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Performance of Clinical Decision Support Algorithms Related to Renal Drug Dose Adjustments

Master's Thesis

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Abstract

Background

Kidney disease is associated with dosing medication errors (MEs) and potential adverse drug events. Clinical decision support (CDS) algorithms check for appropriate renal drug dose adjustments and can improve patient safety during hospitalisation. Implemented algorithms need to be evaluated to determine how well corresponding renal dosing alerts identify such MEs. The aim was to develop a method to assess the performance of these algorithms in terms of specificity and sensitivity.

Methods

We conducted a retrospective, observational study at the cantonal hospital of Aarau (KSA), a tertiary hospital in Switzerland. Operational key figures of all renal dosing alerts were determined by identifying counts and proportions associated with triggered renal dosing alerts, notifications, and MEs in inpatients. To assess the performance of the algorithms over time, the entire duration of the patients' hospitalisation was taken into account by creating time segments (TSs) in which both alert-triggering parameters, estimated glomerular filtration rate and administration of a study drug, remained identical. The TSs were then categorised in a contingency table to calculate specificity and sensitivity. The method was applied to a selection of seven renal dosing alerts.

Results

In 2022, 13.2% (n = 1’922) of all alerts and 9.9% (n = 472) of all notifications were related to renal dosing, with rivaroxaban and metformin algorithms contributing the most alerts and notifications. The specificity was 100.0% for each analysed alert, while the sensitivity ranged from 45.2% to 100.0%. The algorithm for non-steroidal anti-inflammatory drugs (NSAIDs) had the lowest sensitivity due to an implementation error.

Conclusion

Renal dosing alerts are a central part of the CDS system used at KSA. A method was developed to assess the performance of renal dosing alerts over time. The analysed algorithms are successfully implemented with high specificity. To increase the sensitivity of the NSAIDs alert, adjustments to the technical configuration of the algorithm are required for thorough screening of all relevant medications. Future research could investigate the performance of renal dosing alerts depending on additional parameters and in terms of clinical relevance.

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Introduction

Kidney disease is a major health burden (1). It may be classified by different ranges of glomerular filtration rate (GFR), which describes how many millilitres of blood pass through the glomeruli in one minute, oftentimes normalised on body surface (2,3). A GFR ≥ 90 mL/min/1.73m^2 indicates normal or high kidney function, whereas a GFR < 15 mL/min/1.73m^2 indicates kidney failure and the requirement for dialysis (2,4). GFRs can be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (2). During hospitalisation, blood samples are taken for laboratory determination of creatinine levels and the estimated glomerular filtration rate (eGFR) is calculated as part of routine procedures to assess the renal function (5).

Many drugs and their metabolites are excreted through the kidneys (6). A diminished renal function may lead to accumulation and subsequent adverse drug events (ADEs). Therefore the dose of drugs that are eliminated through the kidneys should be adjusted according to the current renal function (4). According to the definitions of the European Medicines Agency, a medication error (ME) is defined as: "(…) an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient." (7). Thus, the failure to adjust a drug dose to renal impairment constitutes a ME. Recommendations and guidelines for renal dosing have been established and are available, for example, in medicinal product information or as handbooks (2,8). However, the prevalence of non-adherence to these guidelines ranges from 19% to 67% in inpatient settings (9).

Clinical decision support systems (CDSSs) are information systems that can improve clinicians' decision-making processes (10). Combined with computerised physician order entry, these knowledge-based information systems can be used to increase patient safety during hospitalisation (10).

As renal function changes, drug dose adjustments are needed accordingly. CDSSs as medication dosing support can be used as a tool to detect the need for such adjustments. Specifically, they can provide the prescriber with relevant clinical information or knowledge and patient-specific information to identify risk constellations associated with MEs and potential ADEs. These constellations, defined by conditions such as eGFR and prescribed drug dose, are periodically screened for by the CDSS, which checks laboratory values and patient data from electronic medical health records (10). Detected risk constellations are then reported as alerts to clinical safety experts via information systems (11).

However, the use of fully automated CDSSs can lead to alert fatigue (11). Excessive exposure to clinically irrelevant alerts can lead to desensitisation and inappropriate overrides, where alerts are dismissed regardless of their importance (10,12). In particular, high specificity of an implemented CDSS is required to prevent alert fatigue, while a high sensitivity is needed to

ensure that few MEs are missed (13). Specificity can be improved by including further patient and treatment information such as age, weight, other medications, chronology and laboratory values in the assessment of constellations (12). In addition, automatically generated alerts can first be reviewed and evaluated by clinical drug safety experts before being forwarded to prescribers with appropriate recommendations for alternative therapy or dose adjustment (11). In recent years, from 2011 to 2021, CDSS alert research has shifted towards evaluating the efficiency and usability of CDSS alerts and override issues (14). CDSSs as a form of technology can be evaluated in the dimension of system quality (15). One category of system quality is technical performance, which uses ,for example, specificity, sensitivity, accuracy, likelihood ratios and area under the curve to measure validity (15). In contrast, the second category takes clinical relevance into account; the positive predictive value (PPV) and the negative predictive value (NPV) can be used to measure a system's performance in terms of reliability (15,16). It is also common to assess the technical use of a CDSS with the acceptance rate of the CDSS itself or the acceptance rate of recommendations or alerts (15).

In 2021, 50 out of 58 main Swiss hospitals were equipped with a clinical information system (CIS) and 29 out of 49 hospitals with electronic prescribing systems had implemented a CDSS (17). The CDSSs installed in the hospitals target different topics such as drug-drug interactions, duplicate prescriptions, paediatric dosing, etc. However, only five hospitals have implemented a specific CDSS for drug dose adjustment in renal insufficiency (17).

The cantonal hospital of Aarau (KSA) is one of these hospitals, where a customised CDSS was implemented in the hospital's CIS (KISIM by CISTEC AG). The CDSS workflow relevant for this study is shown in Supplementary Figure S1. For this customisation, several algorithms were written for different drugs to describe and specify the conditions of different risk constellations and compiled into a CDSS called MAS (multi-agent system).

By periodically assessing patient information from the electronic health records (EHR), MAS automatically generates alerts when specified conditions are met (18). Clinical pharmacists evaluate the alerts for clinical relevance and notify the prescribing physician if they are deemed relevant. Otherwise, the alerts are either paused or terminated by the clinical pharmacists for a reason such as the alerts are incorrect, not relevant, not accepted or the patient has already been discharged.

The overall goal of MAS is to detect MEs and prevent potential ADEs by identifying risk constellations related to prescribed medications during hospitalisation. The development has primarily aimed to achieve high specificity, while maintaining acceptable sensitivity. The thresholds for defining what is high or acceptable depend on the criticality of the ME to be addressed. The system and workflow of MAS has been described in more detail in a previous

study, where MAS was also evaluated in terms of frequency of alerts and acceptance rates (18).

This study takes a deeper look at the alerts related to renal dosing. In addition to determining descriptive statistics of these alerts, we also developed a method to calculate the specificity and sensitivity of these renal dosing alerts, while taking into account the entire duration of the patients' hospital stay. This method was then applied to a selection of renal drug alerts.

Methods

Study Design

We performed a retrospective analysis of the algorithms that detect MEs related to renal dose adjustments during hospitalisation as an observational cross-sectional study at KSA, a tertiary hospital. The study included all inpatients who received at least one of the study drugs. We defined study drug as a drug of interest that corresponds to an algorithm with individual alerts for renal dose adjustments. At KSA, general consent for further use of health data is obtained at the time of hospital admission by default. Patients who explicitly refused consent or were younger than 18 years of age were excluded from the study. Additionally, patients in the emergency department, intensive and intermediate care unit were excluded since different CISs are used there. The observational period for each algorithm analysed was 01 January 2022 to 31 December 2022. This study was approved by the Ethics Committee of Northwestern and Central Switzerland (Project-ID 2021-01379).

The algorithms of MAS cover a variety of risk constellations, each of which corresponds to an individual alert. All alerts with conditions specified for renal dosing are listed in Table 1. An algorithm may have several renal dosing alerts with different eGFR thresholds for the same drug. The eGFR threshold values for triggering an alert are defined based on medicinal product information or KSA internal guidelines. While some alerts solely require a drug prescription and a renal threshold, other alerts have additional conditions, which were also included in Table 1.

Data Source and Cleaning

During hospitalisation, patient information and health data were collected during routine procedures and stored in KISIM. All patient data used in this analysis had been exported bi-weekly from KISIM during the observational period. To reconstruct the patients' hospital stay with prescribed study drugs, we wrote a script to aggregate, clean and compile all relevant data for each alert analysed. For the assessment of the performance, we used the CKD-EPI equation from 2021 to calculate patients' eGFRs (19). Data on all alerts triggered in the course of 2022 was likewise extracted from the KISIM. The script was written using Jupyter® Notebook (version 6.5.2) with Python™ (version 3.11.1). Supplementary Figure S2 illustrates the process from data sourcing to compiling data into a final data set for data analysis.

Data Analysis

Operational Key Figures

The operational key figures were determined by identifying counts and proportions associated with triggered renal dosing alerts, renal dosing notifications, study drug administrations in inpatients, and renal dosing MEs in inpatients. For this analysis, all individual alerts related to renal dose adjustments were analysed (Table 1). To analyse the source entry data of all alerts triggered in 2022, data aggregation, group operations and all related calculations were performed in Microsoft® Excel® for Microsoft 365 MSO Windows (version 2307).

Specificity and Sensitivity

Time segments

We assessed the performance of the algorithms over the entire duration of hospitalisation. Seven individual renal dosing alerts, marked blue in Table 1, were selected for this analysis. As a patient's renal function can change over time and the MAS screens for risk constellations periodically (once an hour), it was necessary to split the duration of hospitalisation into time segments (TSs). Two main conditions are decisive for the alerts to be triggered: the current eGFR and the current dose of study drugs. We therefore divided the duration of a patient's hospitalisation into TSs where both parameters remained identical. The starting point of the first TS was defined as the eGFR measurement prior to the first study drug administration. The time point of the next eGFR measurement was simultaneously the end point of the previous segment and the starting point of the next segment. If the study drug dose was changed during a TS, the TS was further divided at the time of the first administration of the new dose. In this case, the eGFR value from the preceding eGFR measurement was assigned to this segment. The end point of the final segment was defined as the time point of the last study drug administration. An example for visualisation is shown in Supplementary Figure S3, where the hospitalisation was reconstructed for a patient who received one study drug. For each study drug administered to the same patient, the hospitalisation was reconstructed independently for further analysis.

Contingency Table

TSs in which a study drug administration was documented were retrospectively evaluated to determine whether an alert should have been triggered and whether an alert was triggered at all. Each TS was categorised accordingly in a contingency table. Four different cases were categorised.

- True Positive (TP): There was a ME and an alert was triggered.
- False Positive (FP): There was no ME and an alert was triggered.
- True Negative (TN): There was no ME and no alert was triggered.
- False Positive (FN): There was a ME and no alert was triggered.

With this categorisation, the specificity and sensitivity of each alert were calculated using the appropriate equation shown in Figure 1. All specificity and sensitivity calculations were performed in Excel.

Re-evaluation of FNs and FPs

To take into account the technical properties of MAS, the initial FN and FP results of each alert were reviewed and if needed re-evaluated (overview in Figure 2).

We identified two situations that frequently led to FN results during the initial categorisation and expanded the script to correctly re-evaluate and overwrite these initial FN results. In the first situation, when clinical pharmacists were reviewing alerts for clinical relevance, they could choose to pause an alert for a specified number of days. When an alert was paused, the MAS was set to not trigger the same alert for the specified period. The same applied to alerts marked as not relevant or not accepted, as both were equivalent to pausing an alert for 15 days. Therefore, the initial FN results of TSs within paused time periods were overwritten with TN by the script, as it was technically correct for MAS not to generate further alerts. Similarly, in the second situation, while an alert from a previous TS was still active, MAS was set not to trigger any further alerts. The initial FN results of TSs within an active period were overwritten with TN.

All remaining FN and FP TSs were manually reviewed and re-evaluated, where appropriate e.g. when active or paused alerts covered only a part of a TS, when drug administrations were backdated, or when alerts could not be correctly linked to the TS due to multiple alerts being processed and documented for a patient at the same time. The results of the categorisation for the example provided in Supplementary Figure S3, is shown in Supplementary Table S4 and an example of the final data set can be found in the Appendix (Appendix 1).

Results

Operational Key Figures

In total, the MAS had 19 algorithms capable of triggering 193 individual alerts. Of these, 14 algorithms with 48 individual alerts (24.9%) were related to renal drug dose adjustments (Table 1). In 2022, MAS generated a total of 14'557 alerts, of which 4'757 alerts (32.7%) were forwarded as notifications to the prescribing physicians. Renal dosing alerts accounted for 13.2% (n = 1'922) of all triggered alerts and 9.9% (n = 472) of all notifications. The resulting renal notification rate was 24.6%.

The study drugs most frequently involved in triggered renal dosing alerts were apixaban (n = 455) followed by rivaroxaban (n = 254) and metformin (n = 252) (Table 6). The fewest alerts were generated by the digoxin (n = 1) and dabigatran (n = 8) algorithm (Appendix 2).
Regarding notifications, the most were sent for metformin with an eGFR threshold of 45-60 mL/min/1.73m^2 (n = 48), followed by rivaroxaban at an eGFR threshold of 21-49 mL/min/1.73m^2 (n = 39) and again for metformin at an eGFR threshold of 30-45 mL/min/1.73m^2 (n = 34). For some algorithms, the triggered alerts were never forwarded as notifications. For other algorithms, these alerts were always forwarded. Therefore, the proportion of renal dosing alerts sent as notifications varied greatly, ranging from 0.0% to 100.0%.

Of the selected individual alerts that were further analysed, the apixaban algorithm (eGFR threshold < 15 mL/min/1.73m^2) generated the most alerts with 72 alerts, of which eight alerts were forwarded (11.1%) (Table 2). The most notifications were sent for metformin (eGFR threshold < 30 mL/min/1.73m^2) with 17 alerts forwarded as notifications (54.8%), while 31 alerts were triggered in total (Table 2).

Specificity and Sensitivity

The specificity and sensitivity were calculated for seven individual alerts and listed in Table 3 and descriptive statistics of the patient collective were determined.

First for an overview, we determined the number of patients receiving at least one study drug (from Table 3) and having at least one TS. NSAIDs were the most commonly administered study drug class, with 2'728 patients receiving them, whereas edoxaban was the least commonly administered study drug, with 141 patients receiving it.

Then, the number of patients with at least one ME during hospitalisation was determined. In 2022, a total of 142 patients had at least one study drug-related ME, of which approximately

half (76 patients) had at least one ME related to NSAIDs (eGFR threshold < 30 mL/min/1.73m^2). When comparing across alerts, up to 17.7% of the respective patient collective had at least one study drug-related ME. In the highest case, 25 out of 141 patients treated with edoxaban had administrations at an eGFR > 95 mL/min/1.73m^2.

The specificity for all alerts analysed was 100.0%, while the sensitivity ranged from 45.2% to 100.0%. The NSAID algorithm had the lowest sensitivity. The sensitivity of the edoxaban (eGFR threshold ≤ 15 mL/min/1.73m^2) and rivaroxaban algorithm (eGFR threshold < 15 mL/min/1.73m^2) could not be calculated mathematically due to division by zero.

Discussion

Alerts for renal dose adjustment are a central part of MAS, as the 48 individual renal dosing alerts included in this study represent 23.9% of all detectable risk constellations. Proportionally, renal dosing alerts accounted for only 13.2% of all alerts generated. The algorithms for rivaroxaban and metformin generated the most renal dosing alerts and, consequently, the most notifications. This is not surprising as both study drugs are commonly prescribed; of all the study drugs, only NSAIDs had a larger patient collective.
Some renal dosing alerts, such as those for dabigatran, digoxin or methotrexate, generated very few or no alerts (Appendix 2). If we were to assess the performance and necessity of these alerts, the results would be inconclusive and unreliable. Similarly, this applies to alerts that did not result in a notification to the prescriber. Nevertheless, alerts for drugs that are substantially toxic to patients with renal impairment, such as methotrexate, are necessary as a drug safety measure to ensure patient safety during hospitalisation.
Of all study drugs (Table 1), particularly metformin, methotrexate, enoxaparin, digoxin and NSAIDs should be dose adjusted as their use is contraindicated in patients with renal insufficiency (4,6). Such MEs may remain undetected in a system with low sensitivity and could lead to serious and life-threatening ADEs, e.g. metformin could lead to lactic acidosis, methotrexate could cause myelotoxicity and enoxaparin could provoke haemorrhagic events (4). To increase sensitivity, FNs need to be reduced. However, clinical pharmacists working with an alert system can only review and evaluate TPs and FPs. Therefore, algorithms need to be evaluated in terms of specificity and sensitivity, and the potential for improving the algorithms should be assessed, as in this study for a selection of renal dosing alerts (Table 3).

The specificity for each alert analysed was found to be 100%. Data analysis consistently showed no FP alerts. These results are consistent with the intention to implement MAS with a focus on achieving high specificity combined with acceptable sensitivity. Due to time constraints, only a selection of renal dosing alerts with two decisive parameters (renal function and study drug administration of any predefined dose) were further analysed with specificity and sensitivity calculations. If the remaining alerts were to be analysed in the future, we hope to see similarly high specificity, as they were implemented with the same focus on specificity. However, with additional parameters adding to complexity, the specificity might be decreased if, for example, the calculations of the daily doses as an additional parameter were erroneous.

In contrast, sensitivity varied between the alerts analysed, ranging from 45.2% to 100%. The NSAIDs alert had the lowest sensitivity of 45.2% (Table 3). We discovered that this was due to an implementation error that occurred during the expansion of the algorithm configuration,

where the screening of reserve orders was mistakenly deleted. As a result, MAS did not check NSAIDs reserve medication prescriptions in patients with an eGFR < 30 mL/min/1.73m^2.
The use of NSAIDs is contraindicated in these patients because NSAIDs inhibit the formation of prostaglandins, thereby reducing renal perfusion due to acute vasoconstriction and increasing the risk of acute kidney injury (20,21). Reserve medication prescriptions are only administered as needed, that is, when the patient is in pain. Although the risk of ADEs increases with repetitive inadequate dosing, case reports have shown that a single dose of NSAID can lead to renal failure in susceptible patients (22,23). It is therefore important to include reserve medication prescriptions and the algorithm will be adjusted to include reserve medications in a future update. Findings like this underline the need for studies like ours. With this assessment of the performance by calculating the sensitivity, we were able to detect an implementation error and identify an appropriate solution to improve patient safety during hospitalisation.
At least one edoxaban administration at an eGFR above 95 mL/min/1.73m^2 was found in 17.7% of patients prescribed edoxaban (n = 140). This alert was implemented based on a black box warning issued by the United States Food and Drug Administration (FDA). In patients with nonvalvular atrial fibrillation, patients with a creatinine clearance > 95 mL/min who received edoxaban were observed to have an increased risk of stroke or systemic embolism compared to patients treated with warfarin (24). However, the Swiss medicinal product information does not contain this warning. It is possible that different prescribers at KSA do not recognise this as a ME and therefore consider the alert clinically irrelevant and reject it.
This example demonstrates that despite achieving a high specificity and sensitivity of 100%, MEs still occurred. An explanation can be found in the design of MAS, which acts as a safety net by notifying prescribers with non-interruptive alerts of a prescription that has been valid for more than one hour, rather than interrupting the workflow during the prescribing process as commercially available CDSS often do. However, due to this time lag, MAS sometimes cannot prevent the initial ME from occurring, but it can prevent the recurrence and shorten the duration of MEs as MAS periodically screens for risk constellations. A previous study showed that the implementation of MAS led to a decrease in the mean duration of anticoagulants duplications (25). Apart from ensuring patient safety, these non-interruptive alerts sent to prescribers can act as a reminder or learning tool, which could increase awareness of the need for renal dosing and improve prescribing habits.

A method was developed for this study to assess the performance of a periodically screening CDSS over time by including the entire duration of each patient's hospital stay. By including the duration, the dynamic aspect of renal function could be considered in the assessment.

Some alerts had a calculated specificity and sensitivity of 100% each, which contradicts the expectation that a system implemented in a real-world setting cannot achieve 100% specificity and 100% sensitivity (13). One reason for this may be that the method we developed used retrospective data to recreate an algorithm simulating MAS and therefore could fully not reflect the technical capabilities of MAS. With this focus on technical capability, the developed method could not take into account clinical relevance.

To assess the clinical relevance of alerts, all triggered alerts need to be considered in the analysis. Alerts can be triggered regardless of whether the drug is administered to the patient and should be included in the analysis for clinical relevance as MAS is implemented to trigger alerts based on valid prescriptions and the eGFRs independently calculated by MAS using the CKD-EPI equation from 2009. In comparison, our method used the updated CKD-EPI equation from 2021 and was based on study drug administrations only. We designed the method in this way based on the fact that only study drug that were administered could lead to ADEs. In this regard, we only included TSs in which a study drug administration occurred, and consequently triggered alerts attributed to TSs without any administrations were excluded from our analysis. This method allowed us to give more weight in our analysis to patients with multiple study drug administrations.

Our analysis of the performance was measured by specificity and sensitivity, meaning that this study only addressed validity. To assess the reliability of the algorithms' performance and the clinical relevance of alerts, particularly the PPV and NPV should be used as measures. It is recommended that multiple metrics should be adopted to provide comprehensive understanding and that all types of alerts in a system should be included to provide holistic view of alert usage (14).

There may be alerts that are technically correct but not clinically relevant. Due to the fluid nature of renal function and the unstructured availability of some patient information, the assessment of renal dosing alerts for clinical relevance is ambiguous. The assessment and verification of clinically irrelevant alerts is time consuming and does not increase patient safety. In contrast, these cases contribute to alert fatigue among clinical pharmacists at KSA. To address the aspect of clinical relevance, the assessment of alerts would require consideration of the clinical pharmacist's decisions.

This approach was implemented in a previous study investigating the Triple Whammy algorithm of MAS. An overall specificity of 99.7% and an overall sensitivity of 88.3% was determined (23). The methodology used differs from that of this study and therefore the results are only indirectly comparable.

There are four other Swiss hospitals with CDSS implemented for renal dosing (17). However, there were no comparable studies or results found. Only one study was found describing a similar workflow to KSA and similar use of CDSS with renal dosing alerts for metformin (11).

Limitations

This study comes with several limitations.

Firstly, the data size affects the robustness of the results, especially for study drugs that were rarely administered. For a follow-up study, additional observational periods could be included, or a longer observational period could be set.

Also, the simulation of the MAS with a script has several shortcomings, some of which were already discussed above. The MAS has access to and uses additional data to operate than the data was sourced for this study. For the calculation of eGFR, the script applied the most recent CKD-EPI equation from 2021 while MAS uses the one from 2009. The magnitude of the results were comparable, but the equation used by MAS could be updated to ensure timeliness with current research and guidelines.

Further, the reproduction of the hospitalisation timeline was distorted due to several reasons. Documentations of drug administrations were not always accurate, and this affected the assignment of drug administrations to TSs by the script. In some cases, the actual time point of drug administrations was noted as free-text, but not accessible through structured data. Another reason was found in the design of our method. We did not define a maximum duration of a TS for this analysis which led to TS spanning several days and up to weeks. MAS checks the chronology of obtained eGFR measurements and disregards measurements which are not current.

The manual review of FNs and FPs may be influenced by the reviewer’s viewpoint and goal. For this analysis, the technical aspect of MAS was central. The clinical relevance was only represented by the number of TSs for each patient. Patients with many creatinine measurements and study drug administrations generated more TS, which can be seen as a proxy for the need of surveilling this patient. On the other hand, patients who had no creatinine measurements at all are not included in this approach, while they could still be considered as being at risk for an ADE due to missing information.

Outlook

We were able to design an approach to assess the specificity and sensitivity including the duration throughout the hospital stay of each patient. However, due to time constraints the assessment was only carried out on renal dosing alerts which are triggered based on the renal function and the administration of the study drugs of any dose. The assessment of renal dosing alerts based on the renal function and the predefined daily dose of the study drug to be administered could be developed and conducted in a further study.

The applicability of MAS, which is embedded in KISIM only, is limited at KSA since not all inpatients are always in the same ward and can be transferred to different wards at KSA where

different CIS and computerised physician order entry systems are used. For example, EHR and prescriptions of inpatients in intensive care unit are stored in a different system. A solution would be to initiate harmonisation of the CIS and CDSS at KSA in the long-term.

Conclusion

In conclusion, the analysed MAS algorithms are successfully implemented with a high specificity and renal dosing alerts are a central part of MAS. To increase the sensitivity of algorithms, adjustments to the technical setting are required for thorough screening. A method was developed to assess the performance of renal dosing drug safety alerts over a time period by calculating the specificity and sensitivity. This study could be followed up by further investigation of the performance of renal dosing alert which depend on other additional parameters.

Tables and Figures

Tables

Table 1. All algorithms of MAS generating renal dosing alerts.

Algorithm	Alert identifier	eGFR threshold [mL/min/1.73 m^2]	Other parameters specified by individual alerts		
			Prescription details	Age [years]	Body weight [kg]
Apixaban	2*	Creatinine ≥ 133 μmol/L and eGFR > 15	Daily dose ≥ 10 mg	≥ 80	≤ 60
	4**	Creatinine ≥ 133 μmol/L and eGFR > 15	Daily dose < 10 mg and no platelet aggregation inhibitors excl. heparin	≥ 80	≤ 60
	4b***	Creatinine ≥ 133 μmol/L and eGFR > 15	Daily dose < 10 mg and no platelet aggregation inhibitors excl. heparin	≥ 80	≤ 60
	5	< 15	-	-	-
Dabigatran	2°	< 50 and ≥ 30	Daily dose > 220 mg	< 80	-
	4	≥ 50	Daily dose ≤ 220 mg and no platelet aggregation inhibitors excl. heparin	≥ 80	-
	5	< 30	-	-	-
Edoxaban	2♦	< 50 and > 15	Daily dose > 30 mg	-	≤ 60
	4	≥ 50	Daily dose < 60 mg and no strong P-gp inhibitors and no platelet aggregation inhibitors excl. heparin	-	> 60
	5	≤ 15	-	-	-
	6	> 95	-	-	-

Rivaroxaban	2	< 15	-	-	-
	3	≤ 20 and ≥ 15	-	-	-
	4	< 50 and > 20	Daily dose = 20 mg	-	-
	5	≥ 50	Daily dose = 20 mg and (Clopidogrel and/or ASS)	-	-
	6	< 50 and ≥ 15	Daily dose > 10 mg and daily dose ≤ 20 mg and (Clopidogrel and/or ASS)	-	-
	7	≥ 50	Daily dose = 15 mg and no platelet aggregation inhibitors excl. heparin	-	-
Parenteral Anticoagulants	1	< 16	Fondaparinux and no dialysis	-	-
	2	< 30 and ≥ 16	Fondaparinux daily dose > 1.5 mg and no dialysis	-	-
	4	> 30 or no eGFR	Fondaparinux daily dose ≠ 2.5 mg and fondaparinux daily dose ≠ 5 mg	-	< 50
	5	> 30 or no eGFR	Fondaparinux daily dose ≠ 2.5 mg and fondaparinux daily dose ≠ 7.5 mg	-	≥ 50 and ≤100
	6	> 30 or no eGFR	Fondaparinux daily dose ≠ 2.5 mg and fondaparinux daily dose ≠ 10 mg	-	> 100
	7	< 20	Dalteparin daily dose > 5'000 E. and no dialysis	-	-
	9	< 30	Enoxaparin daily dose > 20 mg and no dialysis Nadroparin daily dose > 0 E. and no dialysis	-	-
Digoxin	4	≤ 50 and ≥20	Daily dose > 0.25 mg	-	-
	5	< 20	-	-	-
Allopurinol	2	< 30	Daily dose > 200 mg	-	-
Febuxostat	2	< 30	Daily dose > 40 mg	-	-

Metformin	1	< 30	-	-	-
	2	≥ 30 and < 45	Daily dose > 1'000 mg	-	-
	3	≥ 45 and < 60	Daily dose > 1'500 mg	-	-
Methotrexate	3	≥ 20 and < 50	Weekly dose > 10 mg	-	-
	4	< 20 or dialysis	Weekly dose > 10 mg	-	-
NSAIDs	2	< 30	-	-	-
	7	≥ 30 and < 45	Daily dose > low daily dose◊	-	-
	8	≥ 45 and < 60	Daily dose > middle daily dose◊	-	-
Vancomycin	1	< 30 or > 20% decreased per day	No dialysis	-	-
Cefepime	1	< 30 or > 20% decreased per day	No dialysis	-	-
	2	< 10 or dialysis	Daily dose > 500 mg	-	-
	3	≥ 10 and < 30	Daily dose > 1'500 mg and no dialysis	-	-
	4	≥ 30 and < 50	Daily dose > 2'000 mg and no dialysis	-	-
Amikacin	2	< 30	No dialysis	-	-
	4	< 30 or > 20% decreased per day	No dialysis	-	-
Gentamicin	2	< 30	No dialysis	-	-
	4	< 30 or > 20% decreased per day	No dialysis	-	-
Triple Whammy	1	< 30	Combinations of diuretics, NSAIDs, ACE inhibitors and/or angiotensin receptor antagonists	-	-

	2	≥ 30 and < 60	Combinations of diuretics, NSAIDs, ACE inhibitors and/or angiotensin receptor antagonists	-	-
	3	> 60	Combinations of diuretics, NSAIDs, ACE inhibitors and/or angiotensin receptor antagonists	> 75	-

For some of the individual alerts, in addition to the eGFR threshold, other parameters are specified as conditions. Those conditions are presented here, an '–' indicated that no further conditions were specified. Alerts selected for further evaluation are coloured blue. NSAIDs is specified as a drug class which consists of diclofenac, indomethacin, etodolac, ketorolac, acemetacin, piroxicam, tenoxicam, ibuprofen, naproxen, naproxen sodium, dexketoprofen, dexibuprofen, mefenamic acid, etoricoxib, celecoxib, nimesulide and acetylsalicylic acid (ASS). ACE: angiotensin-converting-enzyme.

* Daily dose ≥ 10 mg and at least two of the other three criteria.
** Daily dose ≥ 10 mg and none of the three criteria.
*** Daily dose < 10 mg and one of the three other criteria.
° Daily dose > 220 mg and at least one of the other two criteria.
♦ Daily dose > 30 mg and at least one of the other two criteria.
◊ Doses according to active ingredient specified in KSA internal dosing guidelines.

Table 2. Triggered and processed renal dosing alerts in 2022.

Algorithm	Alert identifier	Triggered alerts [n]	Notifications sent [n]	Clinically irrelevant alerts [n]	Alerts terminated by MAS [n]	Notification rate [%]
Apixaban	5	72	8	46	18	11.1
Edoxaban	5	7	3	1	3	42.9
	6	34	4	23	7	11.8
Rivaroxaban	2	1	1	0	0	100.0
	3	8	2	1	5	25.0
Metformin	1	31	17	4	10	54.8
NSAIDs	2	23	5	6	12	21.7
[…]	[…]	[…]	[…]	[…]	[…]	[…]
All algorithms*	All renal dosing alerts	1922	472	895	555	24.6

The results of seven renal dosing algorithms that were further analysed in specificity and sensitivity assessments are listed in detail. The algorithms with the alert identifier are referenced in Table 1. The cumulated statistics for all renal dosing alerts in Table 1 are displayed at the bottom. The extensive table with all results is provided in the Appendix (Appendix 2). Clinically irrelevant alerts include all alerts that were paused, classified as not relevant or incorrect, not accepted by the prescriber (previous notification to the prescriber was not accepted) or reviewed as irrelevant because the patient had already been discharged. MAS: multi-agent system.

Table 3. Specificity and sensitivity of analysed renal dosing alerts.

Algorithm	eGFR threshold [mL/min/1.73m^2]	Patients with at least one study drug administration and TS [n]	Patients with at least one ME [n]	Specificity [%]	Sensitivity [%]
Apixaban	< 15	543	26 (4.8%)	100.0	95.5
Edoxaban	≤ 15	141	0 (0.0%)	100.0	Incalculable
	> 95		25 (17.7%)	100.0	100.0
Rivaroxaban	< 15	592	0 (0.0%)	100.0	Incalculable
	≥ 15 and ≤ 20		2 (0.3%)	100.0	100.0
Metformin	< 30	781	13 (1.7%)	100.0	100.0
NSAIDs	< 30	2728	76 (2.8%)	100.0	45.2

The specificity and sensitivity of seven selected renal dosing alerts was calculated and descriptive statistics on patient collective were determined. eGFR: estimated glomerular filtration rate. TS: time segment. ME: medication error.

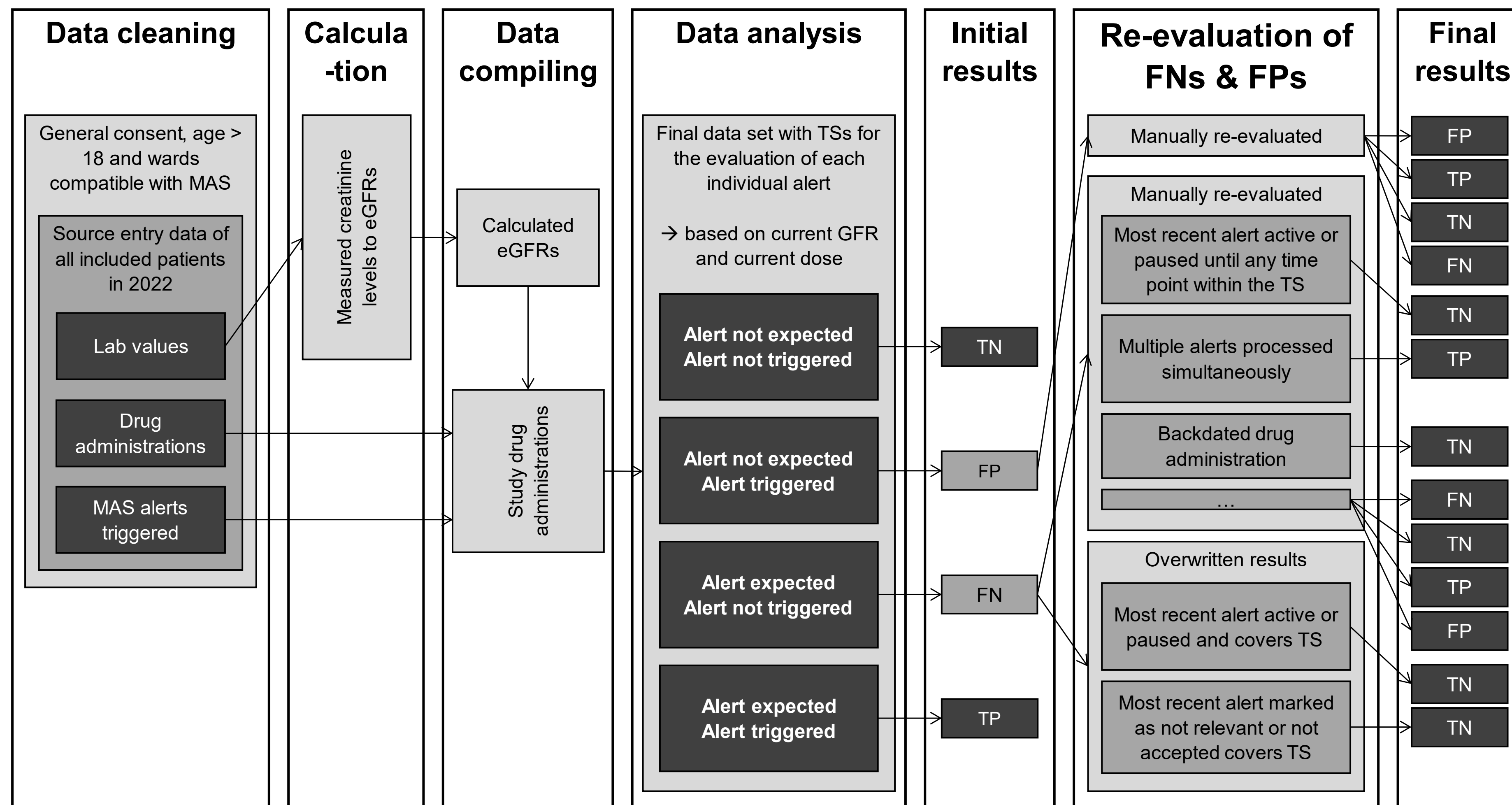
Figures

Figure 1. Contingency table.

	ME	**No ME**	
Alert triggered	True Positive (TP)	False Positive (FP)	
No alert triggered	False Negative (FN)	True Negative (TN)	
	➔ **Sensitivity** = TP / (TP + FN)	➔ **Specificity** = TN / (TN + FP)	Total number of TSs

Contingency table with renal dosing medication error (ME) as the condition observed according to the python script (used as reference standard) and alert triggered by MAS as the test outcome. Adapted from (26). TS: time segment.

Figure 2. Overview of the method developed to determine sensitivity and specificity.



The process from data cleaning to data analysis (compare Supplementary Figure S2) is included of the left for context. Then a decision chart of the categorisation process of each time segment (TS) was developed, with a further re-evaluation of initial false positive (FP) and false negative (FN) results. The final categorisation is depicted in the column on the right. Lab: laboratory. MAS: multi-agent system. eGFR: estimated glomerular filtration rate. TN: true negative. TP: true positive.

References

1. Forni Ogna V, Ogna A, Ponte B, Gabutti L, Binet I, Conen D, et al. Prevalence and determinants of chronic kidney disease in the Swiss population. Swiss Med Wkly. 2016 Apr;146(1718 SE-Original article):w14313.
2. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct;100(4):S1–276.
3. Tarwater K. Estimated glomerular filtration rate explained. Mo Med. 2011;108(1):29–32.
4. Hartmann B, Czock D, Keller F. Arzneimitteltherapie bei patienten mit chronischem nierenversagen. Dtsch Arztebl. 2010 Sep 17;107(37):647–56.
5. Inker LA, Titan S. Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021. Am J Kidney Dis. 2021 Nov;78(5):736–49.
6. Keller F. KAPITEL 17 - Nephrotoxische Störungen und nierenabhängige Arzneimittel. In: Risler T, Kühn KBT-FN, editors. Munich: Urban & Fischer; 2008. p. 891–960.
7. Medication errors | European Medicines Agency [Internet]. [cited 2023 Mar 14]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medication-errors
8. Ashley C, Currie A. The Renal Drug Handbook Third EdiTion. 2009;
9. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with Dosing Guidelines in Patients with Chronic Kidney Disease. http://dx.doi.org/101345/aph1D399 [Internet]. 2004 May 1 [cited 2023 May 30];38(5):853–8. Available from: https://journals.sagepub.com/doi/10.1345/aph.1D399
10. Beeler PE, Bates DW, Hug BL. Clinical decision support systems. Swiss Med Wkly [Internet]. 2014 Dec 15 [cited 2023 Mar 2];144(5152):w14073–w14073. Available from: https://smw.ch/index.php/smw/article/view/1954/2788
11. Niedrig D, Krattinger R, Jödicke A, Gött C, Bucklar G, Russmann S. Development, implementation and outcome analysis of semi-automated alerts for metformin dose adjustment in hospitalized patients with renal impairment. Pharmacoepidemiol Drug Saf [Internet]. 2016 Oct 1 [cited 2023 Mar 15];25(10):1204–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4062
12. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. npj Digit Med 2020 31 [Internet]. 2020 Feb 6 [cited 2023 Mar 2];3(1):1–10. Available from: https://www.nature.com/articles/s41746-020-0221-y
13. Poly TN, Islam MM, Yang HC, Li YCJ. Appropriateness of Overridden Alerts in Computerized Physician Order Entry: Systematic Review. JMIR Med Inf 2020;8(7)e15653 https//medinform.jmir.org/2020/7/e15653 [Internet]. 2020 Jul 20 [cited 2023 Mar 2];8(7):e15653. Available from: https://medinform.jmir.org/2020/7/e15653
14. Chien S-C, Chen Y-L, Chien C-H, Chin Y-P, Yoon CH, Chen C-Y, et al. Alerts in Clinical Decision Support Systems (CDSS): A Bibliometric Review and Content Analysis. Healthc (Basel, Switzerland) [Internet]. 2022 Mar 23 [cited 2023 Jun 6];10(4). Available from: http://www.ncbi.nlm.nih.gov/pubmed/35455779
15. Ji M, Yu G, Xi H, Xu T, Qin Y. Measures of success of computerized clinical decision

support systems: An overview of systematic reviews. Heal Policy Technol [Internet]. 2021;10(1):196–208. Available from: https://www.sciencedirect.com/science/article/pii/S221188372030126X

16. Damoiseaux-Volman BA, Medlock S, van der Meulen DM, de Boer J, Romijn JA, van der Velde N, et al. Clinical validation of clinical decision support systems for medication review: A scoping review. Br J Clin Pharmacol [Internet]. 2022 May 1 [cited 2023 Jun 16];88(5):2035–51. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bcp.15160

17. Vonbach P, Lutters M, Waldispühl Suter B, Voirol P, Higi L, Hufschmid Thurnherr E. Digitalisation of the drug prescribing process in Swiss hospitals – results of a survey. Eur J Hosp Pharm [Internet]. 2022 Nov 1 [cited 2023 Mar 2]; Available from: https://ejhp.bmj.com/content/early/2022/11/01/ejhpharm-2022-003491

18. Dahmke H, Fiumefreddo R, Schuetz P, De Iaco R, Zaugg C. Tackling alert fatigue with a semi-automated clinical decision support system: quantitative evaluation and end-user survey. Swiss Med Wkly [Internet]. 2023 Jul 7;153(7):40082. Available from: https://www.smw.ch/index.php/smw/article/view/3357

19. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. N Engl J Med [Internet]. 2021 Nov 4 [cited 2023 May 2];385(19):1737–49. Available from: https://www.nejm.org/doi/10.1056/NEJMoa2102953

20. Baker M, Perazella MA. NSAIDs in CKD: Are They Safe? Am J Kidney Dis. 2020 Oct;76(4):546–57.

21. Lucas GNC, Leitão ACC, Alencar RL, Xavier RMF, Daher EDF, Silva GB da. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. Vol. 41, Brazilian Journal of Nephrology. scielo ; 2019.

22. Drożdżal S, Lechowicz K, Szostak B, Rosik J, Kotfis K, Machoy-Mokrzyńska A, et al. Kidney damage from nonsteroidal anti-inflammatory drugs—Myth or truth? Review of selected literature. Pharmacol Res Perspect. 2021 Aug;9(4):e00817.

23. Schelshorn JS. MASTER THESIS Awarding the academic title of Evaluation of a drug therapy safety algorithm for the detection of Triple Whammy prescriptions in inpatients at risk of acute kidney injury.

24. de Groot JR, Ruff CT, Murphy SA, Hamershock RA, Vehmeijer JT, Oude Ophuis AJM, et al. Edoxaban versus warfarin in patients with atrial fibrillation in relation to the risk of stroke: A secondary analysis of the ENGAGE AF-TIMI 48 study. Am Heart J. 2021;235:132–9.

25. Zurich E, Stoop SC, Lutters NM, Zaugg C. Evaluation of Clinical Decision Support Systems to Detect Anticoagulant Duplications.

26. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. Front Public Heal. 2017 Nov 20;5:308890.

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Appendix

Appendix 1. Structure of the final data set for each alert.

Patient number	eGFR	Start TS	End TS	Number of drug administrations	Product name and dose	Amount of product	Alert expected?	Number of alerts triggered	Initial result
Integer	Decimal number	Date and time	Date and time	Integer	Drug product name with dose	Integer or decimal number	True or false	Integer	TP or FP or TN or FN

Appendix 1. (continued).

[…]	Alert paused or active?	Overwritten result	Manual re-evaluation of FNs or FPs	Review category of re-evaluation
[…]	True or false	TP or FP or TN or FN	TP or FP or TN or FN	Reason for correction

The script used for data analysis was not included because it contained patient-specific data. eGFR: estimated glomerular filtration rate. TS: time segment. TP: true positive. FP: false positive. TN: true negative. FN: false negative.

Appendix 2. All triggered and processed renal dosing alerts in 2022.

Algorithm or study drug◊	Alert identifier	eGFR threshold [mL/min/1.73 m^2]	Triggered alerts [n]	Notifications sent [n]	Clinicaclly irrelevant alerts [n]	Alerts terminated by MAS [n]	Notification rate for prescriber [%]	Notification rate for clinical pharmacist [%]
Apixaban	2	Creatinine ≥ 133 µmol/L and eGFR > 15	18	11	4	3	61.1	73.3
	4b	Creatinine ≥ 133 µmol/L and eGFR > 15	124	9	83	32	7.3	9.8

	4	Creatinine ≥ 133 µmol/L and eGFR > 15	241	21	158	62	8.7	11.7
	5	< 15	72	8	46	18	11.1	14.8
Apixaban in total	-	-	455	49	291	115	10.8	14.4
Dabigatran	2	< 50 and ≥ 30	0	0	0	0	0	0
	4	≥ 50	8	0	5	3	#DIV/0!	#DIV/0!
	5	< 30	0	0	0	0	#DIV/0!	#DIV/0!
Dabigatran in total	-	-	8	0	5	3	0	0
Edoxaban	2	< 50 and > 15	29	13	10	6	44.8	56.5
	4	≥ 50	59	11	41	7	18.6	21.2
	5	≤ 15	7	3	1	3	42.9	75
	6	> 95	34	4	23	7	11.8	14.8
Edoxaban in total	-	-	129	31	75	23	24	29.2
Rivaroxaban	2	< 15	1	1	0	0	100	100
	3	≤ 29 and ≥ 15	8	2	1	5	25	66.7
	4	< 50 and > 20	106	39	35	32	36.8	52.7
	5	≥ 50	3	0	2	1	0	0
	6	< 50 and ≥ 15	6	3	2	1	50	60
	7	≥ 50	130	18	85	27	13.8	17.5
Rivaroxaban in total	-	-	254	63	125	66	24.8	33.5
Fondaparinux ◊	1	< 16	3	2	0	1	66.7	100
	2	< 30 and ≥ 16	31	11	16	4	35.5	40.7
	4	> 30 or no eGFR	2	0	2	0	0	0
	5	> 30 or no eGFR	13	0	2	11	0	0
	6	> 30 or no eGFR	6	3	1	2	50	75
Fondaparinux◊ in total	-	-	55	16	21	18	29.1	43.2
Dalteparin◊	7	< 20	93	24	40	29	25.8	37.5
Dalteparin in total	-	-	93	24	40	29	25.8	37.5

Enoxaparin◊ (& Nadroparin◊)	9	< 30	2	2	0	0	100	100
Enoxaparin◊ & Nadroparin◊ in total	-	-	2	2	0	0	100	100
Parenteral anticoagulants in total	-	-	150	42	61	47	28	40.8
Digoxin	4	≤ 50 and ≥ 20	1	0	1	0	0	0
	5	< 20	0	0	0	0	#DIV/0!	#DIV/0!
Digoxin in total	-	-	1	0	1	0	0	0
Allopurinol◊	2	< 30	101	17	67	17	16.8	20.2
Febuxostat◊	2	< 30	12	3	8	1	25	27.3
Xanthinoxidase inhibitors in total	-	-	113	20	75	18	17.7	21.1
Metformin	1	< 30	31	17	4	10	54.8	81
	2	≥ 30 and < 45	69	34	9	26	49.3	79.1
	3	≥ 45 and < 60	152	48	62	42	31.6	43.6
Metformin in total	-	-	252	99	75	78	39.3	56.9
Methotrexate	3	≥ 20 and < 50	19	2	15	2	10.5	11.8
	4	< 20 or dialysis	0	0	0	0	#DIV/0!	#DIV/0!
Methotrexate in total	-	-	19	2	15	2	10.5	11.8
NSAIDs	2	< 30	23	5	6	12	21.7	45.5
	7	≥ 30 and < 45	26	12	6	8	46.2	66.7
	8	≥ 45 and < 60	148	31	42	75	20.9	42.5
NSAIDs in total	-	-	197	48	54	95	24.4	47.1
Vancomycin	1	< 30 or > 20% decreased per day	11	4	2	5	36.4	66.7
Vancomycin in total	-	-	11	4	2	5	36.4	66.7
Cefepime	1	< 30 or > 20% decreased per day	12	5	2	5	41.7	71.4

	2	< 10 or dialysis	3	0	3	0	0	0
	3	≥ 10 and < 30	21	4	11	6	19	26.7
	4	≥ 30 and < 50	64	14	27	23	21.9	34.1
Cefepime in total	-	-	100	23	43	34	23	34.8
Amikacin◊	2	< 30	0	0	0	0	#DIV/0!	#DIV/0!
	4	< 30 or > 20% decreased per day	0	0	0	0	#DIV/0!	#DIV/0!
Gentamicin◊	2	< 30	0	0	0	0	#DIV/0!	#DIV/0!
	4	< 30 or > 20% decreased per day	0	0	0	0	#DIV/0!	#DIV/0!
Aminoglycosides in total	-	-	0	0	0	0	#DIV/0!	#DIV/0!
Triple Whammy	1	< 30	37	19	10	8	51.4	65.5
	2	≥ 30 and < 60	118	42	31	45	35.6	57.5
	3	> 60	78	30	32	16	38.5	48.4
Triple Whammy in total	-	-	233	91	73	69	39.1	55.5
All algorithms	All renal dosing alerts	-	1922	472	895	555	24.6	34.5

All The additional parameters for each alert are listed in Table 1. eGFR: estimated glomerular filtration rate. MAS: multi-agent system. #DIV/0: Incalculabe.