

Development and implementation of a new method for medication monitoring of eGFR-signals in Dutch community pharmacies

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Abstract

Introduction – An important aspect of optimising pharmacotherapy is correct dosing of drugs. Dose management is especially essential in people with chronic kidney disease (CKD), as an earlier study showed that 10% of medication-related hospital admissions were related to renal impairment and medication errors. Individual patient characteristics are currently insufficiently used in computerized generation of medication monitoring signals (classical monitoring, CM) for people with CKD. The objective of this study was to improve efficiency and specificity of medication monitoring in renal impaired patients. To achieve this, a new method of monitoring (reassessment-oriented monitoring, ROM) was compared to CM.

Methods – ROM was implemented in three community pharmacies and consisted of two components: I. monitoring incoming renal function values (eGFR-values) of patients and II. an adapted signal list of CM. Over the period of October, November and December 2021 generated signals following both methods were collected and merged into one dataset. Possible overlaps were identified. Subsequently, all signals were assessed as "(potentially) actionable" or "not actionable". To avoid arbitrary classification, signals were classified based on eGFR-values linked to advisory texts for drugs requiring caution in case of reduced renal function. The results were then compared to the currently used system of CM.

Results – In total 10,276 unique signals were generated. 9892 and 3158 signals were generated by CM and ROM, respectively. As a result, ROM has led to a reduction in the signal load of 68.1%. Sensitivity was determined at 98.9% for CM and 100.0% for ROM. For CM a specificity of 4.6% was calculated, as for ROM specificity was determined at 91.3%.

Discussion – The introduction of ROM led to a substantial decrease in signal load. In this context it is important to note that sensitivity did not reduce, whereas specificity strongly improved from 4.6% up to more than 90%. Based on this data, ROM has added value for medication monitoring of renal function signals in Dutch community pharmacies. The level of impact does depend on several conditions, however, and further research into other aspects regarding this method of monitoring is recommended.

1. Introduction

Chronic kidney disease (CKD) has developed into one of the major health issues in our population, with a prevalence of approximately 11% to 13%. In the coming years, the number of patients with reduced renal function will increase as a result of the ageing population and the growing amount of people diagnosed with diabetes and hypertension (1-3). The expanding population of elderly will lead to more complex medical problems. This can be attributed to a higher number of morbidities with which a patient is diagnosed and subsequent concurrent use of several drugs. A multidisciplinary approach is necessary in order to optimise therapy and thus reduce morbidity and mortality (3).

Pharmacists have an important role in the context of medication optimisation. As the pharmacists' specialized perspective can contribute to medication safety of patients, an active role can be assigned to pharmacists regarding optimisation of individual drug therapy. One important aspect of optimising therapy and monitoring medication safety is dose management (4). Dose management is especially essential in people with CKD as reduction in kidney function often leads to an alteration in pharmacokinetics (PK) and pharmacodynamics (PD). It is known that alteration in PK and PD influences the safety and efficacy of medication and people with CKD are at high risk for medication-related issues as a result of multi-drug use (5).

Leendertse et al. concluded that 10% of medication-related hospital admissions were related to renal impairment and medication errors, which might be prevented by correcting pharmacotherapy for renal function (6). In combination with the observation that the availability of patients' renal function data in community pharmacies is not sufficient for medication monitoring, dose management in renal impaired patients requires attention (7).

An important limitation of the current system of medication monitoring (classical monitoring, CM) in community pharmacies is the fact that medication alerts are generated by the computer at the moment a drug prescription is imported in the Clinical Decision Support System (CDSS) and do not take into account individual patient characteristics (e.g. renal function). This results in a high amount of signals that have to be manually assessed and handled by the healthcare professional. However, by the implementation of laboratory values, a CDSS provides improved monitoring for possible adverse drug events (ADEs) (8,9). Additionally, by using a more advanced CDSS, in which more patient characteristics are added, more clinically relevant signals are detected. Several studies acknowledge the fact that an advanced CDSS would reduce the amount of irrelevant alerts generated by the current systems of medication monitoring (10,11). Thereby, it is important to realise that in classical monitoring every time a prescription is entered in the CDSS, an alert is triggered. The only way to avoid signalling is if a pharmacist manually suppresses certain signals (10). Creating a situation in which an alert is only generated when reassessment is necessary, would increase effectivity and reduce possible alert fatigue. Ancker et al. suggested that a reduction in repeated alerts is a potential solution for alert fatigue and alert overrides (12).

The Royal Dutch Pharmacists Association (in Dutch: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP) is the organisation in the Netherlands responsible for the development and maintenance of clinical rules. The organisation aims to make the transition from CM to clinical rules in the coming period, ultimately reducing the number of irrelevant signals. Signalling for these clinical rules is realised through drug-specific flow

charts. For medication monitoring related to kidney function, these clinical rules combine specified cut-off points for each drug with information about a patients' renal function (estimated glomerular filtration rate, eGFR). A signal is then only generated if a drug is to be dispensed and a patients' eGFR-value is below the cut-off point or if renal function is unknown or not recent (13).

Moreover, an incoming eGFR-value can also be crucial for therapy adjustment. Monitoring incoming eGFR-values can provide the opportunity to intervene before the next dispensing takes place. Monitoring incoming eGFR-values can therefore be important for reassessing and optimising medication therapy. To date, no such approach has been integrated into the current system.

The objective of this study was to improve efficiency and specificity of medication monitoring in renal impaired patients. To achieve this, a new method of monitoring (reassessment-oriented monitoring, ROM) was developed which combined both the clinical rule structure of the KNMP and monitoring on incoming eGFR-values. It was implemented in three community pharmacies in Amsterdam, the Netherlands. The results were then compared to the currently used system of CM.

2. Methods

2.1 Study setting

A retrospective, comparative study was conducted in three community pharmacies based in Amsterdam, the Netherlands. The pharmacies had a total patient base of approximately 20,000 patients.

2.2 Systems of monitoring

2.2.1 Classical Monitoring (CM)

The software system of CompuGroup Medical Nederland B.V. "CGM Apotheek" (CGMA) is used in this study. CGMA is a pharmacy information system which contributes to clinical decision support. The system is commonly known in the Netherlands and is being used in 479 pharmacies in the Netherlands. CompuGroup Medical Nederland also makes software available to general practitioners and develops tools for patients as well.

The system is based on the Dutch G-standard. The G-standard contains information on all healthcare products (including drugs) registered in the Netherlands and is monitored and updated by the company Z-index. The database is not only used by pharmacists, but also by other healthcare professionals (14).

When a drug, which requires caution in case of reduced renal function, is entered into the system, a signal is generated each time, if:

- a patient's age is ≥ 70 years
- the contraindication "reduced renal function" is registered in the patient's file

The system provides recommendations on how to deal with the signal. However, assessment of each signal is required by a pharmacist. Depending on the judgement of the pharmacist, signals can be suppressed for a certain time until prescription changes.

2.2.2 Reassessment-Oriented Monitoring (ROM)

The set-up of ROM is based on two components: I. incoming eGFR-values of patients and II. an adapted signal list, containing alerts of CM and focusing on mutations (first dispenses of drugs, dose changes), but also generating absence alerts in case of missing a recent eGFR-value. For the development and implementation of ROM the Business Intelligence (BI) application Crystal Reports 2016 v14.2.7.3069 was used.

I. Monitoring on Lab Value (MoL)

Goal: Medication monitoring on incoming eGFR-values.

In different steps a query was formulated and implemented in BI Software Crystal Reports with regard to incoming eGFR-values.

Step 1: Consult guidelines and literature for setting up clinical rule.

The definition of impaired renal function is based on an advisory document on kidney function of the KNMP (15). The criteria for alerting were mainly derived from this document and partly formulated to ensure sensitivity. A signal should be generated after an incoming eGFR-value, if:

- A. a decline in eGFR of $>3 \text{ ml/min/1,73 m}^2$ in the preceding 365 days took place
- B. an incoming eGFR-value $<60 \text{ ml/min/1,73 m}^2$ is registered and no other eGFR-value in the preceding 365 days is registered
- C. the eGFR-value is below $<10, 30$ or $50 \text{ ml/min/1,73 m}^2$ for the first time

Step 2: Query in Crystal Reports

Based on the guidelines and literature in step 1, a query was formulated for MoL. The query generated a report every day with all incoming alerts from the different categories of MoL. The report also includes a graph showing the development of the eGFR over time. An up-to-date medication overview is also included. An example of a report can be found in *Appendix I*.

Step 3: Trial period with MoL query

A trial period took place over a course of 1.5 months. Daily reports were viewed and assessed. Potential improvements were also noted and implemented as far as possible. These mainly concerned the presentation of the signals on the reports. This trial period also demonstrated that with the MoL query alone, not all relevant signals would be detected. An adjustment of CM was needed.

II. Adjusted CM (aCM)

As MoL had the incoming eGFR-value as its starting point, certain prescription-initiated signals would be missed with MoL alone. This led to the introduction and addition of aCM. aCM is a modified version of the query that leads to the signal list for CM. A report was generated every day. When a drug, which requires caution in case of reduced renal function, is entered into CGMA, an alert is generated by aCM, if a signal was generated by CM and:

- the drug is dispensed for the first time in 365 days
- the last eGFR-value is older than 365 days or unknown
- the last eGFR-value falls into the range requiring dose adjustment for this particular drug

In addition, a selection of the 181 most common renal function signals in CM has been made. Of these medicines, various cut-off values have been linked to KNMP advisory texts for use in patients with reduced renal function (16). These advisory texts are displayed with the alerts.

2.3 Data handling

Anonymised patient data was used for this study. All generated signals of CM and ROM in October, November and December 2021 were merged into one dataset. Same alerts could be generated multiple times by CM, MoL and/or aCM. For an adequate comparison, it is important to identify possible overlaps. The alerts were therefore divided into different subgroups regarding their appearance via CM, MoL and/or aCM.

Subsequently, the signals were assessed per subcategory as "(potentially) actionable" or "not actionable". Actionable is defined as a signal requiring an action by the pharmacist. To avoid arbitrary classification, signals were classified based on eGFR-values linked to the advisory texts for drugs requiring caution in case of reduced renal function (16). Whenever the advice "no action required" was linked to signals, signals were classified as "not actionable". All other signals were considered to be "(potentially) actionable".

2.4 Analysis

Signals were excluded from analysis as the signalling decision tree, according to the G-Standard, marked an alert as "never actionable". All other signals were included for analysis.

Primary outcomes of the study were the reduction in signal load, the reduction of false positive (FP) signals and the proportion of true positive (sensitivity) as well as true negative (specificity) signals. The sensitivity, the ability of a method to identify true positive signals, was determined for both methods following the formula for the true positive rate (TPR):

$$TPR = \frac{\text{True Positive Signals (TP)}}{\text{True Positive Signals (TP)} + \text{False Negative Signals (FN)}}$$

The specificity of both methods, the ability to identify true negative signals, was determined following the formula for the true negative rate (TNR):

$$TNR = \frac{\text{True Negative Signals (TN)}}{\text{True Negative Signals (TN)} + \text{False Positive Signals (FP)}}$$

As secondary outcome the number and proportion of signals in which an absence alert for a recent eGFR-value was generated was determined.

The data were analysed using Microsoft Excel 2021, Microsoft Access 2021 and IBM SPSS Statistics version 28.

3. Results

In the fourth quarter of 2021, a total of 10,276 unique signals were generated by CM and ROM in 1395 different patients. Their mean age was 75.8 years and 52.3% were female. The number of patients and signals varied among pharmacies, with pharmacy 1 having the largest contribution with 44.4% of patients and 42.5% of the alerts (**Table 1**).

Table 1
Dataset characteristics.

Total	N
Unique patients	1395
Unique signals	10,276
Gender	n (%)
Male	666 (47.7)
Female	729 (52.3)
Age (Years)	
Mean	75.8
Minimum	17
Maximum	99
Std. Deviation	8.9
Patients per pharmacy	n (%)
Pharmacy 1	620 (44.4)
Pharmacy 2	473 (33.9)
Pharmacy 3	302 (21.7)
Signals per pharmacy	n (%)
Pharmacy 1	4365 (42.5)
Pharmacy 2	3727 (36.3)
Pharmacy 3	2184 (21.3)

The total number of signals generated amounted 9892 in CM and 3158 in ROM. Therefore, a reduction of 68.1% in signal load was achieved by using ROM. The proportion of TP or "(potentially) actionable" signals was 24.8% in CM compared with 78.6% in ROM. This implies a reduction of 6772 FP or "not actionable" signals. This finding corresponds to a 90.9% reduction of FP (irrelevant) signals, when using ROM instead of CM (**Table 2, Figure 1**). A TPR (sensitivity) was determined at 98.9% and 100.0% for CM and ROM, respectively. For CM a TNR (specificity) of 4.6% was calculated, as for ROM specificity was determined at 91.3% (**Figure 2**).

Table 2

Generated signals in CM versus ROM.

	CM	ROM	Difference	Difference in %
Total number of signals generated	9892	3158	-6734	-68.1%
Total number of TP signals (%)	2455 (24.8%)	2483 (78.6%)	28	1.1%
Total number of FP signals (%)	7437 (75.2%)	675 (21.4%)	-6772	-90.9%
Total number of TN signals	356	7118	6772	1899.4%
Total number of FN signals	28	0	-28	-

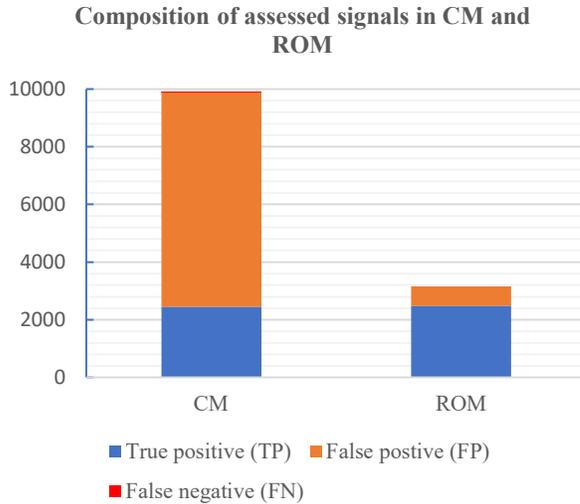


Figure 1. Bar graph of assessed signals in CM and ROM.

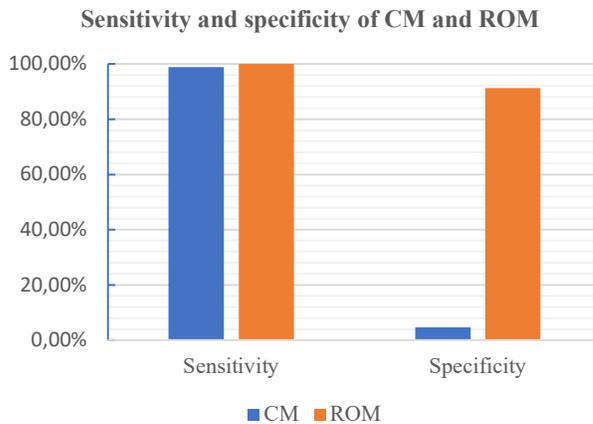


Figure 2. Bar graph of sensitivity and specificity.

With ROM a total of 3158 unique signals were generated, 646 by MoL and 2583 by aCM. In the case of 71 signals, an alert was generated via both MoL and aCM. 26.5% (n = 171) of generated signals was considered TP for MoL. For aCM this percentage of "(potentially) actionable" signals was determined at 92.3% (**Table 3**).

Table 3
Specification of signals generated in ROM.

	MoL	aCM
Total number of signals generated	646	2583
Unique signals (%)	575 (89.0%)	2512 (97.3%)
Double signals (%)	71 (11.0%)	71 (2.7%)
Total number of TP signals (%)	171 (26.5%)	2383 (92.3%)
Total number of FP signals (%)	475 (73.5%)	200 (7.7%)

In 2331 (22.7%) of all signals (n = 10,276) an absence alert for an unknown or not recent eGFR-value was generated. Of all "(potentially) actionable" signals in aCM absence alerts accounted for 97.8% of the alerts.

4. Discussion

An import finding of this study is that the signal load would be reduced with 68.1% (n = 6734) by the implementation of a new way of clinical decision support (ROM). After all, a more advanced CDSS is also known to cause this effect (10,11).

In addition to the reduction in signal load, the percentage of signals which are "(potentially) actionable" has risen sharply in ROM (78.6%) compared with CM (24.8%). Related to this, the increase in specificity obtained using ROM is substantial, as it rises from 4.6% in CM to 91.3% in ROM. It is important to note that sensitivity does not decrease in ROM and in theory even increases. It can therefore be concluded that ROM is not lacking any "(potentially) actionable" signals compared to CM. It should be noted that the increase of sensitivity is minimal (1.1%). This concerns 28 signals that were identified by MoL. These alerts could not be categorised based on an advisory text and there were no dispenses of the concerning medicines during the study period, as they would have been signalled by CM at that point. These 28 signals have therefore been included as "(potentially) actionable". It may be, however, that these signals are "not actionable" after assessment, resulting in a sensitivity of 100% for both CM and ROM.

It is also worth noting that although the proportion of TP signals in ROM (78.6%) has increased overall, it is relatively low for MoL compared to aCM (26.5% vs. 92.3%, respectively). It might be that with the current formulation of the criteria for MoL, requiring a decrease of >3 ml/min/1.73 m², a relatively large number of FP signals are generated and that another cut-off value would improve the proportion of TP signals. Nevertheless, the KNMP document on impaired renal function explicitly mentions the currently chosen value (15). If a stricter formulation of the query is chosen, this will lead to a reduction in signals. The issue, however, is to what extent this will subsequently lead to reduced specificity.

Of all "(potentially) actionable" signals in aCM absence alerts accounted for 97.8% of the alerts. aCM is primarily of importance for detecting unknown or not recent renal function values. For 22.7% of 10,276 unique signals, an eGFR-value was unknown or older than 365 days. This shows that a recent eGFR-value is still not always available in the case of provisions in which it is crucial for adequate processing of medication monitoring signals. Smits et al. concluded that information exchange on renal function could be further improved

(7). Although the current study only focused on the availability of a kidney function at the moment a signal was generated, the finding of Smits et al. deserves continued attention. It should be noted that the current study found heterogeneity among participating pharmacies in terms of the percentage of absence alerts in relation to the total number of generated signals (18.0%-27.2%). According to a study by Koster et al. missing eGFR-values could be retrieved from the GP for the majority of patients (18). In the current study it was not investigated whether missing or not recent kidney functions were available at the GP.

In this study, a recent renal function was defined as an eGFR-value determined within the previous 365 days. However, if a period of 180 days since the last kidney function determination would have been chosen, the number of absence alerts would increase from 2331 to 4726 signals.

It can be considered as a strength of this study that non-arbitrary categorisation was applied based on a measured value and a general advice text, as manual assessment would lead to the introduction of pharmacist-specific considerations.

Another strength is that, as far as known, this is the first study to have investigated the impact of using this type of medication monitoring in community pharmacies in the Netherlands.

This study also has several limitations. Firstly, the study design may overestimate the number of signals categorised as "(potentially) actionable" (TP). Because arbitrary scoring was avoided, cases of doubt were categorised as "(potentially) actionable" on the basis of the accompanying advice text. In reality, this may result in a decrease in the percentage of TP signals and an increase in the percentage of FP signals. In the event that all these signals were in fact "not actionable", this would result in a percentage of "actionable" signals of 75.4%, compared to 78.6% in the current study design.

Secondly, results are made binary in this study, as they were categorised as either "(potentially) actionable" or "not actionable". In reality, this is not the case, as there is often more of a grey area based on the interpretation of the results and advisory texts. The influence of this method on the current results is not known but forms an interesting starting point for follow-up research. It is recommended that a panel of pharmacists is consulted regarding their handling of various signals.

Thirdly, the results of this study cannot be directly extrapolated for the situation of CM in all community pharmacies in the Netherlands. CGMA offers the possibility to manually suppress signals, which obviously leads to a lower signal load. This study assumes a situation in which no signals are suppressed, except for signals that are characterised in the G-Standard as not actionable at any eGFR-value. The use of signal suppression in CM is likely to be heterogeneous between pharmacies.

Fourthly, this study did not take renal function signals that are not detected by CM nor ROM into account. Possible signals that could be classified as "(potentially) actionable" in that category are therefore not included in this study. However, it is not likely that many signals are involved. This could only concern signals which are not monitored by the G-Standard. If such signals exist, sensitivity of both methods would be reduced.

Although alert fatigue is a well-known phenomenon in CM, as signals are in general displayed with each registration in the pharmacy information system, it is also important to

be aware of a lower frequency of the same signals (12,17). In ROM, if a signal is incorrectly handled, it will not be noticed again until reassessment is required, and an incorrect handling of a previous signal may be missed until then.

Thereby, an important condition for the implementation of ROM in a primary care setting is the possibility of structural access to and use of eGFR-values. The proportion of the total patient population that has given permission for the pharmacist to access lab values for medication monitoring can also play a limiting role in the use of ROM. However, if lab values are unknown, the medication of these patients is still monitored by the pharmacist through aCM as a part of ROM. In that case, this will automatically lead to a higher signal load of ROM.

Besides the importance of the number of signals reduced, the presentation of patient data also contributes to the added value that ROM can have for renal function monitoring in primary care. The visual design and direct display of advisory texts with the signal could make it easier to carry out assessments. In patients whose renal function is steadily declining, it may be advisable to reconsider use of certain drugs or to dose them differently in consultation with the prescriber as a precautionary measure. This is probably easier by using MoL and the corresponding representation of data, as set up in this study. It is also an interesting subject for further research whether there are more mutations in patients' medication when using ROM compared to CM.

Thereby, a comparative study into time-investment of medication monitoring following CM versus ROM would contribute to important findings on possible application of ROM. However, due to a reduction in signal load, it is likely that time investment is more efficient when using ROM.

All in all, based on the current data of this study, the conversion of CM to ROM has added value for the monitoring of renal function signals in Dutch community pharmacies. With the implementation of ROM, specificity has increased substantially, as was aimed for, compared to CM. This is an important conclusion, as sensitivity has not been reduced either. Although it is not identical, but contains the same elements, this also seems to apply to the implementation of clinical rules, as the KNMP aims to implement in the Netherlands in the coming years. However, as mentioned, additional research can clarify important elements, such as possible time reduction, when using a more advanced monitoring method as implemented in this study.

5. Acknowledgements

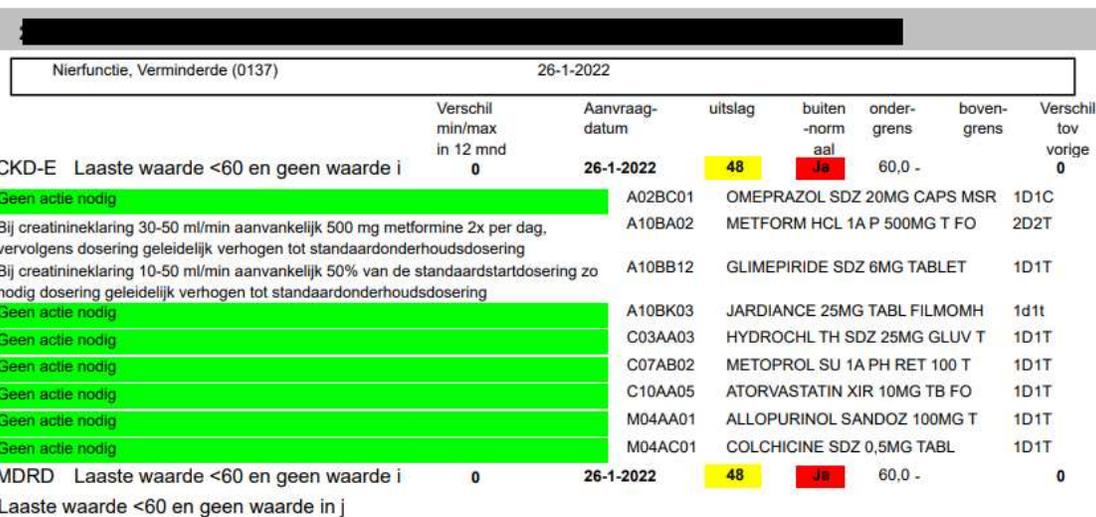
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7. Appendix I: Example report MoL



8. Dutch summary/Nederlandse samenvatting

Inleiding – Een belangrijk aspect van het optimaliseren van farmacotherapie is de juiste dosering van geneesmiddelen. Dosis management is vooral essentieel bij mensen met chronische nierschade (CKD). Bij het genereren van medicatiebewakingssignalen (klassieke medicatiebewaking, CM) voor mensen met CKD wordt momenteel geen rekening gehouden met individuele patiëntkenmerken. Het doel van deze studie was om de efficiëntie en specificiteit van medicatiebewaking bij patiënten met nierinsufficiëntie te verbeteren. Om dit te bereiken werd een nieuwe methode van medicatiebewaking (herbeoordelingsgericht monitoren, ROM) vergeleken met CM.

Methode – ROM werd geïmplementeerd in drie openbare apotheken en bestond uit twee componenten: I. monitoring van inkomende nierfunctiewaarden (eGFR-waarden) van patiënten en II. een aangepaste signaallijst van CM. In de periode oktober, november en december 2021 werden volgens beide methoden gegenereerde signalen verzameld en samengevoegd tot één dataset. Mogelijke overlappingen werden geïdentificeerd. Vervolgens werden alle signalen beoordeeld als "potentieel actiewaardig" of "niet actiewaardig". Om een arbitraire classificatie te vermijden, werden de signalen geclassificeerd op basis van eGFR-waarden die gekoppeld zijn aan adviesteksten voor geneesmiddelen die voorzichtigheid vereisen in geval van verminderde nierfunctie. De resultaten werden vervolgens vergeleken met het momenteel gebruikte systeem van CM.

Resultaten – In totaal werden 10.276 unieke signalen gegenereerd. 9892 en 3158 signalen werden gegenereerd door respectievelijk CM en ROM. Als resultaat heeft ROM geleid tot een vermindering van de signaallast met 68,1%. De gevoeligheid werd bepaald op 98,9% voor CM en 100,0% voor ROM. Voor CM werd een specificiteit van 4,6% berekend, terwijl voor ROM de specificiteit werd bepaald op 91,3%.

Discussie – De invoering van ROM leidde tot een aanzienlijke reductie van de signaallast. In dit verband is het belangrijk op te merken dat de sensitiviteit niet afnam, terwijl de specificiteit sterk verbeterde van 4,6% tot meer dan 90%. Op basis van deze gegevens heeft ROM toegevoegde waarde voor medicatiebewaking van nierfunctiesignalen in Nederlandse openbare apotheken. De mate van impact is echter wel afhankelijk van een aantal voorwaarden en verder onderzoek naar andere aspecten met betrekking tot deze wijze van medicatiebewaking van nierfunctiesignalen is aan te raden.