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ORIGINAL ARTICLE

Clinical rule-guided pharmacists' intervention in hospitalized patients with hypokalaemia: A time series analysis

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Abstract

What is known and objective: Physicians' response to moderate and severe hypokalaemia in hospitalized patients is frequently suboptimal, leading to increased risk of cardiac arrhythmias and sudden death. While actively alerting physicians on all critical care values using telephone or electronic pop-ups can improve response, it can also lead to alert fatigue and frustration due to non-specific and overdue alerts. Therefore, a new method was tested. A clinical rule built into a clinical decision support system (CDSS) generated alerts for patients with a serum potassium level (SPL) <2.9 mmol/L without a prescription for potassium supplementation. If the alert was deemed clinically relevant, a pharmacist contacted the physician. The aim of this study was to evaluate the impact of the clinical rule-guided pharmacists' intervention compared to showing passive alerts in the electronic health records on outcome in patients who developed hypokalaemia (<2.9 mmol/L) during hospitalization.

Methods: A before (2007-2009) and after (2010-2017) study with time series design was performed. Pre-intervention, physicians were shown passive alerts for hypokalaemia in the electronic health records. During the intervention period, in addition to these passive alerts, a pharmacist provided the physician with a specific advice on patients with untreated hypokalaemia, guided by the generated alerts. Unique patients >18 years with SPL <2.9 mmol/L measured at least 24 hours after hospitalization in whom no potassium supplementation was initiated within 4 hours after measurement and normalization of SPL was not achieved within these 4 hours were included. Haemodialysis patients were excluded. The percentage of hypokalaemic patients with a subsequent prescription for potassium supplementation, time to subsequent potassium supplementation prescription, the percentage of patients who achieved normokalaemia (SPL ≥ 3.0 mmol/L), time to achieve normokalaemia and total duration of hospitalization were compared.

Results and discussion: A total of 693 patients were included, of whom 278 participated in the intervention phase. The percentage of patients prescribed supplementation as well as time to prescription improved from 76.0% in 31.1 hours to 92.0% in 11.3 hours ($P < .01$). Time to achieve SPL ≥3.0 mmol/L improved, $P < .009$. No changes, however, were observed in the percentage of patients who achieved normokalaemia or time to reach normokalaemia, 87.5% in 65.2 hours pre-intervention compared to 90.2% ($P = .69$) in 64.0 hours ($P = .71$) in the intervention group. A non-significant

decrease of 8.2 days was observed in the duration of hospitalization: 25.4 compared to 17.2 days (P = .29).

What is new and conclusion: Combining CDSS alerting with a pharmacist evaluation is an effective method to improve response rate, time to supplementation and time to initial improvement, defined as SPL ≥3.0 mmol/L. However, it showed no significant effect on the percentage of patients achieving normokalaemia, time to normokalaemia or hospitalization. The discrepancy between rapid supplementation and improvement on the one hand and failure to improve time to normokalaemia on the other warrants further study.

KEYWORDS

clinical decision support systems, clinical rule, hypokalaemia, pharmacist, time series analysis

1 | BACKGROUND AND SIGNIFICANCE

Hypokalaemia is one of the most frequently occurring electrolyte disturbances in hospitalized patients, with a reported prevalence as high as 20%.[1-4] In contrast to milder hypokalaemias (3.4-2.9 mmol/L) which do not always require immediate treatment, hypokalaemias below 2.9 mmol/L are independently associated with an increased mortality,[5] requiring immediate action, especially in patients with pre-existing cardiac disease.[6-13] Initial corrective action is simple, consisting of potassium supplementation. Thereafter, the treatment of underlying causes is indicated, including cessation of drugs contributing to the hypokalaemia.[4,7,14,15]

Several studies have shown suboptimal response to moderate and severe hypokalaemia in hospitalized patients.[1,10,16,17] A retrospective study performed in a population of 866 hospitalized patients with hypokalaemia <3.0 mmol/L reported that in 24% of the patients, no potassium supplementation was administered. Moreover, in 33% of these cases, no follow-up testing of serum potassium level (SPL) was performed. Failure to initiate appropriate treatment led to failure in achieving normokalaemia, prolonged hospital stay and increased in-hospital mortality.[17] A retrospective study that investigated prevalence and symptoms of hypokalaemia in emergency department patients found that 45% of the 54 patients with SPL < 2.5 mmol/L received no treatment during their stay in the emergency department.[1]

Several approaches have been studied to improve physicians' response to critical laboratory values such as severe hypokalaemia, including alerting physicians to critical laboratory values by phone,[18,19] by SMS[20,21] and by computerized reminders or pop-ups within the electronic health record (EHR).[22-24] Such interventions have been shown to improve physicians' response time to prescribe potassium supplementation,[18,19,24] increase the percentage of patients on whom follow-up SPL measurement was performed,[17] decrease time to mild hypokalaemia or normal potassium status,[22] increase percentage of patients reaching normokalaemia during hospitalization[17] and even decrease the duration of hospitalization.[22]

While computerized active alerting of physicians on all critical laboratory results of hospitalized patients has been shown to be effective in improving physicians' response, there is also a downside to solely using automated alerts. Most alerts do not provide tailored advice and can frequently lead to inadequate follow-up action.[17,25] One study even found a delay in time to normalization of critical care results.[23] Also, the increasing number of active alerts causes alert fatigue and frustration.[20,26,27] Additionally, most studies showing a positive effect of active alerting using automated reminders on patient outcome were conducted before the introduction of fully operational and widely accessible EHRs,[17,18,22] making these results difficult to extrapolate to current practice. An EHR integrating real-time laboratory results enables physicians to easily and quickly access all results. Using a basic laboratory-assisting clinical decision support system (CDSS) allows for passive alerting on critical laboratory results by highlighting them or placing them on a physicians' worklist, potentially increasing response rate and time without an active alerting method. Since 2008, this was also the case in the Catharina Hospital. Introduction of the fully operational EHR however also led to an increased automated alerting and frustration to calls on critical care values that have already been acted upon. For that reason at the end of 2008, the medical board decided to cancel all forms of active automated alerts or telephonic consultations for critical care values of hospitalized patients. This decision, however, led to a significant delay in response time to critical care results for individual patients. Therefore, a new combination of CDSS and human evaluation was implemented. An EHR-based clinical rule alert was evaluated on clinical relevance by a pharmacist. If the alert was deemed relevant, the pharmacist consulted the physician with specific advice. To test this approach, a series of clinical rules were designed and implemented to monitor response to critical care values. Hypokalaemia was among the first in the series to be implemented and was chosen to be studied in further detail because reaction time and clinical impact could be measured directly. The aim of this study was to evaluate the effect of a clinical rule-guided pharmacists' intervention compared to passive alerts

shown in the EHR on patient and process outcomes in hospitalized patients with untreated hypokalaemia < 2.9 mmol/L.

2 | METHODS

2.1 | Setting and study population

This before and after study with a time series design was performed in the Catharina Hospital Eindhoven (CZE), a 700-bed teaching hospital in the Netherlands. Patients over 18 years of age who met the following criteria were included the following: hospitalized during the period of January 2007 to December 2016, having a reported SPL < 2.9 mmol/L measured at least 24 hours after hospital admittance, no potassium supplementation initiated within 4 hours after sampling and normalization of SPL not established within 4 hours. Patients, as well as instances of hypokalaemia <2.9 mmol/L, were included only once. Haemodialysis patients were excluded. The hospital used CS-EZIS® (Chipsoft BV, Amsterdam) as its EHR and pharmacy information system; CS-EZIS® also provided basic decision support. Critically low laboratory values, including a SPL <2.9 mmol/L, were marked with a '–' in bold red font next to the result. Online Appendix A shows an example of a critically low laboratory value displayed in the EHR. No other method to report critical laboratory values of hospitalized patients was operational. To generate the clinical rule-based alerts, the CDSS Gaston® (Gaston Medical BV, Eindhoven) was used. The CDSS was purchased in 2006 to develop and study a wide range of advanced decision support interventions including, but not limited to medication-related interventions. Other clinical rules were already in use by the clinical pharmacy before implementing the hypokalaemia rule, including renal function, opioid-laxative and gastric protection. No additional training, standard operating procedures or staffing were required to implement the intervention, and also, there was no additional reimbursement to provide additional duties. Staff consisted of 6-8 clinical pharmacists and 3 clinical pharmacists in training. Each day there was one pharmacist on clinical duty responsible for checking medication orders, decision support alerts and telephonic consultations for all hospitalized patients. Approval by the Institutional Review Board was not required for this retrospective study.

2.2 | Design

The pre-intervention phase ran from January 2007 to December 2009, and the intervention phase ran from January 2010 to December 2016. Figure 1 shows a schematic representation of the study phases. During the pre-intervention phase, only passive alerts were shown in the laboratory section of the EHR. During the intervention phase, the hypokalaemia clinical rule generated active alerts, shown to a pharmacist, on all hospitalized patients with hypokalaemia <2.9 mmol/L in whom no potassium supplementation had been started in any form.

Online Appendix B provides a graphical representation of the clinical rule flow. The alerts generated by the CDSS contained information on time and result of last SPL, any drugs in use that might contribute to hypokalaemia, advice to start oral or intravenous potassium supplementation depending on severity and symptoms, and advice to stop or decrease the dose of the potassium-lowering drugs if applicable. Online Appendix C provides a screenshot of an alert provided by the clinical rule in the CDSS module. Alerts were generated once daily between 12:30 and 13:00. Between 13:00 and 17:00 on the same day, all of these alerts were reviewed for clinical relevance by a pharmacist. This review consisted of checking whether potassium supplementation had been prescribed in the meantime, whether SPL had improved in the meantime, additional SPL measurement was ordered in the meantime and if treatment had been withdrawn in an end-of-life care situation. The advice given by the pharmacist consisted of one or more of the following: advice to start oral or intravenous potassium supplementation, advice to stop or decrease the dose of the potassium-lowering drugs, start or increase dose of potassium sparing diuretic, performing additional SPL measurement, performing an electrocardiogram (EKG) or switching IV fluid suppletion. A recommendation on potassium supplementation dose was only given on request.

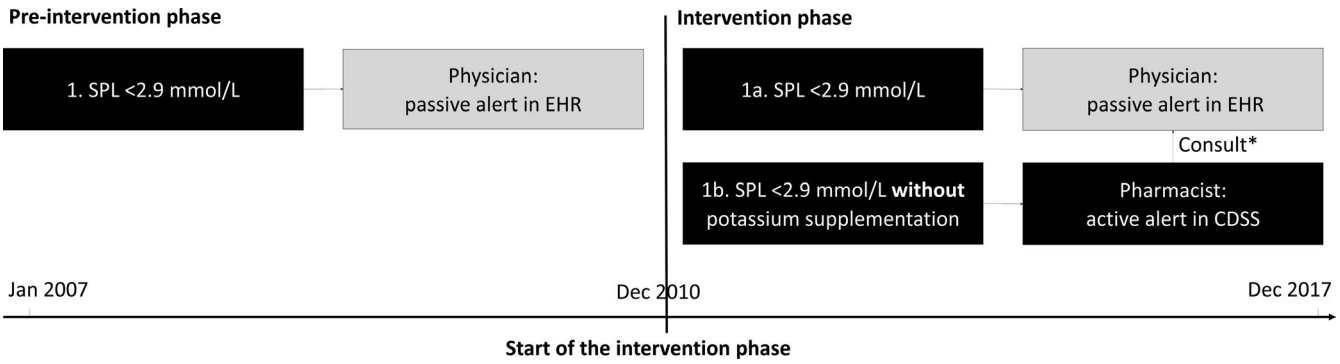

FIGURE 1 Schematic representation of the chronology of the study design including the alerts generated in both phases of the study. CDSS, computerized decision support system; EHR, electronic health record; SPL, serum potassium level; *alerts were reviewed by a pharmacist. If an alert was found to be potentially clinically relevant, the pharmacist consulted the physician and provided him or her with treatment advice

TABLE 1 Comparison of patient characteristics before and after intervention

Variable	Pre-intervention phase (n = 415)			Intervention phase (n = 278)			*P* value
Mean age in years (SD)	67.9 (14.3)			69.0 (14.9)			.20
Gender (%)							
Male	161 (39)			106 (38)			.86
Female	254 (61)			172 (62)			
Treating specialty (%)							
Cardiology	35 (8.4)			35 (12.6)			.64[f]
Internal medicine[f]	122 (29.4)			87 (31.3)			
Surgery[a]	157 (37.8)			71 (25.5)			
Intensive care	11 (2.6)			4 (1.4)			
OBGYNUR[a]	32 (7.9)			37 (13.3)			
Neurology	31 (7.4)			26 (9.4)			
Pulmonology	24 (5.7)			14 (5.0)			
Psychiatry	3 (0.7)			4 (1.4)			
Onset of initial hypokalaemia (%)[d]							
At admission[e]	71 (17.1)			51 (18.3)			**.004**[f]
During hospitalization	223 (55.9)			181 (65.2)			
Unknown (measurement SPL > 24 h)	112 (27.0)			46 (16.5)			
Median time to first SPL measurement (h)	3.1	Range 1037.0	IQR 18.3	0.96	Range 165.4	IQR 18.3	**.003**
Median of first measured SPL (mmol/L)	3.8	Range 6.1	IQR 0.6	3.8	Range 4.9	IQR 0.7	.58
Potentially drug-related hypokalaemia							
Potentially drug-related (%)	202 (48.7)			144 (51.8)			.42[f]
One drug	175 (86.6)			126 (87.5)			
Two or more drugs	27 (13.4)			18 (12.5)			
Causative drugs in use at the time of event (% of total population)							
Loop diuretic	144 (34.7)			110 (39.6)			.19
Thiazide diuretic	69 (16.6)			41 (14.7)			.51
Laxative	13 (3.1)			9 (3.2)			.94
Polystyrene sulphonate	5 (1.2)			2 (0.7)			.53
Hazardous drugs (%)							
Digoxin	12 (2.9)			11 (4.0)			.44

Note: Patient characteristics are shown for unique patients over 18 years of age hospitalized in the period between January 2007 and December 2016 with a serum potassium level (SPL) <2.9 mmol/L more than 24 h after hospitalization, no potassium supplementation at or within 4 h after sampling, and no normalization of SPL within 4 h.

SD, standard deviation; IQR, interquartile range; SPL, serum potassium level.

[a]Surgery includes departments of general surgery, cardiothoracic surgery, lung surgery and orthopaedic surgery.

[b]Internal medicine includes departments of nephrology, gastrointestinal and liver diseases, geriatrics, haematology and oncology.

[c]OBGYNUR includes obstetrics, gynaecology and urology.

[d]Patients with a SPL < 2.9 mmol/L at admission were not included, and therefore, at admission SPL was 2.9-3.5 mmol/L.

[e]SPL 2.9-3.5 mmol/L measured within 24 h after hospitalization.

[f]Chi-square test was used to test for difference in proportions.

Statistical significance $P < .05$ is indicated in bold.

2.3 | Endpoints

The following endpoints included in earlier studies[17-19,22,24] were included as endpoints in the current study: percentage of patients for whom treatment was started,[22] time until treatment start,[18,19,24] percentage of patients achieving normokalaemia,[17,18,22] time until normokalaemia[18] and duration of hospitalization.[22] The percentage of patients achieving mild hypokalaemia, defined as SPL ≥3.0 mmol/L, and time to achieve it were added as additional endpoints. These endpoints were added because they most directly reflect response

to the intervention. In addition, supplementation of patients with an SPL ≥3.0 mmol/L is not directly associated with improved clinical outcomes. Response rate is calculated as the percentage of patients achieving a certain endpoint, and response time as the time until that endpoint is achieved. Taken together, these led to the following four primary endpoints, which were compared to assess the effect of the intervention:

1. prescription for potassium supplementation (a. percentage of patients and b. time to prescription);
2. mild hypokalaemia, SPL ≥3.0 mmol/L (a. percentage of patients and b. time to achieve it);
3. normokalaemia, SPL ≥3.5 mmol/L (a. percentage of patients and b. time to achieve it); and
4. duration of hospitalization.

2.4 | Data analysis

To compare endpoints, a time series analysis was performed using segmented regression with inverse variance-weighted ratios per 12-month period.[28,29] Only the first occurring instance of SPL <2.9 mmol/L was used for each patient. Regressions of the pre-intervention and intervention phases were also compared to the inverse variance-weighted ratios per 12-month period of hospitalization duration of a control population consisting of patients admitted to the hospital in the same period without hypokalaemia <2.9 mmol/L. Additional analysis was done to visualize the number data points throughout the study. A Durbin-Watson test was performed to check for first-order autocorrelation on all regressions.[30] If first-order autocorrelation was detected, the Prais-Winsten method was used.[31] Statistical analyses were performed using SPSS for Windows, version 25.0.0 (SPSS, IBM). Acceptance rate of the alerts was calculated dividing the number of potassium supplementation started after telephonic consultation the same day by the total number of telephonic consultations based on generated alerts.

3 | RESULTS

3.1 | Inclusion and exclusion

During the study period, there were 295 945 hospitalizations. Including only hospitalizations of adult patients with a SPL <2.9 mmol/L left 3622 (1321 pre-intervention vs 2301 in the intervention phase) hospitalizations. Of these, 2398 (924 pre-intervention vs 1474 in the intervention phase) developed hypokalaemia <2.9 mmol/L at least 24 hours after hospitalization. Sixty-five (25 pre-intervention vs 40 in the intervention phase) patients were excluded based on haemodialysis. Potassium supplementation was already prescribed at the time of SPL sampling in 672 patients (262 pre-intervention versus 410 in the intervention phase) and within 4 hours after sampling in 647 patients (189 pre-intervention versus 458 in the intervention phase); these patients were excluded as well. Another 55 patients (20 pre-intervention versus 35 in the intervention phase) were excluded because normal SPL was measured within 4 hours after initial sampling. Finally, including only unique patients left 913 eligible for inclusion: 415 patients from the pre-intervention phase and 278 patients during the intervention phase.

3.2 | Patient characteristics

Table 1 show the patient characteristics of participants included in the analysis. No differences were found in general patient characteristics between the two phases. Median time until first SPL measurement was significantly shorter in the intervention phase, 1.0 hours compared to 3.1 hours pre-intervention, $P = .003$. Related to this, significantly fewer patients had no SPL measured within the first 24 hours of hospitalization, 27.0% pre-intervention versus 16.5% in the intervention phase, $P = .004$. There was no statistical difference in drug-related hypokalaemia, 48.7% pre-intervention and 51.8% in the intervention phase, $P = .42$. Loop diuretics accounted for the most instances of drug-related hypokalaemia, 34.7% and 39.6%, respectively, also without a statistical difference between the two groups, $P = .19$.

3.3 | Analysis

Figures 2, 3, 4 and 5 show the time series analyses of the primary endpoints, including intercepts and slopes of all regressions. A significant increase was observed in the percentage of patients subsequently prescribed potassium supplementation, from 76.0% (CI 65.8-86.3%) in the pre-intervention to 92.0% (CI 86.4-97.7%) in the intervention phase, $P = .002$. Moreover, time to potassium supplementation was reduced to 11.3 hours (CI 5.5-16.9 hours) compared to 31.1 hours (CI 20.7-41.4 hours), $P = .009$. The percentage of patients reaching mild hypokalaemia, SPL ≥3.0 mmol/L, during hospitalization did not change, 94.1% (CI 84.1-104.2%) pre-intervention compared to 95.8% (CI 90.2-101.3%), $P = .74$. No difference between the two was observed in intercepts on time to ≥3.0 mmol/L, 35.2 hours (CI 29.1-41.3 hours) and 34.2 hours (CI 30.8-37.5 hours) respectively, $P = .09$. However, comparison of slopes shows a significant decrease in time to ≥3.0 mmol/L, from −0.2 (CI −2.9 to −2.5) pre-intervention to −1.7 (CI −2.8 to −0.6) in the intervention phase, $P = .009$.

No significant changes were observed in percentage of patients reaching normokalaemia or time to reach normokalaemia; pre-intervention, 87.5% (CI 72.6-102.3%) reached normokalaemia with a mean time intercept of 65.2 hours, compared to 90.2% (CI 82.0-98.4%), with a mean time intercept of 64.0 hours in the intervention phase, $P = .69$ for percentage and $P = .71$ for time. A non-significant decrease of 8.2 days was observed in hospitalization, from 25.4 days (CI 11.4-39.2) pre-intervention to 17.2 days (CI 9.5-24.9), $P = .29$. No significant change in level or slope was observed for hospitalization

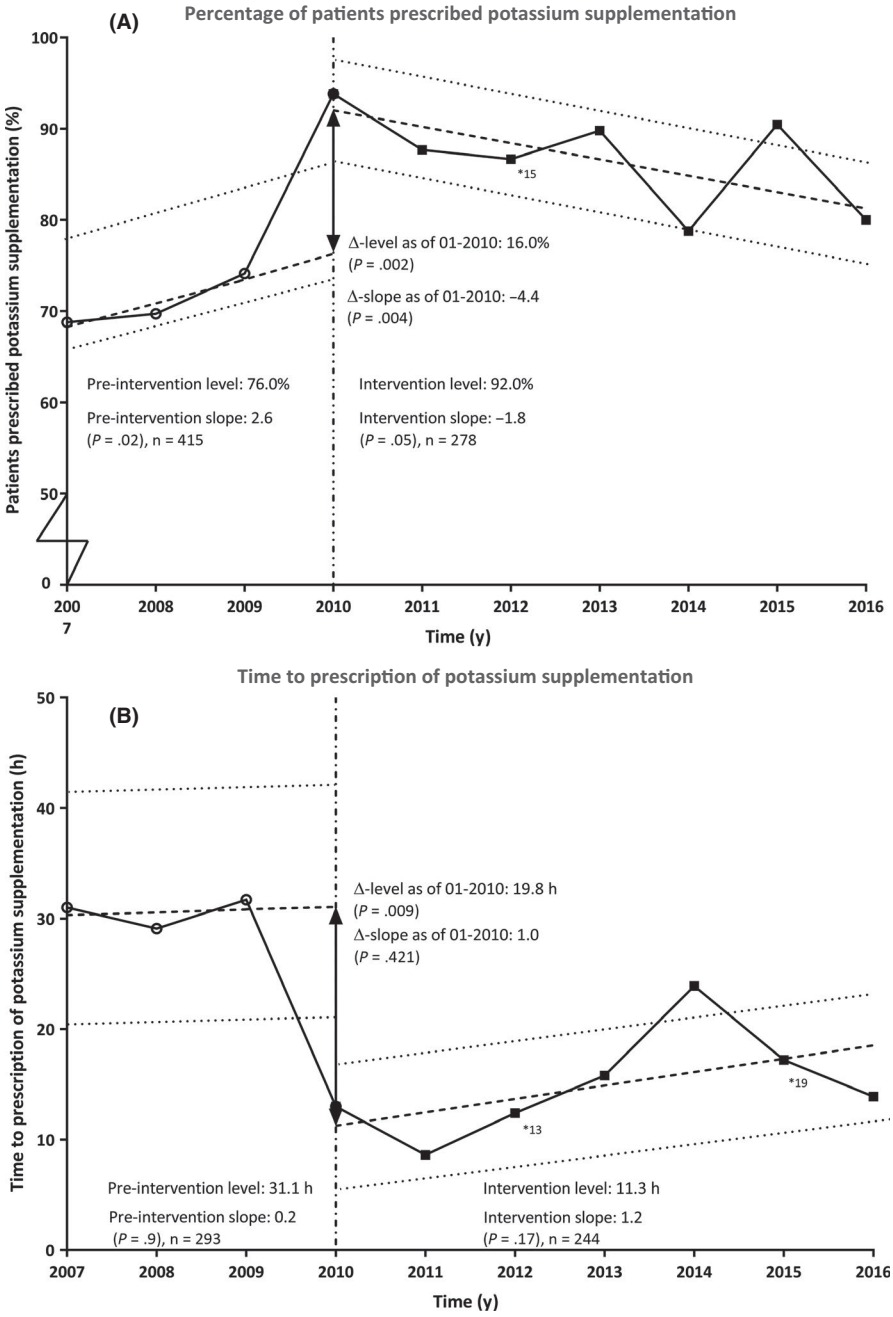

FIGURE 2 A,B, Graphical representation of the data points and segmented regressions using inverse variance-weighted ratios per 12-month period for percentage of patients prescribed potassium supplementation (Panel A) and time to prescription of potassium supplementation (Panel B). On the x-axis, time is shown; on the y-axis, the respective endpoints. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point

in patients without hypokalaemia during the same period as the study. Figure 6 shows the number of data points during the entire study period, revealing a trend towards a smaller number of sub-optimally treated incidents of hypokalaemia <2.9 mmol/L.

4 | DISCUSSION

This study demonstrated a positive effect of the clinical rule-based pharmacists' intervention on the percentage of patients for whom potassium supplementation was initiated during hospitalization, time needed to initiate this treatment and time to achieve mild hypokalaemia. Nevertheless, this study did not demonstrate improvement in percentage of patients reaching normokalaemia or time to reach normokalaemia and only showed a trend towards shorter hospitalization.

Failure to improve percentage of patients normalizing and time to normalize SPL is in contrast to the study performed by Paltiel et al.[17] A possible explanation for these contrasting results could be the differences in baseline and approach to treating SPL <2.9 mmol/L. In our study, a high percentage of patients—87.5%—already reached normokalaemia during hospitalization at baseline compared to 70%-75% in other studies.[17,32] Baseline response rate and time could also have been underestimated in our study, as only electronic orders were used to measure them. Improvement in time to mild hypokalaemia but not time to normokalaemia suggests a different approach to treating hypokalaemia compared to the study performed by Paltiel et al.[17] It

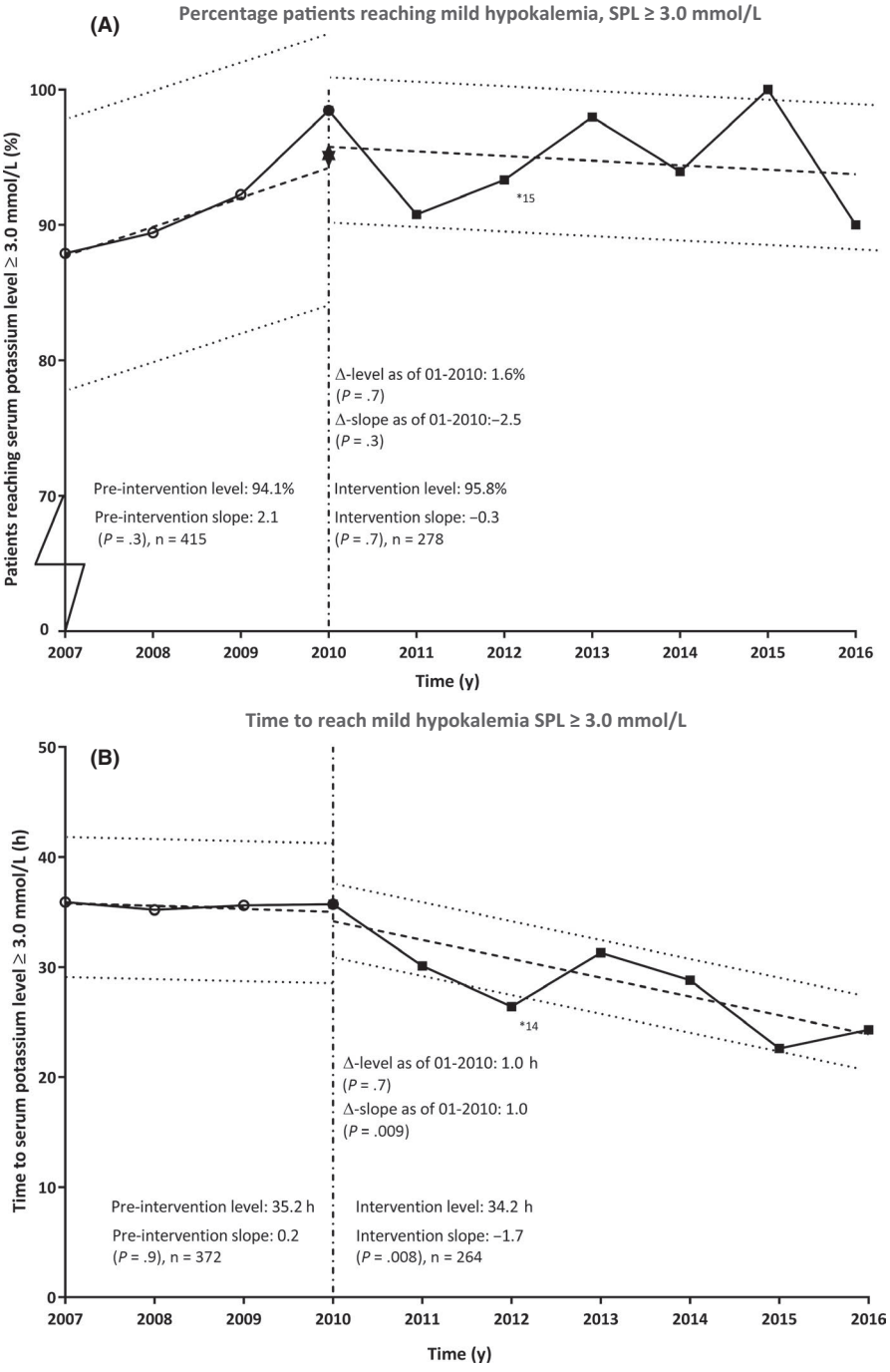

FIGURE 3 A,B, Graphical representation of the data points and segmented regressions using inverse variance-weighted ratios per 12-mo period for percentage of patients reaching mild hypokalaemia, SPL ≥3.0 mmol/L (Panel A), and time to reaching mild hypokalaemia (Panel B). On the x-axis, time is shown; on the y-axis, the respective endpoints. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting the EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point

is also possible that the advice regarding potassium supplementation dose was too conservative to improve time to reach normokalaemia.

Total duration of hospitalization was not significantly reduced despite a clinically significant reduction of hospitalization by 8.1 days, or more than 32.0%. This result is in contrast to an earlier study by Tate et al, which found a significant decrease in hospitalization duration.[22] A possible explanation for this is the small number of data points in the pre-intervention phase, which creates a sizable confidence interval for duration of hospitalization. Additionally, the long mean hospitalization duration compared to the control population and the literature suggests that in our study population, severe hypokalaemia is likely to be a symptom of severe illness instead of, for example overdosing a loop diuretic. Therefore, hypokalaemia probably only plays a partial role in total hospitalization time.

To our knowledge, this is the longest study to evaluate the effect of a clinical rule-based intervention over time. It is also the first study to use a time series analysis to study the effect of such an intervention. Using a time series analysis corrects for non-stationary means, which could have led to false-positive conclusions in earlier studies.[33] However, the study did not fully meet the recommended criterion of at least 20 observations per data point to attain an acceptable level of variability.[34] One data point, the year 2012, consisted of 15 observations. Nevertheless, no significant difference

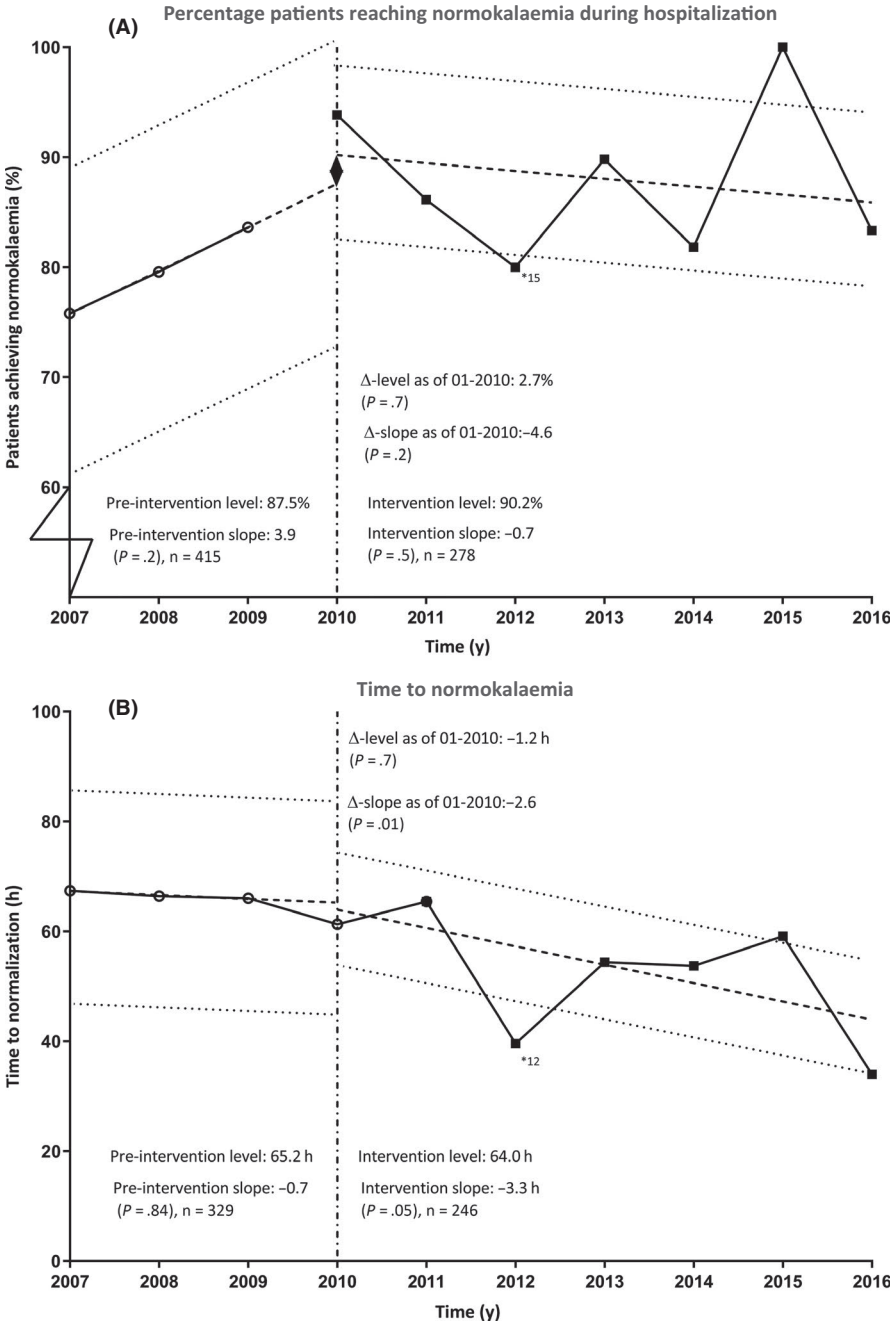

FIGURE 4 A,B, Graphical representation of the data points and segmented regressions using inverse variance-weighted ratios per 12-month period for percentage of patients reaching normokalaemia (Panel A) and time to reach normokalaemia (Panel B). On the x-axis is time; on the y-axis, the respective endpoints. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting the EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point

was observed in the regressions including or excluding this specific data point. Consequently, we assumed that an acceptable level of variability was achieved. The number of observations over time decreased, as seen in Figure 6, causing a large fluctuation in means during the intervention period. The decreasing number of patients could be explained as an effect of the intervention itself or as a sign of overall improvement in care, indicating that hypokalaemia is noticed and treated at an earlier stage.

One of the limitations of this study was its retrospective design. While inferior to prospective design with respect to data collection, preventing bias and so on, ITS design has been accepted as one of the best alternatives in cases where trial design is not an option. Another limitation to this study is not including clinical findings, observed symptoms, EKG findings and cardiac events. Moreover, the current once daily approach can cause significant lag time if SPL is not routinely measured. One option to overcome this limitation is increasing the number of CDSS runs. However, the collected data suggest that the benefit would be minimal because, due to the urgency of the request, response rate and time to stat laboratory orders were already very rapid.

The aim of studying this intervention was to test whether the approach could effectuate an improvement in response time to critical care values in individual patients while minimizing alert fatigue and frustration. While the latter two were not directly measured, a periodic evaluation was performed as part of the regular plan-do-check-act (PDCA) cycle.[35] Among other reasons, physicians positively assessed the intervention because of the negligible number of

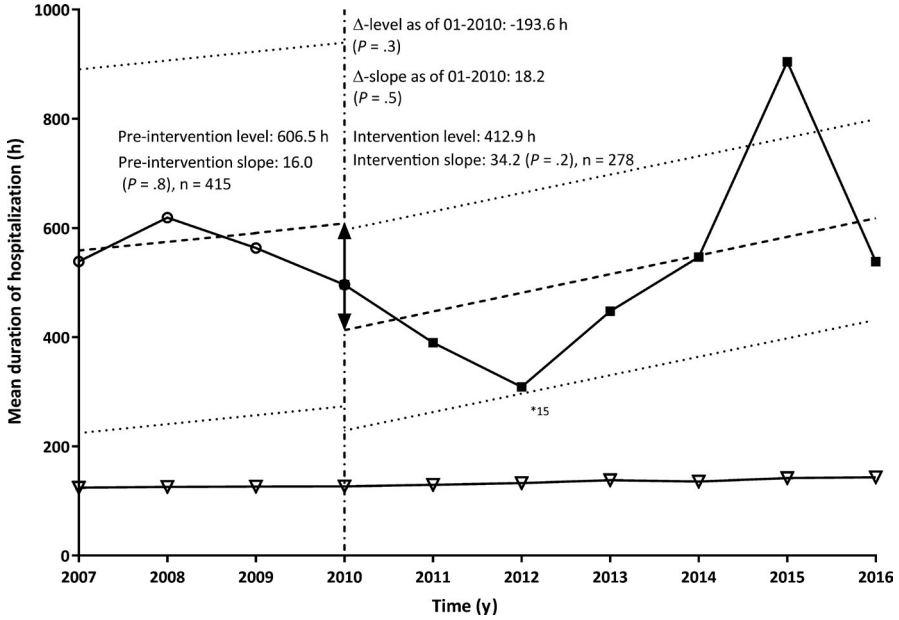

FIGURE 5 Graphical representation of the data points and segmented regressions using inverse variance-weighted ratios per 12-mo period for total duration of hospitalization. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The open rectangles represent the mean hospitalization times for control patients without SPL < 2.9 mmol/L during hospitalization. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting the EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point

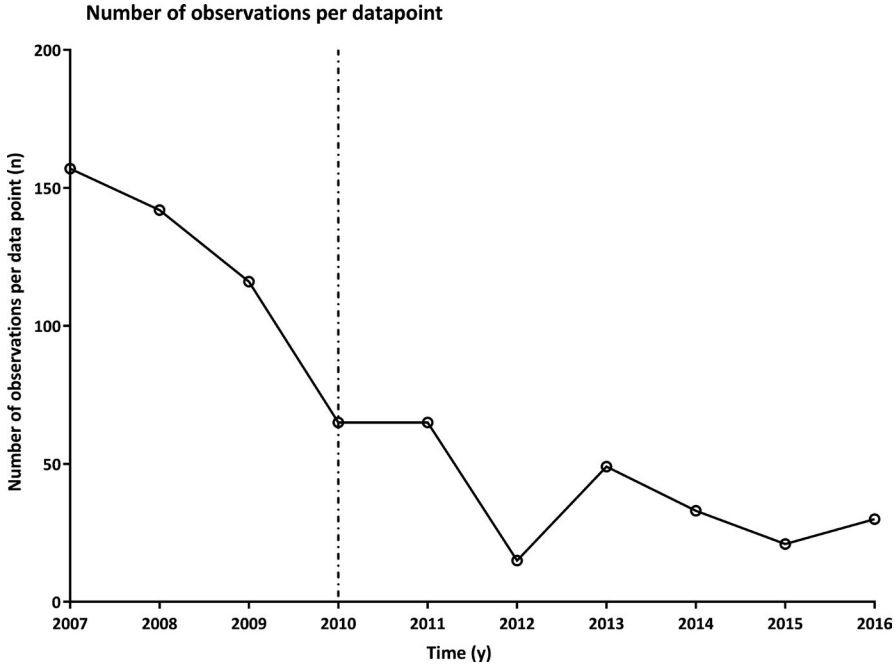

FIGURE 6 Graphical representation of the number of observations per data point included in the analysis. On the x-axis is time; on the y-axis, the number of observations

times they were called. An average of 1.2 calls per week were placed to approximately 20 resident physicians directly involved in clinical care. Acceptance rate was 88%. Based on these evaluations, the hypokalaemia clinical rule was expanded and other clinical rules were added monitoring response to critical care values.

5 | CONCLUSION

Implementation of a clinical rule-guided pharmacists' intervention is possible and produced improvement in response rate and time to prescription. Improvement in time to achieve mild hypokalaemia

suggests that improvement in response rate and time to prescription resulted in measurable improvement in correction of serum level potassium. However, no significant effect was found on percentage and time to normokalaemia or duration of hospitalization.

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REFERENCES

1. Marti G, Schwarz C, Leichtle AB, et al. Etiology and symptoms of severe hypokalemia in emergency department patients. *Eur J Emerg Med*. 2014;21(1):46-51.
2. Paice BJ, Paterson KR, Onyanga-Omara F, et al. Record linkage study of hypokalaemia in hospitalized patients. *Postgrad Med J*. 1986;62(725):187-191.
3. Crop MJ, Hoorn EJ, Lindemans J, et al. Hypokalaemia and subsequent hyperkalaemia in hospitalized patients. *Nephrol Dial Transplant*. 2007;22(12):3471-3477.
4. Schulman M, Narins RG. Hypokalemia and cardiovascular disease. *Am J Cardiol*. 1990;65(10):E4-E9. discussion 22E–23E.
5. Jensen HK, Brabrand M, Vinholt PJ, et al. Hypokalemia in acute medical patients: risk factors and prognosis. *Am J Med*. 2015;128(1):60-67. e61.
6. Kim GH, Han JS. Therapeutic approach to hypokalemia. *Nephron*. 2002;92(Suppl 1):28-32.
7. Pepin J, Shields C. Advances in diagnosis and management of hypokalemic and hyperkalemic emergencies. *Emerg med pract*. 2012;14(2):1-17; quiz 17–18.
8. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA*. 2012;307(2):157-164.
9. Gennari FJ. Hypokalemia. *N Engl J Med*. 1998;339(7):451-458.
10. Kjeldsen K. Hypokalemia and sudden cardiac death. *Exper Clin Cardiol*. 2010;15(4):e96-e99.
11. Alderman MH, Piller LB, Ford CE, et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension*. 2012;59(5):926-933.
12. Suhail AM, Mosin SK, Syed M, et al. Clinical and etiological profile of hypokalemia: a prospective study in a tertiary care hospital. *Clin Med Diagn*. 2017;7(5):107-112.
13. Kardalas E, Paschou SA, Anagnostis P, et al. Hypokalemia: a clinical update. *Endocr Connect*. 2018;7(4):R135-R146.
14. Dutch Association of Internal Medicine (NIV). *Richtlijn elektrolytstoornissen*. In: NIV, ed. Utrecht: NIV; 2012.
15. Kim HJ, Han SW. Therapeutic approach to hyperkalemia. *Nephron*. 2002;92(Suppl 1):33-40.
16. Jordan M, Caesar J. Hypokalaemia: Improving the investigation, management and therapeutic monitoring of hypokalaemic medical inpatients at a district general hospital. *BMJ Qual Improv Rep*. 2015;4(1):u209049.w3670.
17. Paltiel O, Gordon L, Berg D, et al. Effect of a computerized alert on the management of hypokalemia in hospitalized patients. *Arch Intern Med*. 2003;163(2):200-204.
18. Kuperman GJ, Teich JM, Tanasijevic MJ, et al. Improving response to critical laboratory results with automation: results of a randomized controlled trial. *J Am Med Inform Assoc*. 1999;6(6):512-522.
19. Etchells E, Adhikari NK, Cheung C, et al. Real-time clinical alerting: effect of an automated paging system on response time to critical laboratory values–a randomised controlled trial. *Qual Saf Health Care*. 2010;19(2):99-102.
20. Park HI, Min WK, Lee W, et al. Evaluating the short message service alerting system for critical value notification via PDA telephones. *Annals Clin Lab Sci*. 2008;38(2):149-156.
21. Piva E, Sciacovelli L, Zaninotto M, et al. Evaluation of effectiveness of a computerized notification system for reporting critical values. *Am J Clin Pathol*. 2009;131(3):432-441.
22. Tate KE, Gardner RM, Weaver LK. A computerized laboratory alerting system. *MD Comput*. 1990;7(5):296-301.
23. Kilpatrick ES, Holding S. Use of computer terminals on wards to access emergency test results: a retrospective audit. *BMJ*. 2001;322(7294):1101-1103.
24. Segal E, Toderis L, Livingstone D, et al. A computerized alert system for hypokalemia can decrease time to treatment. *Crit Care*. 2005;9(Suppl 1):P410-P410.
25. McCoy AB, Waitman LR, Lewis JB, et al. A framework for evaluating the appropriateness of clinical decision support alerts and responses. *J Am Med Inform Assoc*. 2012;19(3):346-352.
26. Reddy MC, McDonald DW, Pratt W, et al. Technology, work, and information flows: lessons from the implementation of a wireless alert pager system. *J Biomed Inform*. 2005;38(3):229-238.
27. van der Sijs H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc*. 2006;13(2):138-147.
28. Mol PG, Wieringa JE, Nannanpanday PV, et al. Improving compliance with hospital antibiotic guidelines: a time-series intervention analysis. *J Antimicrob Chemother*. 2005;55(4):550-557.
29. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.
30. Durbin J, Watson GS. Testing for serial correlation in least squares regression. II. *Biometrika*. 1951;38(1–2):159-178.
31. Judge GG, Griffiths WE, Hill RC, et al. *The Theory and Practice of Econometrics*. New York: John Wiley & Sons; 1985.
32. Paltiel O, Salakhov E, Ronen I, et al. Management of severe hypokalemia in hospitalized patients: a study of quality of care based on computerized databases. *Arch Intern Med*. 2001;161(8):1089-1095.
33. Verburg HA, Wasylewicz ATM, Vromen ME, et al.Clinical rule reduces time to normalisation of serum potassium level. Paper presented at: NVKFB annual scientific spring meeting 2014; Utrecht.
34. The Cochrane Effective Practice and Organisation of Care Group (EPOC). EPOC Methods Paper Including Interrupted Time Series (ITS) Designs in a EPOC Review. 1998; http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/inttime.pdf. Accessed 24-03-2015.
35. Scheepers-Hoeks AM, Grouls RJ, Neef C, et al. Strategy for implementation and first results of advanced clinical decision support in hospital pharmacy practice. *Stud Health Technol Inform*. 2009;148:142-148.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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