using generalized additive models, and the thresholds of the prediction strategies were calculated by applying Youden’s J statistic to receiver operation characteristic curves. Half of the data served as the calibration set, half as the validation set. RESULTS: We identified 132 incidences of hyperkalemia induced by 8413 potentially severe potassium-increasing DDIs among 76 467 patients. The positive predictive value (PPV) of those strategies predicting hyperkalemia at the onset of DDI ranged from 1.79% (undifferentiated anticipation of hyperkalemia due to the DDI) to 3.02% (additionally considering the baseline serum potassium) and 3.10% (including further patient parameters). Continuous monitoring significantly increased the PPV to 8.25% (considering the current serum potassium) and 9.34% (additional patient parameters). CONCLUSION: Continuous monitoring of the risk for hyperkalemia based on current potassium level shows a better predictive power than predictions triggered at the onset of DDI. This contrasts with efforts to improve DDI alerts by taking into account more patient parameters at the time of ordering.

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Emmanuel Eschmann¹, Patrick E. Beeler¹, Markus Schneemann², Jürg Blaser¹

Developing Strategies for Predicting Hyperkalemia
in Potassium-Increasing Drug-Drug Interactions

¹Research Center for Medical Informatics; Directorate of Research and Education; University Hospital Zurich and University of Zurich; Zurich; Switzerland

²Division of Internal Medicine; University Hospital Zurich and University of Zurich; Zurich; Switzerland

Corresponding author:

e-mail address: emanuel.eschmann@usz.ch

telephone: +41 44 255 11 32

fax: +41 44 634 55 03

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ABSTRACT

Objective
To compare different strategies predicting hyperkalemia (serum potassium level ≥5.5mEq/l) in hospitalized patients for whom medications triggering potassium-increasing drug-drug interactions (DDIs) were ordered.

Materials and Methods
We investigated 5 strategies which combined the features (i) prediction triggered at onset of DDI vs. continuous monitoring, with (ii) taking into account an increasing number of patient parameters. The considered patient parameters were identified using generalized additive models, and the thresholds of the prediction strategies were calculated by applying Youden’s J statistic to receiver operation characteristic curves. Half of the data served as calibration set, half as validation set.

Results
We identified 132 hyperkalemias induced by 8,413 potentially severe potassium-increasing DDIs among 76,467 patients. The positive predictive value (PPV) of those strategies predicting hyperkalemia at onset of DDIs ranged from 1.79% (undifferentiated anticipation of hyperkalemia due to the DDI) to 3.02% (additionally considering the baseline serum potassium) and 3.10% (including further patient parameters). However, continuous monitoring significantly increased the PPV to 8.25% (considering the current serum potassium) and 9.34% (additional patient parameters).
Conclusion

Continuous monitoring of the risk for hyperkalemia based on the current potassium level shows a better predictive power than predictions triggered at onset of DDIs. This contrasts with efforts improving DDI alerts by taking into account more patient parameters at the time of ordering.
BACKGROUND AND SIGNIFICANCE

Drug-drug interactions (DDIs) are an important cause of adverse drug events (ADEs) leading to increased morbidity and mortality.\(^{(1, 2)}\) Although most DDIs are preventable, up to 28% of inpatients suffer from DDI-induced ADEs.\(^{(3)}\)

It has been suggested that clinical decision support (CDS) can intercept the ordering of medications triggering DDIs.\(^{(4, 5)}\) While some authors have pointed out that DDI alerts may prevent ADEs,\(^{(6)}\) so far no study showed that CDS significantly reduces the frequency of ADEs. In particular, alert override rates of up to 98% hamper the potential of CDS interventions.\(^{(7, 8)}\) Reasons for non-adherence are the low specificity and clinical insignificance of electronic alerts.\(^{(9)}\) Therefore, electronic warnings displayed for patients with a low risk for developing respective ADEs should be suppressed.\(^{(8-11)}\)

Approaches to increase the alert specificity are focusing on high-priority DDIs or tiering DDIs by severity,\(^{(12-14)}\) considering patient factors and co-medication in order to suppress insignificant alerts,\(^{(15)}\) and combinations of these approaches.\(^{(9, 16-18)}\) On the one hand, patient factors are typically considered only at the time of ordering, on the other hand, conditions changing later on may critically influence the risk that an ADE occurs.\(^{(9, 15, 16)}\) Therefore, sophisticated algorithms taking into account the change of dynamic patient parameters over time have been advocated.\(^{(17-20)}\) A promising approach to improve medication safety may be to display warnings as soon as an ADE is imminent or likely to occur, instead of undifferentiated alerts at the time of ordering. However, to our knowledge, no comparison of (i) predictions of ADEs triggered at the time of
ordering with (ii) serial predictions based on a continuous monitoring has been published so far.

We undertook this comparison study using retrospective data on potassium-increasing DDIs. These DDIs occur in up to 10% of hospitalized patients (1, 3). Hyperkalemia is found in 1.9% of these DDIs (21) and can induce life-threatening cardiac arrhythmias. (22) To our knowledge, the number of hyperkalemiyas due to avoidable potassium-increasing DDIs has not been quantified so far, and therefore we also included the results of this prerequisite in our results section.

OBJECTIVE

To model and compare different strategies predicting hyperkalemia in hospitalized patients for whom medications triggering potassium-increasing DDIs were ordered.
MATERIALS AND METHODS

Setting

The University Hospital Zurich, Switzerland, is a tertiary care academic medical center with 850 beds and approximately 35,000 admissions per year. We included data of all inpatients from 1st of December 2009 to 31st of December 2011. Patients undergoing dialysis and those hospitalized in intensive care units were excluded.

The local research ethics committee approved the analyses, and patient consent was waived.

Analyzed Patient Parameters

We analyzed the following patient parameters potentially influencing the serum potassium (K⁺) level: age, gender, medications (severity level of potassium-increasing DDI, duration of potassium-increasing DDI, numbers of concurrent potassium-increasing drugs, number of concurrent potassium-decreasing drugs), recent blood transfusion, comorbidities (kidney failure expressed by glomerular filtration rate, kidney transplant, diabetes mellitus, hypertension, heart failure, lung transplant), the unit (surgical versus non-surgical specialties), most recent serum K⁺ within 48 hours prior to the onset of the DDI (“baseline K⁺”), and finally the temporal change of the serum K⁺ level during the DDI.(21)

DDIs and Potassium-Increasing Drugs

DDIs were identified using the knowledge base galdat/hospINDEX (distributed by e-mediat AG, Berne, Switzerland; derived from ABDATA Pharma-Daten Service, Werbe- und Vertriebsgesellschaft Deutscher Apotheker, Eschborn, Germany), which tiers DDIs into six levels of severity.(23) Levels 1 to 3 categorize severe
DDIs (1: recommendation “contraindicated”, 2: “contraindicated as precaution”,
3: “monitoring or adaptation required”) and were considered in the present
study, whereas levels 4 to 6 were excluded (4: “monitoring or adaption in case of

Potassium-increasing drugs were defined as drugs involved in severe potassium-
increasing DDIs, including angiotensin-converting enzyme inhibitors (ACE
inhibitors), angiotensin antagonists (angiotensin-receptor blockers), direct renin
inhibitors, immunosuppressive agents (calcineurin inhibitors), potassium-sparing
diuretics (aldosterone-receptor antagonists and epithelial sodium channel
blockers), K⁺ supplements and trimethoprim (ingredient of co-trimoxazole).

Hyperkalemia

Hyperkalemia was defined as serum K⁺ level of ≥5.5 mEq/l.(24) Each
hyperkalemia was verified by chart review, and cases with documented
measurement issues, e.g. incorrect blood sampling or incorrect handling, were
excluded. In addition, corrective actions taken by the healthcare professionals
were recorded and compared to the best therapeutic options on a case-by-case
basis.(25) Only occurrences of hyperkalemia detected during potassium-
increasing DDIs were reviewed. The chart review was performed by an
experienced internist (M.S.).

Modeling of Prediction Strategies

We modeled five different prediction strategies (labelled “P” as in “Prediction”,
figure 1) comparing their strength to correctly predict the occurrence of
hyperkalemia during potassium-increasing DDIs. Data from patients already
presenting a hyperkalemia at onset of the DDI were excluded.
The three “P\textsubscript{initial}” prediction strategies were triggered only once, i.e. at onset of the potassium-increasing DDI. Thus, they predicted the risk of hyperkalemia for the entire DDI period (referred to as “long-term predictions”). These “P\textsubscript{initial}” strategies took into account a stepwise increasing number of factors influencing the serum K\textsuperscript{+} level:

(i) no parameter at all (P\textsubscript{initial, none})
(ii) the baseline serum K\textsuperscript{+} level (P\textsubscript{initial,K+}) and
(iii) all patient factors significantly influencing the K\textsuperscript{+} level (P\textsubscript{initial,GAM}) according to prior work.(21)

In contrast, both “P\textsubscript{during}” prediction strategies were triggered not only at onset of the DDI, but again for each serum K\textsuperscript{+} level measured during the DDI. These strategies predicted the risk of hyperkalemia for the next 48 hours (referred to as “short-term predictions”) and considered

(iv) merely the current serum K\textsuperscript{+} level (P\textsubscript{during,K+}), versus
(v) all patient parameters affecting the serum K\textsuperscript{+} progress (P\textsubscript{during,GAM}).

The patient data were split into a calibration set (used for building the strategies) and a validation set (used for validating the strategies) by applying a sample cube method (26) in order to generate robust models and to avoid overfitting. A balanced distribution was obtained by splitting the patients under consideration of a balanced allocation of patient factors influencing the serum K\textsuperscript{+} level.

The calibration was performed depending on the prediction strategy: For strategy “P\textsubscript{K+}\textsubscript{initial}”, the threshold for predicting a hyperkalemia was calculated by applying Youden’s J statistic to a receiver operation characteristic (ROC) curve built on the baseline serum K\textsuperscript{+} level.(27) The strategy “P\textsubscript{K+}\textsubscript{during}” additionally took
into account all K\(^+\) levels measured during the DDI period (followed by at least 48 hours of unchanged potassium-increasing drug orders). \(p_{\text{GAM initial}}\) was modeled using a generalized additive model (GAM): this algorithm selected those parameters at onset of the DDI that were most predictive for calculating the long-term risk of developing a hyperkalemia.(28) The threshold was again defined by applying Youden’s J statistic to the resulting ROC curve. For \(p_{\text{GAM during}}\), the GAM took into account all patient parameters that were predictive for the short-term risk of developing a hyperkalemia.

The ROC areas under the curve (AUCs) were compared with DeLong’s Test,(29) and the p value was adjusted with Hommel’s method.(30)

For the validation of \(P_{\text{initial}}\) predictions, a subsequent hyperkalemia was defined as a hyperkalemia occurring anytime during the DDI. In contrast, for the validation of \(P_{\text{during}}\) predictions, an imminent hyperkalemia was defined as a hyperkalemia occurring between the current time and the next 48 hours. In order to give equal weight to each patient and the respective parameters, the validation of the prediction strategies considered only the first event (subsequent risk of or occurrence of hyperkalemia) per patient.

**Hypothetical Monitoring Reminders**

We added two hypothetical monitoring reminders (labelled “M” as in “Monitoring”, figure 1) to foster periodic serum K\(^+\) measurements, a prerequisite for the prediction strategies studied: \(M_{\text{initial}}\), ensuring that a recent serum K\(^+\) level is known at onset of the DDI, and \(M_{\text{during}}\), encouraging regular serum K\(^+\) monitoring.
The number of hypothetical monitoring reminders required was calculated using the same validation set as the one used to validate the prediction strategies. The analysis was carried out with two different intervals: The short monitoring interval of 48 hours was adopted from our previous study which showed that monitoring intervals exceeding 48 hours during potassium-increasing DDIs were associated with a higher risk for hyperkalemia.\(^{(21)}\) However, the other defined interval was 72 hours in order to investigate a potential reduction of the number of hypothetical monitoring reminders.

**Statistical analyses**

Data analyses, model constructions and statistical tests were performed using the R language and environment for statistical computing, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The R package “sampling” was used to split the data into calibration and validation set, “pROC” to plot ROC curves, and “mboost” to model and validate GAMs. \(p\) values of \(\leq 0.05\) were considered to be statistically significant.
RESULTS

We analyzed the data of 76,467 inpatients (mean age 49.6 years, 50.3% females) for whom a total of 1,543,578 drugs were prescribed, including 77,799 potassium-increasing drugs (5.0%). They resulted in 8,413 potentially severe potassium-increasing DDIs concerning 5,637 inpatients (mean age 65.8 years, 31.3% females).(21) Of those patients, 90 developed a total of 132 hyperkalemic events during the DDIs.

The charts reviews to record the measures taken after these hyperkalemic events revealed that more than half of the DDIs remained unchanged although a number of corrective actions should have been taken (table 1). The finding that only half of the orders were modified after a hyperkalemic event despite the fact that this would have been appropriate for all cases documents the need to alert the physician in charge when a hyperkalemia has occurred.
Table 1:

Observed versus preferred actions following the 132 hyperkalemic K⁺ levels measured during potassium-increasing drug-drug interactions.

<table>
<thead>
<tr>
<th>Actions</th>
<th>Observed¹</th>
<th>Preferred²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modifying the drug order of ≥1 interacting drug</td>
<td>47 (43.2%)</td>
<td>132 (100.0%)</td>
</tr>
<tr>
<td>Discontinuing ≥1 interacting drug</td>
<td>26 (19.7%)</td>
<td>36 (27.3%)</td>
</tr>
<tr>
<td>Switching ≥1 interacting to another drug</td>
<td>0 (0.0%)</td>
<td>89 (67.4%)</td>
</tr>
<tr>
<td>Pausing ≥1 interacting drug</td>
<td>31 (23.5%)</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Starting potassium-decreasing therapy</td>
<td>62 (47.0%)</td>
<td>112 (84.8%)</td>
</tr>
<tr>
<td>No measures taken</td>
<td>39 (29.5%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

¹ Actions observed within 24h of hyperkalemic K⁺ level measurements. The actions consist of modifications of actual potassium-increasing drug orders and / or of beginning a potassium-decreasing therapy.

² Action recommended by expert based on chart review.

K⁺, serum potassium level.
The investigated five prediction strategies are presented in figure 1. Three of them, the “P\text{\tiny initial}” predictions, were triggered at onset of each potassium-increasing DDI only. The risk of hyperkalemia was calculated for the entire period of the DDI (long-term predictions), taking into account an increasing number of parameters influencing the serum K\text{\tiny +} level. The two “P\text{\tiny during}” predictions were additionally triggered for each serum K\text{\tiny +} level measured during the DDI, and calculated the risk of hyperkalemia for the next 48 hours (short-term predictions).

The predictive power of the strategies divides them into two categories (table 2): The short-term predictions of hyperkalemia (P\text{\tiny during}) featured a significantly higher positive predictive value (PPV) than the long-term predictions (P\text{\tiny initial}). In contrast, within the two categories, there was only a trend of the predictive strength between the strategies: The long-term PPV insignificantly increased from “P\text{\tiny initial}none”, through “P\text{\tiny initial}K\text{\tiny +}” to “P\text{\tiny initial}GAM”. Also, a trend of the PPV was observed between the short-term predictions from “P\text{\tiny during}K\text{\tiny +}” to “P\text{\tiny during}GAM”. The increase of the predictive power is reflected by the ROC AUC: Both strategies using short-term predictions performed significantly better compared to the long-term prediction “P\text{\tiny initial}K\text{\tiny +}”.
### Table 2:

Evaluation of strategies predicting hyperkalemia in potassium-increasing drug-drug interactions.

<table>
<thead>
<tr>
<th>Label</th>
<th>Model calibration</th>
<th>Model validation¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameters used</td>
<td>ROC AUC</td>
</tr>
<tr>
<td>pNone_initial</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>pK⁺_initial</td>
<td>Last K⁺ before onset of DDI</td>
<td>0.603</td>
</tr>
<tr>
<td></td>
<td>≥ 4.3 mEq/l</td>
<td></td>
</tr>
<tr>
<td>pGAM_initial</td>
<td>7 patient parameters:</td>
<td>0.786 vs. pK⁺_initial (0.067)</td>
</tr>
<tr>
<td></td>
<td>last K⁺ before onset of DDI, GFR, number of potassium-increasing drugs, number of potassium-decreasing</td>
<td></td>
</tr>
</tbody>
</table>

¹ Validated using leave-one-year-out cross-validation with 22 years of data and sensitivity analysis with a range of 0.05 to 0.90.
² p-values are calculated using McNemar’s test.
³ Number of alerts generated for each strategy.
| $p^k_+$ during | Current $K^+ \geq 4.5$ mEq/l | 0.839 vs. $P^k_+$ initial (0.007*)  
| | vs. $P^GAM_+$ initial (0.770) |
| | 303 25 278 13 1'133 65.8% 80.3% 8.25% 98.9% 5.41-11.94% |
| $p^GAM_+$ during | 5 patient parameters: | 0.841 vs. $P^k_+$ initial (0.006*) |
| | current $K^+$, severity level of DDI, number of potassium-increasing drugs, number of potassium-decreasing drugs, duration since onset of DDI  
| | 289 27 262 7 756 79.4% 74.3% 9.34% 99.1% 6.25-13.30% |

1 In order to give equal weight to each patient and to his or her specific set of parameters, the validation assessed merely the first event per patient (either alert or hyperkalemic event).
calculated on the basis of DeLong's Test for comparison; subsequently corrected with Hommel's method for adjustment of p values for multiple comparisons.

numbers of hypothetical alerts calculated by simulations using data from the validation set.

ROC AUC, area under the receiver operating characteristic curve.

TP, true positive. FP, false positive. FN, false negative. TN, true negative. Sens., sensitivity. Spec., specificity. PPV, positive predictive value. NPV, negative predictive value, CI, confidence interval.

GFR, glomerular filtration rate, *, statistically significant.
The ROC of “P_{during}^{K^+}” illustrates the tradeoff between specificity and sensitivity in function of the threshold value (figure 2). The superimposed ROC curves of all five strategies (figure 3) show that the short-term predictions “P_{during}^{K^+}” and “P_{during}^{GAM}” have similar curves and perform better than the long-term predictions “P_{initial}”.

We added hypothetical K^+ monitoring reminders to the prediction strategies to ensure that K^+ levels would be available to the prediction models (figure 1). The simulation of the required monitoring reminders showed that medications triggering potassium-increasing DDIs were ordered without knowledge of the current serum K^+ level in 12% to 15% of the patients (time intervals of 72 and 48 hours, respectively; table 3). Considering the K^+ monitoring during the entire duration of the DDIs, the serum K^+ was not measured within monitoring intervals of 72 hours in 22% and within intervals of 48 hours in 36% of the patients.

Table 4 illustrates the potential alert burden by summarizing the number of hypothetical monitoring reminders and the number of hypothetical alerts warning against the risk of hyperkalemia according to the five strategies analyzed.
Table 3:

Numbers of hypothetical reminders for different serum K⁺ monitoring strategies during potassium-increasing DDIs.

<table>
<thead>
<tr>
<th>Δt</th>
<th>Reminders at onset of DDI¹</th>
<th>Reminders at onset of and during DDI²</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Label</td>
<td>Trigger</td>
</tr>
<tr>
<td>48h</td>
<td>$M_{48h}^{\text{initial}}$</td>
<td>if no K⁺ level is available within 48h prior to the onset of the DDI</td>
</tr>
<tr>
<td>72h</td>
<td>$M_{72h}^{\text{initial}}$</td>
<td>if no K⁺ level is available within 72h prior to the onset of the DDI</td>
</tr>
</tbody>
</table>

¹ In order to allow for comparison with table 2, merely the first event per patient was assessed.

² Reminders in percentage of the total number of patients included within the validation set.

³ This condition is continuously tested during the entire period of each potassium-increasing DDI.
Table 4:

Number of hypothetical alerts warning against the risk for hyperkalemia and of hypothetical potassium monitoring reminders.

<table>
<thead>
<tr>
<th>Triggering event</th>
<th>Alerts</th>
<th>Reminders</th>
<th>Total¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>strategy</td>
<td>#</td>
<td>strategy</td>
</tr>
<tr>
<td>Start of DDI</td>
<td>p&lt;sub&gt;none&lt;/sub&gt; initial</td>
<td>1,619</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>p&lt;sub&gt;K⁺&lt;/sub&gt; initial</td>
<td>398</td>
<td>M&lt;sub&gt;72h&lt;/sub&gt; initial</td>
</tr>
<tr>
<td></td>
<td>p&lt;sub&gt;GAM&lt;/sub&gt; initial</td>
<td>387</td>
<td>M&lt;sub&gt;72h&lt;/sub&gt; initial</td>
</tr>
<tr>
<td>Start of DDI and each serum</td>
<td>p&lt;sub&gt;K⁺&lt;/sub&gt; during</td>
<td>303</td>
<td>M&lt;sub&gt;72h&lt;/sub&gt; during</td>
</tr>
<tr>
<td>K⁺ measurement during DDI</td>
<td>p&lt;sub&gt;GAM&lt;/sub&gt; during</td>
<td>289</td>
<td>M&lt;sub&gt;72h&lt;/sub&gt; during</td>
</tr>
</tbody>
</table>

¹ sum of number of alerts plus number of reminders.
DISCUSSION

The goal of the study was to evaluate and compare five distinct strategies in terms of their ability to predict the risk of hyperkalemia during potassium-increasing DDIs in order to prevent hyperkalemia by means of alerts. Our analysis shows that short-term predictions, similar to a continuous monitoring of DDIs, perform significantly better than long-term predictions exclusively triggered at onset of potassium-increasing DDIs.

Besides providing up to three times higher PPVs, the switch from long-term to short-term predictions also improved the ROC AUC of the respective strategies, increased the sensitivity, but still decreased the potential alert burden. Of note, only short-term predictions achieved sensitivities of nearly 70%, a sensitivity considered to be adequate. (32) In contrast, taking into account further patient parameters affecting the development of hyperkalemia showed only a modest gain. Short-term predictions performed better with fewer parameters and thus with lower costs than long-term predictions.

The GAM algorithm selected different patient parameters for the long- vs. short-term prediction strategies: “\( p_{\text{initial}}^{\text{GAM}} \)” used the last serum K\(^+\) level measured before onset of the DDI and considered the number of drugs ordered affecting the serum K\(^+\) level, the kidney function, blood transfusions, age, and the unit. In contrast, “\( p_{\text{during}}^{\text{GAM}} \)” considered the severity level of the DDI, the previous duration of the DDI, and the number of drugs ordered affecting the serum K\(^+\) level and monitored the current serum K\(^+\) level. This is in line, however, with our observation (21) that the severity level is not helpful for long-term predictions of developing hyperkalemia. Noteworthy, the ordering of level 1 DDIs often relates
to the correction of hypokalemia, and this intentional treatment appears to be less likely to induce a hyperkalemia, possibly due to a closer serum K⁺ monitoring by the healthcare professionals in charge.

Serial predictions of the risk for hyperkalemia during potassium increasing DDIs require regularly updated laboratory values. Therefore, there is a need to stimulate the K⁺ monitoring by the providers. Such monitoring reminders may increase the alert burden, potentially undermining the aim to reduce the number of displayed notifications. However, an innovative approach mitigating this issue would be the automated generation of K⁺ measurement orders – and no more monitoring reminders would then be necessary.

If our described strategies would be implemented in an electronic health record as automated notifications, both (i) alerts warning against the risk of hyperkalemia, and (ii) monitoring reminders, could unobtrusively make recommendations to the providers at the time of order entry. Also, (i) alerts and (ii) monitoring reminders triggered during the DDI could be displayed in a non-interruptive manner e.g. in the overview of current medication orders or laboratory results. Overdue serum K⁺ measurements could be prefilled automatically in laboratory order forms. The alerts warning against the risk of hyperkalemia described above should be complemented by actual hyperkalemia alerts (serum potassium level ≥5.5mEq/l). These supplementary alerts would draw the physician’s attention to the fact that the actual drug therapy may aggravate the already present hyperkalemia.

Our study has several limitations. First, the data were obtained from a single site, which may limit the generalizability of the findings. In this context, the high
proportion of multimorbid patients and the frequent monitoring of laboratory results at our institution may have influenced the model thresholds, which should be validated on site before use in other institutions. Nevertheless, the described predictions can easily be implemented at other institutions, since the proposed strategies have been disclosed in detail. Second, only a single expert reviewed the patient charts to retrospectively assess treatment options following hyperkalemic events. Third, we assumed that the consequences of false positive and false negative alerts are comparable. We therefore calculated the alert threshold using the optimality criterion of Youden’s J statistic, giving equal weight to both specificity and sensitivity. Anyway, CDS interventions incorporating such predictions could take into account the stakeholders’ preference for specificity or sensitivity. Fourth, a PPV of less than 10% may appear insufficient, but this has to be interrelated with the low frequency of hyperkalemia during potassium-increasing DDIs (1.9%).(21, 33)

Various approaches to improve the specificity of DDI alerts have been proposed, including focusing on high-priority DDIs,(12) tiering DDIs by severity,(13, 14) taking into account patient factors and co-medications,(15) and also considering the change of conditions over time (19), or a combination of these strategies.(9, 16-18) However, the effects of these approaches have rarely been quantified: Paterno et al. demonstrated that tiering DDI alerts by severity increased the compliance by 19%.(13) Helmons et al. reduced the number of alerts by 55% by focusing on high-priority DDIs and considering critical patient parameters 3 times a day.(18)
To our knowledge, this is the first study comparing prediction strategies triggered exclusively at onset of potassium-increasing DDIs (long-term predictions) with serial prediction recalculations throughout the duration of the DDIs (short-term predictions). Our observation that the predictive power of alerts can be improved by focusing on short-term predictions may positively influence the crucial efforts to reduce the alert burden which in turn would minimize the risk for alert fatigue. Furthermore, this approach may be of importance for various other categories of prescription warnings, provided that the risk of potential ADEs may be monitored.

Finally, predictions recalculated throughout the duration of DDIs can be combined with human factors principles.(34-39) For instance, the models presented could generate alerts with graduated priorities as a function of the alert threshold, such as medium risk notifications vs. warnings against a high risk of an imminent hyperkalemia. Finally, since alerting at the appropriate time is a central aspect of human factors principles, short-term predictions constitute a novel and important approach to address human factors.

CONCLUSION

In conclusion, our findings show that a continuous monitoring of the risk for hyperkalemia based on the current potassium levels shows a better predictive power than predictions triggered at onset of DDIs. This contrasts with efforts of improving DDI alerts by taking into account more detailed patient data at the time of ordering, whereas algorithms continuously monitoring only the prime patient parameter perform likewise well.
Figure Captions

Figure 1: Design of alert and reminder strategies

Figure 2: Receiver operating characteristic curve of prediction strategy $p_{\text{K}^+}^{\text{during}}$ predicting hyperkalemia for the next 48 hours based on the current serum potassium level

Figure 3: Comparison of the receiver operating characteristic curves of all evaluated prediction strategies

Contributions of Authors statement

E. Eschmann designed and performed the research, analyzed and interpreted data, and wrote the manuscript.

M. Schneemann contributed to the research, assessed patient history, interpreted data, and edited the manuscript.

P. Beeler contributed to the research, interpreted data, and edited the manuscript.

J. Blaser designed the research, interpreted data, and edited the manuscript.

All authors approved the manuscript.

Competing Interests

The authors declare that they have no conflict of interest.

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Reference List

<table>
<thead>
<tr>
<th>Triggering event</th>
<th>Warning against</th>
<th>Label</th>
<th>Parameters considered</th>
<th>Triggering times and potential alerts/reminders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of DDI</td>
<td>Risk of hyperkalemia during the entire period of DDI</td>
<td>$P_{\text{none initial}}$</td>
<td>None</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Alerting for risk of hyperkalemia" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P_{K^+ \text{ initial}}$</td>
<td>Last serum K$^+$ before onset of DDI</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Potentially alerting for risk of hyperkalemia" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P_{\text{GAM initial}}$</td>
<td>All patient parameters relevant at onset of DDI</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Potential monitoring reminder" /></td>
</tr>
<tr>
<td>Start of DDI and each serum K$^+$ measurement during DDI</td>
<td>Risk of hyperkalemia within the next 48h</td>
<td>$P_{K^+ \text{ during}}$</td>
<td>Current serum K$^+$</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Alerting for risk of hyperkalemia" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P_{\text{GAM during}}$</td>
<td>All current relevant patient parameters</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Potentially alerting for risk of hyperkalemia" /></td>
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<tr>
<td>Last serum K$^+$ measurement</td>
<td>Serum K$^+$ monitoring overdue</td>
<td>$M_{\text{initial}}$</td>
<td>Duration since last K$^+$ measurement before onset of DDI</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Alerting for risk of hyperkalemia" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$M_{\text{during}}$</td>
<td>Duration since last K$^+$ measurement</td>
<td><img src="https://mc.manuscriptcentral.com/jamia" alt="Potentially alerting for risk of hyperkalemia" /></td>
</tr>
</tbody>
</table>

- ![Alerting for risk of hyperkalemia](https://mc.manuscriptcentral.com/jamia)
- ![Potentially alerting for risk of hyperkalemia](https://mc.manuscriptcentral.com/jamia)
- ![Potential monitoring reminder](https://mc.manuscriptcentral.com/jamia)

- ![Serum K$^+$ measurement](https://mc.manuscriptcentral.com/jamia)

Potassium-increasing DDI

https://mc.manuscriptcentral.com/jamia
Figure 2: Receiver operating characteristic curve of prediction strategy $p^{X^+}_{\text{during}}$ predicting hyperkalemia for the next 48 hours based on the current serum potassium level.
Figure 3: Comparison of the receiver operating characteristic curves of all evaluated prediction strategies.