# The clinical pharmacist improves pharmacotherapy in hospital patients

van de Laar, Inge

*DOI:*
10.33612/diss.182126573

# The clinical pharmacist improves pharmacotherapy in hospital patients

*Medication reviews – Metformin toxicity – Binding interactions*

Inge van Berlo – van de Laar

# Colophon

The clinical pharmacist improves pharmacotherapy in hospital patients: medication reviews, metformin toxicity and binding interactions.

Thesis, University of Groningen, Groningen, the Netherlands.

The work described in this thesis was performed at the department of Clinical Pharmacy of the Deventer Hospital.

Publication of this thesis was financially supported by the Groningen Graduate School of Science and Engineering (GSSE), the university of Groningen, Stichting Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP) Fondsen and the Deventer Hospital.

Cover design/lay out: Antje van Deursen | www.antjeontwerpt.nl
Printed by: drukbedrijf.nl

rijksuniversiteit
groningen

# The clinical pharmacist improves pharmacotherapy in hospital patients

Medication reviews – Metformin toxicity – Binding interactions

## Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

vrijdag 26 november 2021 om 14.30 uur

door


## Inge Regina Francina van de Laar

geboren op 10 november 1974
te Gemert

## Promotores

Prof. dr. F.G.A. Jansman
Prof. dr. K. Taxis

## Beoordelingscommissie

Prof. dr. T. van Gelder
Prof. dr. D.J. Touw
Prof. dr. P.M.L.A. van den Bemt

# Contents

# Chapter 1

General introduction

# General introduction

Clinical pharmacists are specialized pharmacists providing patient care that ensures the appropriateness, effectiveness, and safety of the patients' medication use and promotes health, wellness, and disease prevention. They work in different health care settings, directly with physicians, other health professionals and patients to ensure that the drugs prescribed contribute to the best possible health outcomes. Clinical pharmacists possess in-depth knowledge of drugs including drug action, dosing, adverse effects and drug interactions that is integrated with relevant understanding of biomedical, pharmaceutical and clinical sciences. To achieve desired therapeutic goals, the clinical pharmacist applies evidence-based therapeutic guidelines and relevant professional principles.[1,2] Furthermore, clinical pharmacists are a primary source of scientifically valid information on advice regarding the safe, appropriate, and cost-effective use of drugs. There are numerous examples in literature how clinical pharmacist researchers generate, disseminate, and apply knowledge that contributes to optimizing drug use, avoiding adverse effects and improving health and quality of life.[3-8]

This thesis describes, in three different parts, how the clinical pharmacist can contribute in improving pharmacotherapy of hospital patients.

## 1. Medication reviews

Pharmacist-led medication reviews aim to improve patient outcomes by preventing adverse drug events and decreasing healthcare utilization. A medication review is a judgement of the pharmacotherapy by the patient, pharmacist and physician by means of a structured critical evaluation of the medical, pharmaceutical and utilization information. In agreement with the patient and his physician, the pharmacist identifies areas of improvement and suggests a follow-up treatment plan.[9-11] Several studies in community pharmacy show that pharmacists, in a multidisciplinary approach, can play an important role in reducing drug related problems by conducting medication reviews.[5-8] In the Netherlands, as well as in a number of other countries, performing medication reviews in community pharmacy is routine practice.[12] In contrast, medication reviews are uncommonly done in hospital patients.

We investigated the benefits of pharmacist-led medication reviews in clinical practice for two complex patient groups in hospital. In our case, we use the concept of a complex patient group for patients with chronic polypharmacy having a high risk to experience drug related problems and being under treatment of one or more specialists in the hospital: pre-dialysis/ dialysis patients and older patients with cancer receiving intravenous chemotherapy.[13]

Pre-dialysis and dialysis patients have a high risk of drug related problems. They have a high incidence of comorbidities like hypertension, cardiovascular diseases, diabetes mellitus and mineral and bone diseases and as a result, they use on average 10-12 different drugs prescribed by multiple physicians. The frequency of hospitalization is high and almost 20% of the hospital admissions might be directly related to drug related problems.[14] Although there is considerable research showing some evidence for beneficial outcomes of pharmacist-led medication reviews in patients with chronic kidney disease, studies are generally of low methodological quality and included small number of patients. Practical aspects are insufficiently described and evaluated in clinical practice and clinical relevance and follow up of pharmacists' interventions are lacking.[15]

Another complex patient group are older patients with cancer. Ageing, multiple morbidities, and the use of multiple medicines make older patients a high-risk group for drug-related problems. The diagnosis of cancer further increases this risk. Cancer treatment leads to the use of more medicines, multiple involved health care providers, and a higher disease burden. Frequent hospital visits and the associated transfer of information about medication use are additional risk factors for drug related problems, which can lead to compromised cancer management plans.[16] Since future life expectancy is increasing, addressing the appropriateness of medication use in this population will become more important.[17] The Dutch multidisciplinary guideline 'polypharmacy in the elderly' recommends comprehensive medication reviews in patients aged ≥65 years with polypharmacy and having at least one predefined risk factor.[10,11] Oncological diseases are not mentioned as a specific risk factor in this guideline and no Dutch study was found investigating appropriateness of medication and the impact of pharmacist-led comprehensive medication reviews in this population. In addition, studies found in literature addressing the appropriateness of the medication in older patients with cancer have various limitations and methods and results differ highly.[16,18]

## 2. Metformin toxicity

Metformin is the most commonly prescribed oral antidiabetic drug in non-insulin dependent type 2 diabetes mellitus. Although metformin is considered to be a safe and well-tolerated drug, its use may rarely be complicated by lactic acidosis.[19,20] There appears to be a clear relationship between metformin accumulation and lactic acidosis, although some authors have pointed out that several such patients had other confounding risk factors for lactic acidosis.[20-22]

The incidence of metformin associated lactic acidosis (MALA) reported in studies varies tremendously and may increase in the coming years due to the increase in the number of type 2 diabetes mellitus patients and the use of metformin.[20] Several studies

suggest that early recognition of MALA and timely starting the right treatment may reduce morbidity and mortality.[21-25] However, differentiating between various origins of hyperlactatemia can be very difficult in clinical practice and there is a risk of misclassification. For example, the clinical symptoms of MALA and sepsis are similar, but the treatment is different.[26,27] Clinical parameters that can be used to identify MALA patients in patients with suspected sepsis induced lactic acidosis in the emergency department are therefore warranted. In the treatment of MALA, extracorporeal treatments may be necessary to remove metformin, clear lactate and correct acid-base abnormalities. The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) formulated specific recommendations for starting extracorporeal treatment in metformin poisoning.[19] However, the evidence levels of these criteria are low and their validity in clinical practice has not been assessed yet.

## 3. Binding interactions

Resins such as, sevelamer and polystyrene sulfonate, are used for binding phosphate and potassium to treat hyperphosphatemia and hyperkaliemia which can cause serious complications in patients with Chronic Kidney Disease.[28] Because of their binding properties, these resins can also bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. This is confirmed in literature for several drugs.[29,30] In the Netherlands, these known binding interactions are included in the electronic medication surveillance systems with the advice for staggered dosing between drugs. This is, however, difficult to accomplish in a patient group using on average 8 different drugs a day. In addition, nephrologists may not be aware of binding interactions of these resins with co-medication and their clinical implications.[29] There are potentially many more drugs binding to Sevelamer or polystyrene sulfonate that are not accounted for in the current medication surveillance systems, leading to ineffective treatment in clinical practice. Therefore, knowledge about new binding interactions with sevelamer and polystyrene sulfonate is relevant for management in clinical practice.

## Aim of the thesis

The aim of this thesis is to describe in three different areas how the clinical pharmacist can improve pharmacotherapy in hospital patients. The focus of the thesis is on medication reviews, metformin toxicity and binding interactions.

## **Part 1**: Medication reviews

In chapter 2 we investigated the benefit of pharmacist-led medication reviews in pre-dialysis and dialysis patients by determining the number and type of drug related problems, nephrologist acceptance of pharmacist interventions and time investment.
In chapter 3 we determined the prevalence of Potentially Inappropriate Medications (PIMs) and Potentially Omitted Medications (POMs) in older patients with cancer by performing comprehensive pharmacist-led medication reviews: the PIM POM-study.

## **Part 2**: Metformin toxicity

We estimated the incidence of MALA in type 2 diabetes mellitus patients by means of metformin serum concentration measurements and we investigated the correlation of metformin serum concentration with the clinical outcome of MALA in chapter 4. In chapter 5 we explored clinical parameters to identify patients with MALA in patients with suspected sepsis induced lactic acidosis in the emergency department. Finally, in chapter 6, we assessed whether extracorporeal treatment improves outcome of patients with MALA and we evaluated the clinical applicability of the EXTRIP-criteria for starting extracorporeal treatment in metformin poisoning.

## **Part 3**: Binding interactions

In chapter 7 we describe a case report of a patient with unexplainable low quetiapine concentrations. With an *in vitro* and *in vivo* experiment, we observed a potential drug-drug interaction between quetiapine and sevelamer and quetiapine and polystyrene sulfonate, which were not described in literature before. This case report led to a study in which we explored co-dispensed drug use in patients on sevelamer and or polystyrene sulfonate using an *in silico* approach. We identified potential new binding interactions with Sevelamer and polystyrene sulfonate based on the chemical properties of the most co-dispensed drugs. This study is described in chapter 8. We selected several drugs, that we had identified as potential new drug binding interactions with Sevelamer and polystyrene sulfonate and performed *in vitro* experiments which is presented in chapter 9. Finally, in chapter 10, we investigated the potential binding interaction between amitriptyline and polystyrene sulfonate *in vivo* in healthy volunteers in the BIND-study.

In chapter 11, the general discussion, the main findings are discussed and reviewed in the broader context.

# References


1. Jacobi J. Clinical pharmacists: practitioners who are essential members of your clinical care team. *Rev med Clin Condes* 2016;27(5):571-577
2. American College Clinical Pharmacy. Accessed at www.accp.com. Consulted on 23 April 2021
3. Khalil H, Kynoch K, Hines S. Interventions to ensure medication safety in acute care: an umbrella review. *Int J Evid Based Healthc* 2020;18:188-211
4. Christensen M, Lundh A. Medication review in hospital patients to reduce morbidity and mortality. *Cochrane Database of Systematic Reviews* 2016;2:CD008986
5. Chau SH, Jansen AP, Van de Ven PM, Hoogland P, Elders PJ, Hugtenburg JG. Clinical medication reviews in elderly patients with polypharmacy: a cross-sectional study on drug-related problems in the Netherlands. *Int J Clin Pharm* 2016;38:46-53.
6. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging* 2013;30:285-307.
7. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* 2014:CD008165.
8. Onder G, Van der Cammen TJ, Petrovic M, Somers A, Rajkumar C. Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age Ageing* 2013;42:284-91.
9. Dutch Pharmacists Organisation. [KNMP Guideline 'medication review' 2013]. Den Haag, 2013
10. Dutch College of General Practitioners. Multidisciplinary guideline 'polypharmacy in the elderly' 2012. Accessed at https://richtlijnen.nhg.org//files/2021-02/2021-02-02%20%20Eindversie%20MDR%20Polyfarmacie.pdf. Consulted on 23 April 2021
11. Dutch College of General Practitioners. Module Medication Review 2019. Accessed at https://richtlijnen.nhg.org//files/2020-05/final_module_medicatiebeoordeling_2019.pdf. Consulted on 23 April 2021
12. Verdoorn S, Kwint HF, Blom JW, Gussekloo J, Bouvy ML. Effects of a clinical medication review foccussed on personal goals, quality of life and health problems in older persons with polypharmacy: a rondomized controlled trial (DREAMeR-study). *PLoS Med* 2019;16(5):e1002798
13. Manning E, Gagnon M. The complex patient: a concept clarification. *Nurs Health Sci* 2017;19(1):13-21
14. Patricia NJ, Foote EF. A pharmacy-based medication reconciliation and review program in hemodialysis patients: a prospective study. *Pharmacy Practice* 2016;14:785. Doi: 10.18549/PharmPract.2016.03.785.
15. Al Raiisi F, Stewart D, Fernandez-Llimoos F, Salgado TM, Mohamed MF, Cunningham S. Clinical Pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *Int J Clin Pharm* 2019;41:630-666.
16. Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *J Clin Oncol* 2015;33:1453-9.

17. Kontis V, Bennett JE, Methers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet* 2017;389(10076):1323-1335
18. Feng X, Higa GM, Safarudin F, Sambamoorthi U, Tan X. Potentially inappropriate medication use and associated healthcare utilization and costs among older adults with colorectal, breast, and prostate cancers. *J Geriatr Oncol* 2019;10:698-704.
19. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med* 2015;43(8):1716-1730
20. Lalau JD, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): Moving towards a new paradigm. *Diabetes Obes Metab* 2017;19(11):1502-1512
21. Boucaud-Maitre D, Ropers J, Porokhov B, Altman JJ, Bouhanick B, Doucet. J et al. Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. *Diabet Med* 2016;33:1536-1543
22. Corchia A, Wynckel A, Journet J, Frances JM, Skandrani N, Lautrette A. et al. Metformin-related lactic acidosis with acute kidney injury: results of a French observational multicentre study. *Clin Toxicol* 2019;aug 6:1-8
23. Moioli A, Maresca B, Manzione A, Napoletano AM, Coclite D, Pirozzi N, et al. Metformin associated lactic acidosis (MALA): clinical profiling and management. *J. Nephrol* 2016;29(6):783-789
24. Mariano F, Pozzato M, Inguaggiato P, Guarena C, Turello E, Manes M, et al. Metformin-Associated Lactic Acidosis Undergoing Renal Replacement Therapy in Intensive Care Units: A Five Million Population-Based Study in the North-West of Italy. *Blood Purif* 2017;44(3):198-205
25. Angioi A, Cabiddu G, Conti M, Pili G, Atzeni A, Matta V, et al. Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long term follow up. *BMC Nephrol* 2018;19(1):77
26. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care* 2010;14:R226
27. Nouland van den DPA, Brouwers MCG, Stassen PM. Prognostic value of plasma lactate levels in a retrospective cohort presenting at a university hospital emergency department. *BMJ Open* 2017;7:e011450
28. KDIGO. 2012 Clinical Practice Guidelines for the Evaluation and management of Chronic Kidney Disease. Accessed at www.kdigo.org. Consulted on 11 November 2019
29. Sanjuan JB, Navarro-Gonzalez JF, Arenas MD, Torregrosa J-V, Menendez JT, de Francisco ALM et al. Pharmacological interactions of phosphate binders. *Nefrologia* 2018;38(6):573–578
30. U.S. Food and Drug Administration. Accessed at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-recommends-separating-dosing-potassium-lowering-drug-sodium. Consulted on 11 November 2019

# Part 1

Medication reviews

# Chapter 2

## Pharmacist-led medication reviews in predialysis and dialysis patients

*Res Soc Adm Pharm. 2020; 16(12): 1718-1723*

Inge RF van Berlo – van de Laar
Henk E Sluiter
Esther van 't Riet
Katja Taxis
Frank GA Jansman

# Abstract


## Background

Pre-dialysis and dialysis patients are at risk for drug related problems (DRPs) due to a high incidence of comorbidities. Pharmacist-led medication reviews might reduce the number of DRPs.

## Objectives

The aim of this study was to evaluate pharmacist-led medication reviews in pre-dialysis and dialysis patients by determining the number and type of DRPs, nephrologist acceptance of pharmacist interventions and time investment.

## Methods

From September 2017 until December 2018, pharmacist-led medication reviews were performed on pre-dialysis and dialysis patients. DRPs (medication discrepancies, prescribing issues related to drug and dose selection, drug use problems) were identified using the pharmacists' expert opinion and the STOPP/START criteria. Number and type of accepted pharmacist interventions, sustainability of interventions after at least 1 month and time investment were determined. Practical barriers in the process were appraised.

## Results

One-hundred twenty five patients were reviewed: 37 pre-dialysis and 88 dialysis patients. In 100 (80%) patients 277 medication discrepancies were identified of which 224 (81%) were accepted by the nephrologist. Pharmacists suggested 422 interventions concerning drug or dose selection for 115 patients; 106 interventions were accepted by the nephrologist, which resulted in 60 patients having medication changed. Ninety percent of those changes remained implemented on follow-up after at least 1 month. In 46 (37%) patients, the clinical pharmacist detected DRPs concerning the drug use process and performed patient counseling. The average time investment was 85 minutes per patient for the clinical pharmacist and 15 minutes for the nephrologist. Besides time investment, unclear responsibility for medication management due to multiple prescribers was an important barrier in the process and the main reason for nephrologists to reject pharmacist interventions.

## Conclusion

Pharmacist-led medication reviews in pre-dialysis and dialysis patients led to medication changes in half of the patients. However, efficiency should be improved before adopting pharmacist-led medication reviews into clinical practice.

# Introduction

Pre-dialysis and dialysis patients are at risk for drug related problems (DRPs) defined as events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes.[1,2] These patients have a high incidence of comorbidities like hypertension, cardiovascular diseases, diabetes mellitus and mineral and bone diseases. As a result, they use on average 10-12 different drugs prescribed by multiple physicians.[2] The frequency of hospitalization is high and almost 20% of the hospital admissions might be directly related to DRPs.[2] Different types of DRPs have been found in pre-dialysis and dialysis patients. Medication discrepancies, the use of potentially inappropriate medication and user problems as non-adherence are frequently described DRPs in this patient group.[2-15] A systematic approach of medication reviews might reduce DRPs in (pre)dialysis patients leading to a reduction in hospitalization, length of stay and health care costs.[16-21] Several studies have shown that pharmacist interventions in patients with chronic kidney disease led to a reduction of DRPs, polypharmacy, improved management of anemia, blood pressure, calcium and phosphate parameters, lipid parameters, medication adherence and quality of life.[19-21, 28-31] Two controlled studies investigating pharmacist-led medication reviews on outcomes in hemodialysis patients found that the frequency of hospitalization and drug use were reduced and showed a trend towards a shorter length of hospital stay compared to the usual care group.[32,33] For implementation of this approach, a prominent role for the clinical pharmacist has been proposed.[16-25] Moreover, literature showed that nephrologists and dialysis teams are willing to cooperate with clinical pharmacists.[26,27]

Although there is considerable research showing some evidence for beneficial outcomes of pharmacist-led medication reviews in patients with chronic kidney disease, studies are generally of low methodological quality and included small number of patients.[20] In particular, studies lacked detailed descriptions of the interventions providing the interested readers insufficient information to allow reproduction of the intervention in clinical practice. In the majority of studies, pharmacists seemed to perform only a medication chart review to identify DRPs and did not specify the role of patients in identifying DRPs. In addition, studies did not address the clinical relevance and whether changes in medication were implemented or not. Furthermore, studies did not investigate why pharmacists' recommendations were not followed. Few studies provided data on time spent on specific activities.[19-21] In addition, previous studies have been carried out mostly in North America and Asia and results are not necessarily applicable to countries with other health care systems.[21] In the search for successful health care interventions, which are suitable for wide implementation, extended guidance on development and evaluation has been developed.[34] The importance of testing the interventions' potential

effect and evaluating how interventions work in practice is now widely recognized.[35] Therefore, the aim of this study was to evaluate pharmacist-led medication reviews in pre-dialysis and dialysis patients by determining the number and type of DRPs, nephrologist acceptance of pharmacist interventions and time investment.

# Methods

## Setting and study population

This study was conducted in the period September 2017 – December 2018 in the Deventer Hospital, a teaching hospital in the Netherlands. Pre-dialysis and dialysis patients, over 18 years of age, who were capable and willing to join this study were included. All dialysis patients and pre-dialysis patients were asked to join the study by the secretary of the dialysis ward. Patients received an appointment letter with information about the medication review procedure when they wanted to join the study. During the study period, there were 110 hemodialysis patients and 92 pre-dialysis patients under treatment in the hospital.

## Description of the pharmacist-led medication review procedure

Pharmacist-led medication reviews were conducted in the dialysis ward by one trained clinical pharmacist. Patients were asked to bring all their medication or a medication list to the dialysis ward. In addition, through a safe electronic platform, a complete medication history based on dispensing data of the patients' community pharmacy was obtained by the hospital pharmacy, which is common practice for Dutch hospital pharmacies. The clinical pharmacist interviewed hemodialysis patients during the dialysis session. Pre-dialysis patients were interviewed one week prior their regular visit with the nephrologist. The actual medication use, including non-prescription medicines, was verified with the patient and problems with medication use were addressed using a standardized questionnaire. The clinical pharmacist identified DRPs using her own clinical experience interpreting Dutch standard guidelines, relevant international guidelines, the deprescribing management of McIntyre et al. and the medication safety signals generated by the electronic medication surveillance system.[30, 37-39] We call this "expert opinion" in the following paragraphs. Furthermore, the second revised version of the STOPP/START criteria applicable to the Dutch situation was used to identify potentially inappropriate medication and potentially omitted medication classified as DRPs concerning prescribing issues related to drug selection.[36] The majority of the patients was over 65 years of age (>75%). All recommendations were communicated to the nephrologist. The completion of the pharmacist-led medication review consisted of sending the actual medication list to the patients' general practitioner, to the patients' community pharmacy and directly to the patient. The specific workflow is summarized in figure 1.

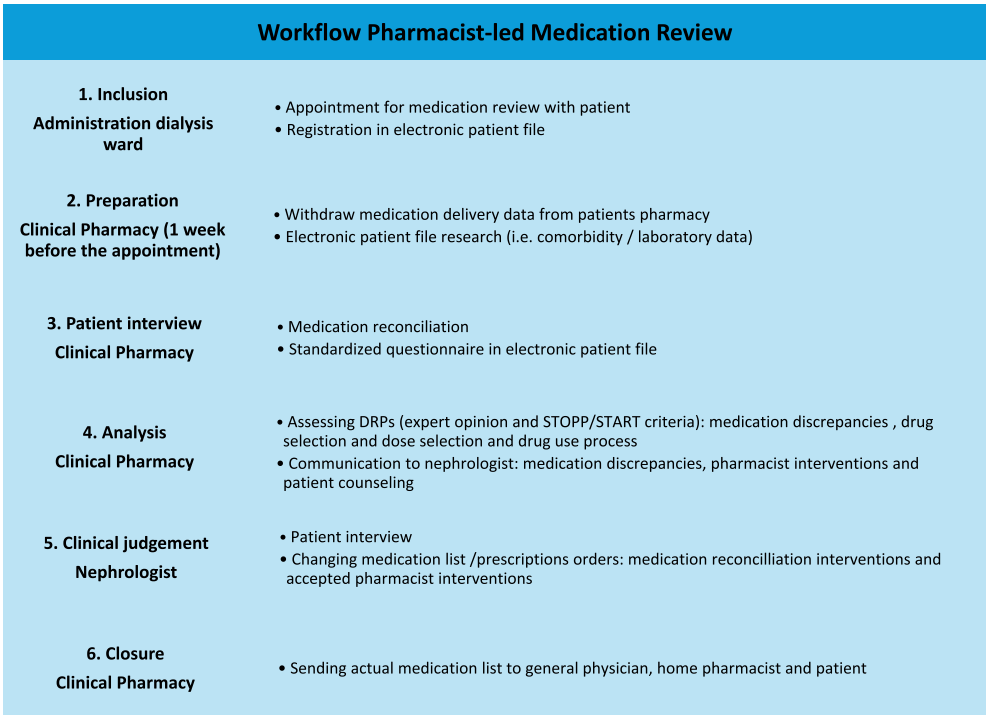


**Figure 1 Workflow pharmacist-led medication review**

## Data collection

Each DRP and the clinical pharmacists' actions were categorized in one of the following three categories:

1. Medication discrepancies, defined as a difference in medication identified when comparing information from the pharmacy record in combination with information from the patient with the hospital medication list.[40]
   The nephrologist decided whether medication had to be changed. In case of change, this was categorized as an accepted medication reconciliation intervention.
2. Prescribing issues related to drug selection and dose selection.
   Drug selection: inappropriate drug due to contraindication, ineffectiveness, regimen or safer alternative available, no indication for drug or indication not treated (missing) therapy.
   Dose selection: drug dose too low, drug dose too high or dosage regimen inadequate according to standard reference sources. The clinical pharmacist recommended changes to the nephrologist which were defined as pharmacist interventions

(stopping a drug, starting a drug or changing a dosage).[41] In case the nephrologist changed the medication, this was categorized as an accepted intervention. For each accepted intervention, the pharmacological category and the type of change (start, stop or dose change) was noted. In addition, it was determined whether the intervention was based on STOPP/START-criteria.

3. Drug use problems by patients were defined as inappropriate timing of administration or drug over- or underused.[1] The clinical pharmacists' actions on these problems were defined as counseling including patient instructions for appropriate timing of administration and education to improve adherence. In general, those actions did not require approval of the nephrologist.

At least one month after the accepted pharmacist interventions, the medical records were reviewed again to check whether changes were persistent, i.e. to establish if the specific medication order remained changed.

The clinical pharmacist actively measured the time investment to perform the whole medication review, during the period January 2018 – July 2018. The time investment per patient for the nephrologist was based on measurements from one nephrologist in 12 patients of time investment for judging and implementing the pharmacists' recommendations.

Furthermore, practical barriers in the process of medication reviews and reasons for rejection of pharmacists' interventions by the nephrologist were documented by the clinical pharmacist.
The pharmacist documented all identified DRPs and associated data. The following data were anonymously collected from medical records, pharmacy records and patient interviews: gender, age, pre-dialysis or dialysis patient, number of drugs used and comorbidity.

## Analysis

In order to characterize the patients, the Charlson Comorbidity Index (CCI) was calculated per patient, representing the 10-year survival prediction in patients with comorbidities as an indication for the patients' comorbidity burden.[42] We also calculated the percentage of polypharmacy patients, defined as chronic use of 5 or more drugs from different therapeutic groups or subgroups.[43]

The percentage of patients with the different categories of DRPs and the average number per patient was calculated. Furthermore, the percentage of accepted pharmacist interventions still implemented at least one month after the intervention, the percentage of accepted pharmacist interventions detected with the STOPP/START criteria and the percentage start, stop or dose changes were determined.

The time investment for one accepted pharmacist intervention was calculated by multiplying the total time investment (clinical pharmacist and nephrologist) by the total number of patients included, divided by the total number of accepted pharmacist interventions.

# Results

One-hundred-twenty-five patients were included: 88 dialysis and 37 pre-dialysis patients. This was 80% and 40%, respectively, of the total hemodialysis and pre-dialysis patients treated at the Deventer Hospital in the study period. Sixty percent of the approached pre-dialysis patients declined a medication review. The main reasons mentioned were extra time investment (visit to the hospital) and no need according to the patient. The patient characteristics are depicted in table 1. The study sample can be described as older patients with polypharmacy and comorbidity with an average Charlson Comorbidity Index of 7, which is associated with a very low 10-year life expectancy. The results of the pharmacist-led medication reviews are summarized in table 2.

**Table 1 Patient characteristics**

| Patient characteristic | Outcome<br>*n* = 125 |
|---|---|
| Age, years (mean ± sd; range) | 72 ± 12 (33-91) |
| Gender (n (%)) | |
| Male | 70 (56) |
| Female | 55 (44) |
| Dialysis (n (%)) | 88 (70) |
| Pre-dialysis (n (%)) | 37 (30) |
| Number of medicines used (mean ± sd; range) | 14 ± 5 (3-27) |
| Polypharmacy (n (%)) | |
| yes | 114 (91) |
| no | 11 (9) |
| CCI (mean ± sd; range) | 7 ± 2 (2-13) |

CCI: Charlson Comorbidity Index

**Table 2 Results of pharmacist-led medication reviews**

| Parameter | Result (n (%)) |
|---|---|
| *Medication discrepancies:* | |
| Patients with medication discrepancies | 100 (80) |
| Medication discrepancies | 277 (2.8 per patient) |
| Medication reconciliation interventions | 224 |
| *Drug and dose selection:* | |
| Patients with pharmacist interventions | 115 (92) |
| Pharmacist interventions | 422 (3.7 per patient) |
| Patients with accepted pharmacist interventions | 60 (48) |
| Accepted pharmacist interventions | 106 (1.8 per patient) |
| Pharmacist interventions still implemented after at least 1 month | 95 |
| Accepted pharmacist interventions detected with the STOPP/START criteria | 49 |
| *Drug use process:* | |
| Patients with patient counseling | 46 (37) |
| *Time investment:* | |
| Average time investment (per patient) | |
| Clinical Pharmacy | 85 minutes |
| Nephrologist | 15 minutes |
| Time investment for one accepted pharmacist intervention | 118 minutes |

## Medication discrepancies

In 100 (80%) patients, 277 medication discrepancies were established (2.8 discrepancies per patient). Two-hundred-twenty-four (81%) of these discrepancies were corrected in the electronic patient file (medication reconciliation interventions) by the nephrologist or by the clinical pharmacist at the request of the nephrologist. These discrepancies mostly concerned medication prescriptions not prescribed by the nephrologist, i.e. prescribed by other physicians, for example dermal products, inhalation medication and psychoactive drugs.

## Drug selection and dose selection

In 115 (92%) patients, the clinical pharmacist detected 422 DRPs from the categories drug selection and dose selection with the pharmacists' expert opinion and the STOPP/START criteria. This resulted in 3.7 pharmacist interventions per patient. In 60 (48%) patients, the nephrologist accepted 106 pharmacist interventions (1.8 pharmacist intervention per patient) and changed the medication prescription order accordingly. In total, 106 of 422 (25%) of the pharmacist interventions were accepted by the nephrologist and therefore considered as clinically relevant. Of the accepted pharmacist interventions, 95

of 106 (90%) persisted for at least one month after the identification of the DRP. Forty-nine (46%) of these interventions were detected with the STOPP/START criteria. Of the 106 accepted pharmacist interventions 25 (24%) concerned starting new medication, 48 (45%) stopping medication and in 30 (28%) the dose was changed. In table 3, the accepted pharmacist interventions are stratified per pharmacological category. Most changed medication prescription orders were related to kidney disease treatment.

**Table 3 Pharmacological categories of accepted pharmacist interventions**

| Pharmacological category | Number of accepted pharmacist interventions (n (%)) |
|---|---|
| Vitamin D analoga, calcimimetics and phosphate binding agents | 19 (18) |
| Erytropoeitine stimulating agents and iron suppletion | 15 (14) |
| Antihypertensiva (ACE-inhibitors, betablockers and diuretics) | 15 (14) |
| Proton pump inhibitors | 12 (11) |
| Gout agents | 11 (10) |
| Statins | 8 (8) |
| Antihistaminic agents | 3 (<1) |
| Benzodiazepines | 3 (<1) |
| Urologic spasmolytica | 3 (<1) |
| Other | 17 (16) |

## Drug use problems

In 46 (37%) patients, the clinical pharmacist detected DRPs in the drug use process and performed patient counseling. This concerned advice about changing the time of ingestion, i.e. ingestion of specific drugs after dialysis instead of before dialysis, medicines use not concomitantly due to absorption interactions, food effects or circadian dosing of statins in relation to cholesterol synthesis). Furthermore, medication adherence was stimulated by explaining why and how to take the medicines.

## Time investment

The estimated average time investment was 85 minutes per patient for the clinical pharmacist (N=80) and 15 minutes for the nephrologist (N=12). The time for one accepted pharmacist intervention was calculated at 118 minutes.

### Reasons for nephrologists not to accept pharmacists' interventions

The most common reason for the nephrologist not to accept the pharmacist intervention and not to change the medication prescription order was that another physician initiated the medication. Other reasons for not accepting the interventions were no valid indication for stopping or starting the drug, the patient did not want to change, the patient had no complaints or was not adherent. Finally, interventions were rejected when laboratory values were acceptable, the nephrologist wanted to wait for further results, the patients' situation had changed during the medication review process, i.e the medication had already been changed, new laboratory results were available or the patient was hospitalized.

## Discussion

Pharmacist-led medication reviews in pre-dialysis and dialysis patients identified a large number of different types of DRPs. Overall, 80% of the patients had on average three medication discrepancies per patient and the majority could be resolved. Patient counseling to improve adherence and adequate timing of administration was performed in 37% of patients. In addition, medication reviews resulted in prescription changes in 48% of the patients with nearly two medication changes per patient. These results are in line with literature and show that pharmacist-led medication reviews lead to a high number of accepted medication reconciliation and pharmacist interventions, potentially leading to a significant reduction of DRPs in this patient group.[2-14, 19-21]

The acceptance rate of pharmacist recommendations in this study was 81% for medication discrepancies. Most discrepancies concern non-(pre)-dialysis associated medication that had been prescribed initially by other providers than nephrologists. Nephrologists have to take over these prescriptions to complete the medication list in the electronic patient file. The latter leads to the high number and acceptance rate of medication discrepancies. The acceptance rate was 25% for pharmacist interventions concerning DRPs of drug selection and dose selection. This is in line with the study of Patricia et al. (acceptance rate of medication discrepancies 85% and for DRPs 27%, respectively).[2] The acceptance rate in two systematic reviews about clinical pharmacy practice in the care of chronic kidney disease patients varied from 33% to 95%, but this represented all accepted recommendations including medication reconciliation interventions in the total group of chronic kidney disease patients.[20,21]

Parker et al. found the STOPP criteria to be more suitable for elderly hemodialysis patients than the Beers criteria; because more potentially inappropriate medication use was detected with the STOPP criteria compared to the Beers criteria.[10] We detected

46% of the accepted pharmacist interventions with the STOPP/START criteria, whereas 54% was based on the clinical pharmacists' expert opinion. STOPP/START criteria miss clinically relevant DRPs and some of the criteria are not suitable for this patient group. More specific criteria for medication reviews in this patient population are needed. An example of a limited set of specific criteria already described are the deprescribing tools in hemodialysis patients published by McIntyre et al, which we also used in our expert opinion judgement.[30] Based on the results of this study a more complete set of specific criteria for this patient group can be developed and validated in further research. However, not all DRPs can be captured in a set of standardized criteria and the knowledge and expertise of a pharmacist remains necessary to attribute these criteria.[44]

The main strength of our study is the detailed description of a pharmacist-led medication review workflow in a patient group at risk for DRPs. The medication review was initiated by the clinical pharmacist but is performed multidisciplinary. The clinical pharmacist had access to the electronic patient file and laboratory data. The patient was interviewed and the workflow was implemented in daily clinical practice. The lack of detailed descriptions of pharmacists' interventions is one of the flaws in studies concerning clinical pharmacists' interventions in this patient group.[20] In this study time investment and reasons for rejection of pharmacists' interventions were appraised which were lacking in the reviews of Salgado et al. and Stemer et al.[20,21] DRPs were not only identified but the follow up and persistence of accepted and therefore clinically relevant pharmacist interventions was also established. Limitations of the study were the performance of the medication reviews by a single clinical pharmacist and not measuring patients' satisfaction in this study.

## Recommendations

Before adopting pharmacist-led medication reviews in clinical practice, the following barriers have to be dealt with. First, time investment is relatively high, i.e. the time needed to establish one accepted pharmacist intervention is 118 minutes. Second, recommendations were sometimes outdated by the time the nephrologist dealt with them as the patient's clinical situation had changed. Third, about 60% of the approached pre-dialysis patients declined a medication review mostly because they had to invest extra time. In contrast, hemodialysis patients were already at the hospital, so no extra time investment was necessary. Finally, nephrologists sometimes were not willing to alter the medications prescribed by other physicians which shows that it was not always clear who took control (and responsibility) of overall medication management. The efficiency of pharmacist-led medication reviews could be improved by developing specific STOPP/START criteria for hemodialysis patients and pre-dialysis patients based on the clinical important DRPs identified in this study. These criteria can be implemented in

the electronic prescribing system as clinical rules leading to smarter and more efficient medication guidance. For example, coupling laboratory results to starting and stopping of phosphate binders, vitamine D analogues and calcimimetics. Implementing such clinical rules in the electronic prescribing system leads to continuous medication surveillance and -intervention instead of periodical medication reviews 1-2 times a year. This is more effective than periodic review as shown by Tuttle et al.[45] Besides the nephrologist, other prescribers of the patient should be involved in the medication review process. There is a role for the clinical pharmacist in taking control of medication management of this patient group. Outcomes of pharmacists prescribing activities in patients with chronic kidney disease have not been investigated systematically, therefore, we suggest this to be a subject for further research.[20] Responsibilities of the clinical pharmacist in the Netherlands should be expanded to stopping, changing and prescribing of agreed medication and ordering laboratory tests. For specialized nurses this is already regulated by law in the Netherlands. In the United Kingdom, United States of America and New Zealand prescribing and modifying medicines by clinical pharmacists is implemented in practice for several years now.[20] Therefore, this should be pursued for clinical pharmacists in the Netherlands also. Further evaluation of these approaches is necessary.[34,35]

## Conclusions

Pharmacist-led medication reviews identified a high number of DRPs in pre-dialysis and dialysis patients and led to medication changes in half of the patients. Before adopting this into clinical practice, efficiency should be improved for example by developing specific STOPP/START criteria to allow continuous electronic medication monitoring and assigning medication management to one designated caretaker, for instance the clinical pharmacist.

## Acknowledgements

We thank the nephrologists and the staff of the dialysis ward of the Deventer Teaching Hospital for their cooperation in this study.

# References


1. Basger BJ, Moles RJ, Chen TF. Development of an aggregated system for classifying causes of drug related problems. *Annals of Pharmacotherapy* 2015;49:405-418
2. Patricia NJ, Foote EF. A pharmacy-based medication reconciliation and review program in hemodialysis patients: a prospective study. *Pharmacy Practice* 2016;14:785. Doi: 10.18549/PharmPract.2016.03.785
3. Manley HJ, Drayer DK, McClaran M, Bender W, Muther RS. Drug record discrepancies in an outpatient electronic medical record: frequency, type and potential impact on patient care at a hemodialysis center. *Pharmacotherapy* 2003;23:231-239
4. Chan WWY, Mahalingam G, Richardson RMA, Fernandes OA, Battistella M, Dan L. A formal medication reconciliation programme in a haemodialysis unit can identify medication discrepancies and potentially prevent adverse drug events. *Journal of Renal Care* 2015:104-109
5. Ledger S, Choma G. Medication reconciliation in hemodialysis patients. *CANNT J* 2008;18:41-43
6. Philips M, Wilson J, Aly A et al. An evaluation of medication reconciliation in an outpatient nephrology clinic. *CANNT J* 2016;26:29-32
7. Wilson J, Ladda MA, Tran J et al. Ambulatory Medication Reconciliation in Dialysis Patients: Benefits and Community Practitioners Perspective. *Can J Hosp Pharm* 2017;70:443-449
8. Kondo N, Nakamura F, Yamazaki S et al. Prescription of potentially inappropriate medications to elderly hemodialysis patients: prevalence and predictors. *Nephrol Dial Transplant* 2015;30:505-513
9. Rankovic GN, Jankovic SM, Velickovic R et al. Potentially inappropriate prescribing of drugs in elderly patients on chronic hemodialysis treatment. *Clinical Nephrology* 2018;89:453-460
10. Parker K, Aasebo W, Stavem K. Potentially Inappropriate Medications in Elderly Haemodialysis Patients Using the STOPP Criteria. *Drugs – Real World Outcomes* 2016;3:359-363
11. Kaplan B, Mason NA, Shimp LA, Ascione FJ. Chronic hemodialysis patients. Part I: characterization and drug related problems. *Ann Pharmacother* 1994;28:316-319
12. Jones SA, Bhandari S. The prevalence of potentially inappropriate medication in elderly patients with chronic kidney disease. *Posgrad med J* 2013;89:247-250
13. Grabe DW, Low CL, BailieGR, Eisele G. Evaluation of drug-related problems in an outpatient hemodialysis unit and the impact of a clinical pharmacist. *Clinical Nephrology* 1997;47:117-121
14. Schmid H, Hartmann B, Schiffl H. Adherence to prescribed oral medication in adult patients undergoing chronic hemodialysis: a critical review of the literature. *Eur J med res* 2009;14:185-190
15. Ghimere S, castelino RL, Jose MD, Zaidi STR. Medication adherence perspectives in haemodialysis patients: a qualitative study. *BMC Nephrol* 2017;18:167. Doi: 10.1186/s12882-017-0583-9
16. Pai AB, Cardone KE, Manley HJ et al. Medication reconciliation and therapy management in dialysis-dependent patients: need for a systematic approach. *Clin J Am Soc Nephrol* 2013;8:1988-1999. Doi 10.2215/CJN.01420213
17. St. Peter WL. Management of polypharmacy in dialysis patients. *Seminars in Dialysis* 2015;28:427-432. Doi: 10.1111sdi.12377

18. St. Peter WL, Wazny LD, Patel UD. New models of chronic kidney disease care including pharmacists: improving medication reconciliation and medication management. *Curr. Opin Nephrol Hypertens* 2013;22:656-662. Doi 10.1097/MNH.0b013e328365b364
19. Al Raiisi F, Stewart D, Fernandez-Llimoos F, Salgado TM, Mohamed MF, Cunningham S. Clinical Pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *Int J Clin Pharm* 2019;41:630-666
20. Salgado TM, Moles R, Benrimoj SI, Fernadez-Llimos F. Pharmacists interventions in the management of patients with chronic kidney disease: a systematic review. *Nephrol Dial Transplant* 2012;27:276-292
21. Stemer G. Lemmens-Gruber R. Clinical pharmacy activities in chronic kidney disease and end-stage renal disease patients: a systematic literature review. *BMC Nephrol* 2011;12:35
22. Mason NA. Polypharmacy and medication-related complications in the chronic kidney disease patient. *Curr Opin Nephrol Hypertens* 2011;20:492-497. Doi 10.1097/MNH.0b013e328349c261
23. Mason NA, Bakus JL. Strategies for reducing polypharmacy and other medication-related problems in chronic kidney disease. *Seminars in dialysis* 2010;23:55-61. Doi 10.1111/j.1525-139x.2009.00629.x
24. Salgado TM, Correr CJ, Moles R, Benrimoj SI, Fernadez-Llimos F. Assessing the implementability of clinical pharmacist interventions in patients with chronic kidney disease: an analysis of systematic reviews. *Annals of Pharmacotherapy* 2013;47:1498-1506. Doi: 10.1177/060028013501802
25. St Peter WL. Improving medication safety in chronic kidney disease patients on dialysis through medication reconciliation. *Advances in Chronic Kidney Disease*. 2010;17:413-419. Doi: 10.1053/j.ackd.2010.06.001
26. Salgado TM, Moles R, Benrimoj SI, Fernandez-Llimos F. Exploring the role of pharmacists in outpatient dialysis centers: a qualitative study of nephrologists views. *Nephrol Dial transplant* 2013;28:397-404. Doi: 10.1093/ndt/gfs436
27. Parker WM, Jang SM, Muzzy JD, Cardone KE. Multidisciplinary views toward pharmacist-delivered medication therapy management services in dialysis facilities. *J Am Pharm Assoc* 2015;55:390-397. Doi: 10.1331/JAPhA.2015.14168
28. Wee HL, Seng BJJ, Lee, JJ et al. Association of anemia and mineral and bone disorder with health-related quality of life in asian pre-dialysis patients. *Health and Quality of life outcomes* 2016;14:94. Doi: 10.1186/s12955-016-0477-8
29. Aspinall SL, Cunningham FE, Zhao X et al. Impact of pharmacist-managed erythropoiesis stimulating agents clinics for patients with non-dialysis- dependent CKD. *AJKD* 2012;60:371-379
30. McIntyre C, McQuillan R, Bell C, Batistella M. Targeted deprescribing in an outpatient hemodialysis unit: a quality improvement study to decrease polypharmacy. *Am J Kidney Dis* 2017;14:1-8. Doi: 10.1053/j.ajkd.2017.02.374
31. Dashti-Khavidaki S, Sharif Z, Khalili H et al. The use of pharmaceutical care to improve health related quality of life in hemodialysis patients in Iran. *Int J Clin Pharm*. 2013;35:260-267
32. Chia BY, Cheen MHH, Gwee XY et al. Outcomes of pharmacist-provided medication review in collaborative care for adult singaporeans recieving hemodialysis. *Int J Clin Pharm*. 2017;39:1031-1038
33. Pai AB, Boyd A, Depczynski J, Chavez IM, Khan N, Manley H. Reduced drug use and hospitalization rates in patients undergoing hemodialysis who received

pharmaceutical care: a 2-year, randomized, controlled study. *Pharmacotherapy* 2009;29:1433-1440.
34. Developing and evaluating complex interventions. Medical Research Council. https://mrc.ukri.org/documents/pdf/complex-interventions-guidance. Accessed 1 Nov 2019
35. Levati S, Campbell P, Frost R et al. Optimisation of complex health interventions prior to randomised controlled trial: a scoping review of strategies used. *Pilot Feasibility Stud* 2016;2:17
36. Knol W, Verduijn MM, Lelie-van der Zande AC et al. Detecting inappropriate medication in older people: the revised STOPP/START criteria. *Ned Tijdschr Geneeskd* 2015;159:A8904
37. Nederlands Huisartsen Genootschap (NHG) standaarden. https://www.nhg.org/nhg-standaarden. Accessed during study period
38. Nederlandse Federatie Nefrologie (NFN) richtlijnen. https://www.nefro.nl/richtlijnen. Accessed during study period
39. KDIGO guidelines. https://kdigo.org/guidelines. Accessed during study period
40. Stuijt CCM, vd Bemt B, Boerlage VE, Taxis K, Karapinar F. Determinants for medication reconcilliation interventions on hospital admissions and discharge: An observational multi-centr study. *Eur J Intern Med* 2017;46:e20-e22
41. Maes KA, Bruch S, Hersberger KE, Lampert ML. Documentation of pharmaceutical care: development of an intervention orientated classification system. *Int J Clin Pharm* 2017;39:354-363
42. Charlson ME, Pompei P, Ales KL, MacKensie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987;40:373-383
43. Dutch Multidisciplinary Guideline Polypharmacy 2012. https://www.nhg.org/themas/publicaties/multidisciplinaire-richtlijn-polyfarmacie-bij-ouderen. Accessed 1 April 2019
44. L. Abramsson, M. Gustafsson. Prevalence of drug related problems using STOPP/START and medication reviews in elderly patients with dementia. *Res Social Adm Pharm* 2019; jun 5
45. Tuttle KR, Aicic RZ, Short RA, et al. Medication therapy management after hospitalization in CKD. *Clin J Am Soc Nephrol* 2018;13:231-241

# Chapter 3

## Prevalence and follow-up of Potentially Inappropriate Medication and Potentially Omitted Medication in older patients with cancer – the PIM POM study

*J Geriatr Oncol. 2021; 12(1): 80-84*

Fianne MAM van Loveren*
Inge RF van Berlo – van de Laar*
Alex LT Imholz
Esther van 't Riet
Katja Taxis
Frank GA Jansman

*Both authors contributed equally to the manuscript

# Abstract


## Objectives

To determine the prevalence of Potentially Inappropriate Medication (PIMs) and Potentially Omitted Medication (POMs) in older patients with cancer.

## Materials and methods

In this prospective observational study (hospital) pharmacists conducted comprehensive medication reviews in older patients with cancer (aged ≥65 years) receiving parenteral chemotherapy and/or immunotherapy at the Deventer Hospital. PIMs and POMs were identified using the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP), the Screening Tool to Alert doctors to the Right Treatment (START), and pharmacists' expert opinion. Recommendations regarding PIMs and POMs were communicated to the patient's oncologist/haematologist and follow-up was measured. Associations between covariates and the prevalence of PIMs and POMs were statistically analysed.

## Results

For the 150 patients included, 180 PIMs and 86 POMs were identified with a prevalence of 78%. Using pharmacists' expert opinion in addition to only STOPP/START criteria contributed to 49% of the PIMs and 23% of the POMs. A follow-up action was required in 73% of the 266 PIMs and POMs. Number of medicines and Charlson Comorbidity Index score were both associated with having at least one PIM and/or POM ($p$ = .031 and $p$ = .016, respectively).

## Conclusion

The prevalence of PIMs and POMs and subsequent follow-up in older patients with cancer is high. A pharmacist-led comprehensive medication review is a good instrument to identify these PIMs and POMs and to optimize patients' treatment. A complete approach, including pharmacists' expert opinion, is recommended to identify all PIMs and POMs in clinical practice.

## Introduction

Ageing, multiple morbidities, and the use of multiple medicines make older patients a high-risk group for drug-related problems (DRPs). The diagnosis of cancer further increases this risk. Cancer treatment leads to the use of more medicines, multiple involved health care providers, and a higher disease burden. Frequent hospital visits and the associated transfer of information about medication use are additional risk factors for DRPs, which can lead to compromised cancer management plans. Since this population will continue to grow, addressing the appropriateness of medication use in this population will become even more important.[1-5]

Several studies show that pharmacists, in a multidisciplinary approach, can play an important role in reducing DRPs by conducting medication reviews.[6-9] Different criteria are used to identify Potentially Inappropriate Medications (PIMs) and Potentially Omitted Medications (POMs). Potentially Inappropriate Medications are defined as medicines that are used by a patient, but are either unnecessary or do not have additional value, or can be optimized in their use. Potentially Omitted Medications refer to medicines that are not used by a patient, but adding them is clinically indicated and can be beneficial for the patient. In Europe, the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START) are most recommended to identify PIMs and POMs.[10] However, using only these criteria does not lead to identification of all relevant PIMs and POMs and therefore a more comprehensive medication assessment is needed.[2,11]

The Dutch multidisciplinary guideline 'polypharmacy in the elderly' recommends comprehensive medication reviews in patients aged ≥65 years with polypharmacy and having at least one predefined risk factor.[12] Oncology is not mentioned as a specific risk factor in this guideline and no Dutch study was found investigating PIMs and POMs and the impact of pharmacist-led comprehensive medication reviews in this population. In general, studies on the prevalence of PIMs and POMs in older patients with cancer have various limitations and methods and results differ highly.[3-5,13-17]

Therefore, this study aims to determine the prevalence of PIMs and POMs in older patients with cancer by conducting pharmacist-led comprehensive medication reviews. Secondary objectives are to examine subtypes of PIMs and POMs, to determine follow-up of PIMs and POMs, and to assess risk factors for PIMs and POMs.

## Methods

In this prospective observational study, pharmacist-led comprehensive medication reviews were conducted in a multidisciplinary team with older patients with cancer between May 2018 and January 2019 at the Deventer Hospital (a middle-sized teaching

hospital in The Netherlands). Patients aged ≥65 years, treated for cancer by a medical oncologist/haematologist, and receiving parenteral chemotherapy and/or immunotherapy at the day care unit were enrolled in this study. Patients at the start of therapy as well as patients who already started therapy were included.

Patients were asked to bring all their medication or a medication overview to the day care unit. While receiving chemotherapy or immunotherapy, a pharmacist or pharmacist in training interviewed the patient. The actual medication use, including non-prescription medicines, was verified with the patient (medication reconciliation) and problems with usage of medication were addressed using a questionnaire. Based on this information and the patient's medical records, PIMs and POMs were identified by the pharmacist using the revised STOPP/START criteria (2015)[18] and pharmacists' expert opinion. Expert opinion consisted of interpretation of medication surveillance signals, practical recommendations, and guideline adherence. Reviewing medication surveillance signals generated from the pharmacy information system is standard practice in Dutch hospital pharmacies. The pharmacists' expert opinion was part of the typical work and knowledge of a hospital pharmacist responsible for medication reconciliation and medication review. No specific framework, process, or list was used for the pharmacists' expert opinion. All identified PIMs and POMs and their corresponding recommendations were double-checked and if necessary complemented by a hospital pharmacist before communicating them to the patient's oncologist/haematologist. If there were discrepancies between the pharmacist and hospital pharmacist, the PIMs and POMs and their corresponding recommendations were based on consensus between the two. For each PIM/POM the oncologist/haematologist decided if a follow-up action was required. Two follow-up actions were possible: the recommendation was implemented by the oncologist/haematologist or the PIM/POM with corresponding recommendation was sent to the patient's general practitioner.

The prevalence of PIMs and POMs (percentage of patients with at least one PIM and/or POM) was determined for PIMs and POMs combined as well as separately. PIMs and POMs were further classified by the Anatomical Therapeutic Chemical (ATC) classification, by the classification used in the STOPP/START criteria, and by the classification used in the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method.[12,18,19]

To determine the association of covariates with the prevalence of PIMs and POMs, the following information was collected for each patient: age, gender, number of different medicines, polypharmacy, use of a medication roll (medication pre-packaged per intake moment), cancer type, curative intent, and the Charlson Comorbidity Index (CCI) score. The number of different medicines included all medication used at home at the time of the interview, as well as the chemotherapy and/or immunotherapy, and accompanying supportive care agents. Polypharmacy was defined as concurrent use of

five or more medicines for chronic use with a different ATC classification on ATC3-level, excluding medicines for dermal use (definition by the Dutch guideline 'polypharmacy in the elderly'[12]). Use of a medication roll was included as a measure for "self-management". The patient's oncologist/haematologist indicated whether the cancer treatment was intended to be curative or not. Finally, the CCI score, determined by the classic scoring index by Charlson et al.[20], was included as a measure for vulnerability and was based on the patient's medical records.



Differences in these covariates for patients with and without PIMs/POMs were assessed using descriptive statistics (independent-samples T-test, Mann-Whitney U Test, Pearson's $\chi^2$ test, or Fisher's exact test). For factors significantly associated with the prevalence of PIMs and POMs ($p$-value <0.05), univariate logistic regression followed by multivariate logistic regression was used to assess odds ratios (ORs) and 95% confidence intervals (CIs). This study was assessed and approved by the Medical Ethics Committee of Isala Hospital as a non-interventional study. All patients signed a written consent form prior to participating in this study.

## Results

For this study, 159 patients were approached to participate of which four patients refused participation and five patients had their appointment rescheduled until after the research period. The patients' characteristics of the 150 patients included in this study are depicted in Table 1. In total, these patients used 1656 medicines, with a mean of eleven medicines per patient (range 3-21). One hundred and forty-four patients (96%) used five or more medicines and 99 patients (66%) used ten or more medicines. When excluding the chemotherapy and/or immunotherapy regimen and accompanying supportive care agents at the day care unit, the mean number of medicines per patient was seven with 77% and 23% of the patients using five or more and ten or more medicines, respectively.

**Table 1 Patient characteristics**

| | *n* = 150 |
|---|---|
| Age, years (median (IQR) [range]) | 72 (8) [65-90] |
| Gender (*n* (%)) | |
| Male | 88 (59) |
| Female | 62 (41) |
| Number of medicines (mean (SD) [range]) | 11.0 (3.8) [3-21] |
| Number of medicines without chemotherapy, immunotherapy and supportive care agents (mean (SD) [range]) | 7.2 (3.6) [0-17] |
| Polypharmacy [a] (*n* (%)) | |
| Yes | 91 (61) |
| No | 59 (39) |
| Medication roll (*n* (%)) | |
| Yes | 18 (12) |
| No | 132 (88) |
| Cancer type (*n* (%)) | |
| Solid tumours | 102 (68) |
| Haematologic malignancies | 48 (32) |
| Curative intent (*n* (%)) | |
| Yes | 34 (23) |
| No | 116 (77) |
| CCI score (median (IQR) [range]) | 4 (1) [3-9] |

[a] Chronic use of ≥5 different medicines, excl. dermal use

Abbreviations: CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation.

A total of 180 PIMs and 86 POMs were identified. These 266 PIMs and POMs give a mean of 1.8 per patient (range 0-8). PIMs and POMs were prevalent in 117 (78%) of the patients. The prevalence of PIMs and POMs separately was 65% and 46%, respectively (Figure 1).

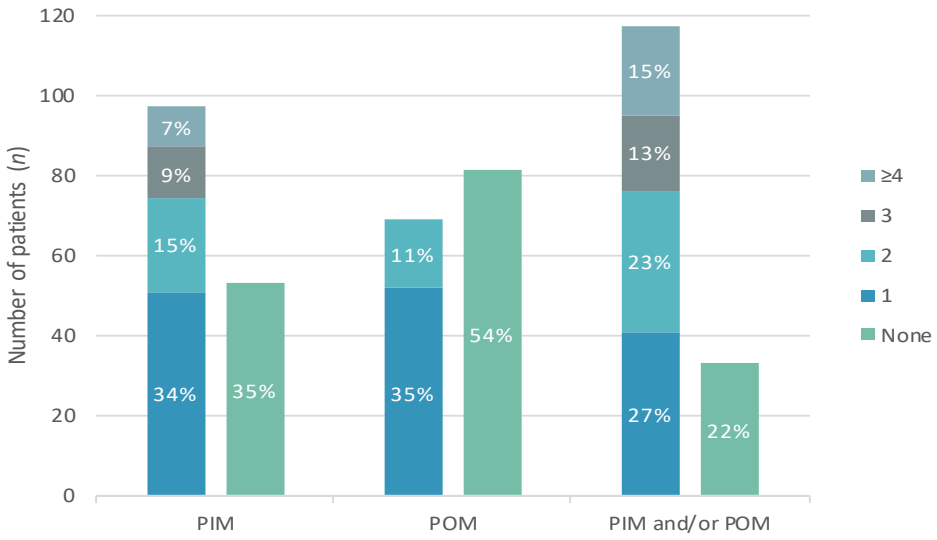


**Figure 1 Prevalence of PIMs and POMs**

The number of patients with no, 1, 2, 3, or ≥4 PIMs (separately), POMs (separately), and PIMs and/or POMs (combined). Percentages are calculated as part of the total (*n* = 150) per category. Abbreviations: PIM, Potentially Inappropriate Medication; POM, Potentially Omitted Medication.

Based on the ATC classification, the most common groups of medication for the 180 PIMs were proton pump inhibitors (PPIs) (19%), antihypertensive drugs (11%), benzodiazepine agonists (9%), analgesics (8%), alpha-adrenoreceptor antagonists (6%), and antidepressants (6%). Four PIMs (2%) concerned antineoplastic agents. The most common groups of medication for the 86 POMs were statins (40%), antihypertensive drugs (19%), and vitamin D (15%). Table 2 specifies the criteria used for identification of the PIMs and POMs.

**Table 2 Criteria used for identification of PIMs and POMs**

| Criteria | Classification | *n* (%) |
|---|---|---|
| *PIMs* | | 186 (100)[a] |
| STOPP criteria | Total | 95 (51) |
| | A1. No evidence-based indication | 42 (23) |
| | A2. Usage longer than recommended | 25 (13) |
| | A3. Double medication | 8 (4) |
| | D5. Benzodiazepine ≥4 weeks | 12 (6) |
| | Other | 8 (4) |
| Expert opinion | Total | 91 (49) |
| | Medicine not effective | 24 (13) |
| | Over treatment | 15 (8) |
| | (Potential) side effect | 9 (5) |
| | Contraindication or interaction | 2 (1) |
| | Incorrect dosage | 15 (8) |
| | Problem with usage | 26 (14) |
| *POMs* | | 86 (100) |
| START criteria | Total | 66 (77) |
| | B4. Antihypertensives, high BP | 7 (8) |
| | B5. Statins, high cardiovascular risk | 30 (35) |
| | H2. Bisph/vitD/calc, chronic prednisone use | 10 (12) |
| | H3. VitD/calc, osteoporosis | 6 (7) |
| | H5. VitD/calc, home bound / fall incidents | 4 (5) |
| | J2. ACE-inhibitor, DM with kidney damage | 5 (6) |
| | Other | 4 (5) |
| *Expert opinion* | Total | 20 (23) |
| | Under treatment | 20 (23) |

[a] The total number of criteria used for identification of PIMs (186) exceeds the total number of PIMs (180) because 6 PIMs were identified using two criteria.
Abbreviations: ACE, angiotensin converting enzyme; bisph, bisphosphonate; BP, blood pressure; calc, calcium; DM, diabetes mellitus; PIM, potentially inappropriate medication; POM, potentially omitted medication; START, screening tool to alert doctors to the right treatment; STOPP, screening tool of older persons' potentially inappropriate prescriptions; vitD, vitamin D.

For 195 (73%) of the 266 identified PIMs and POMs a follow-up action was required according to the oncologist/haematologist. PIMs required more frequently a follow-up action than POMs, 76% vs 67% respectively. For 39% of the PIMs and POMs requiring a follow-up action, this action was realized by the oncologist/haematologist. The distribution of follow-up actions is summarized in Figure 2.

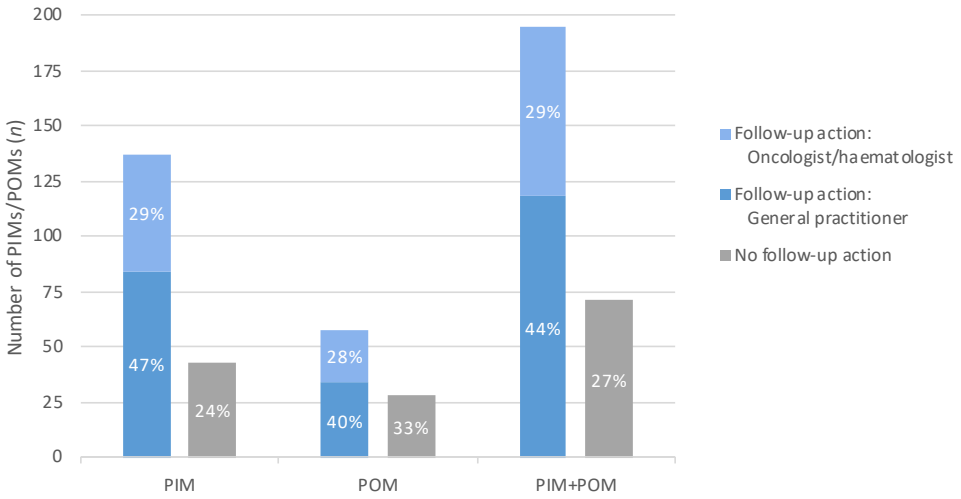


**Figure 2 Follow-up actions of PIMs and POMs**
Follow-up actions of 180 PIMs (separately), 86 POMs (separately), and 266 PIMs and POMs (combined). Percentages are calculated as part of the total per category.
Abbreviations: PIM, Potentially Inappropriate Medication; POM, Potentially Omitted Medication.

PIMs and POMs with a follow-up action realized by the oncologist/haematologist predominantly concerned PPIs (PIMs), anti-infectives (PIMs), antineoplastic agents (PIMs), musculoskeletal medication (PIMs/POMs), and vitamin D (POMs). Potentially Inappropriate Medications and Potentially Omitted Medicationss that were sent most frequently to the general practitioner were alpha-adrenoreceptor antagonists (PIMs), respiratory medication (PIMs), antihypertensive drugs (PIMs/POMs), and statins (POMs). PIMs identified with STOPP criterion A3 'double medication' or expert opinion 'contraindication or interaction' were always considered as requiring a follow-up action. Follow-up was also high for expert opinion 'incorrect dosage' and 'problem with usage' with a follow-up action required for 87% and 86% of the PIMs, respectively. Follow-up was the lowest for START criterion B5 'statins for patients with high cardiovascular risk' with no follow-up action required for 43% of the POMs.
The number of medicines and the CCI score were associated with having at least one PIM and/or POM (Table 3). The other covariates were not statistically significant associated with the prevalence of PIMs and POMs. For an increase of one medicine, the odds of having at least one PIM and/or POM increased with 1.125. For an increase of one point in the CCI score, the odds of having at least one PIM and/or POM increased with 1.501. In multivariate logistic regression analysis both associations were no longer statistically significant. The Pearson correlation coefficient between the variables number of medicines and CCI score was 0.4.

**Table 3 Associations between covariates and prevalence of PIMs and POMs**

| Covariate | Descriptive statistics | | | Logistic regression | |
|---|---|---|---|---|---|
| | No PIMs/POMs | Any PIMs/ POMs[a] | *p*-value | Univariate analysis OR (95% CI) | Multivariate analysis OR (95% CI) |
| Total (*n* (%)) | 33 (100) | 117 (100) | | | |
| Age, years (median (IQR)) | 71 (7) | 73 (9) | 0.059[b] | | |
| Gender, male (*n* (%)) | 21 (64) | 67 (57) | 0.512[c] | | |
| Number of medicines (mean (SD)) | 9.8 (4.0) | 11.4 (3.7) | 0.031[d] | 1.125 (1.009-1.253) | 1.084 (0.963-1.221) |
| Polypharmacy, yes (*n* (%)) | 16 (48) | 75 (64) | 0.105[c] | | |
| Medication roll, yes (*n* (%)) | 2 (6) | 16 (14) | 0.364[e] | | |
| Cancer type, solid tumours (*n* (%)) | 19 (58) | 83 (71) | 0.146[c] | | |
| Curative intent, yes (*n* (%)) | 10 (30) | 24 (21) | 0.235[c] | | |
| CCI score (median (IQR)) | 4 (2) | 4 (1) | 0.016[b] | 1.501 (1.043-2.160) | 1.360 (0.922-2.006) |

[a] This group consists of all patients who have at least one PIM and/or POM.

[b] Mann-Whitney U Test; [c] Pearson's $\chi^2$ test; [d] independent-samples T-test; [e] Fisher's exact test.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; IQR, interquartile range; OR, odds ratio; PIM, potentially inappropriate medication; POM, potentially omitted medication; SD, standard deviation.

# Discussion

A high prevalence of PIMs and POMs (78%) was found in older patients with cancer by conducting pharmacist-led comprehensive medication reviews using both STOPP/START criteria and pharmacists' expert opinion.

The prevalence of PIMs in the current study is higher than in most previous studies. This might be due to a more thorough and complete approach for the comprehensive medication reviews. Most studies based their PIMs on the medical records rather than having an interview involving the patient. Furthermore, the current study used pharmacists' expert opinion in addition to the standardized STOPP/START criteria.

Studies that did not include a patient interview and only used standardized criteria (Beers or STOPP) found a prevalence of PIMs ranging from 16% to 57%.[5,13-16] Fourteen percent of the PIMs in the current study regarded problems with usage, most of which were identified based on the interview with the patient. These PIMs were missed in these previous studies. In addition, the medication reconciliation with the patient attributes to a more complete overview of the actual medication use and therefore to

potentially more PIMs. Reis et al.[17], Nightingale et al.[3], and Deliens et al.[4] found a prevalence of 48%, 51%, and 52%, respectively, when interviewing the patient or conducting a full comprehensive medication review. However, not all PIMs and POMs can be identified with a set of standardized criteria and therefore the knowledge and expertise of a pharmacist is necessary to attribute to these criteria. This is well shown in this study where half of the PIMs and a quarter of the POMs were identified by pharmacists' expert opinion.



To fully optimize patients' treatment, inappropriate medication should be addressed as well as omitted medication. Only two studies were found in which POMs were identified in older patients with cancer, with a prevalence of 34% and 98%.[4,5] The high prevalence found by Paksoy et al.[5] is largely attributed to omitted vaccinations, which is not applicable to the Dutch situation. In the Netherlands, older patients are annually offered an influenza vaccination and a pneumococcal vaccine is not included in the Dutch START criteria.[18]

The high prevalence of PIMs on PPIs and benzodiazepine agonists and POMs on statins, antihypertensive drugs, and vitamin D are in line with several other studies in patients with cancer as well as patients without cancer.[4,6,16,17,21,22] Only four PIMs concerned antineoplastic drugs. Because most PIMs involved regular medication, the problems identified in the oncology population may not be much different from other populations of older polypharmacy patients and therefore STOPP/START criteria seem well applicable. Associations with the prevalence of PIMs and POMs were found for the number of medicines and the CCI score, in line with previous studies.[3,5,13] However, in this study these variables were not very strongly associated and borderline significant. The significant associations were no longer present in the multivariate logistic regression analysis possibly due to a lack of power and the mild correlation (Pearson correlation coefficient 0.4) between CCI score and number of medicines. Because of the time investment needed, implementation in daily practice can be challenging. This study indicates that a specific focus on patients with more medicines and/or a higher CCI score could be considered. However, ORs were small, associations were not statistically significant in multivariate logistic regression analysis, and this study was not designed to determine which (sub) group of patients would benefit most from pharmacist-led comprehensive medication reviews. Future research could provide more insight on this subject.

Measuring follow-up further distinguishes this study from previous studies on PIMs and POMs in older patients with cancer. It was outside the scope of this study to assess actual changes in medication, additional laboratory measurements, or actions by the general practitioner, which could lead to an overestimation of the follow-up on PIMs and POMs. However, the follow-up percentage found in this study (73%) is in line with other studies that found action to be taken in 69%-82% of recommendations made by

pharmacists.[6,23,24] For all STOPP/START criteria, a follow-up action was required for the majority of PIMs and POMs. Even for criteria that might seem less relevant in older patients with cancer (for example starting statins or vitamin D + calcium), more than half of the POMs required a follow-up action and were therefore considered clinically relevant by the oncologist/haematologist. This shows that the criteria, which were used, are relevant to this patient population.

Strengths of this study are the combination of a pharmacist-led comprehensive medication review and medication reconciliation with the patient, the incorporation of pharmacists' expert opinion, the identification of PIMs as well as POMs, and measuring the follow-up of recommendations. Limitations are that this is a single-institution study and only patients who received parenteral chemotherapy and/or immunotherapy were included. In addition, only the prevalence of PIMs and POMs was measured with the immediate follow-up, so long-term outcomes for patient and healthcare cannot be assessed.

In conclusion, PIMs and POMs are highly prevalent among older patients with cancer and a pharmacist-led comprehensive medication reviews is a good instrument to optimize patients' treatment. A complete approach, including pharmacists' expert opinion, is recommended to identify all PIMs and POMs.

## Acknowledgements

The authors thank pharmacists in training Carlijn van der Velde and Marjolein Niewenhuijse for their contribution to the comprehensive medication reviews and data collection.

# References


1. Hamaker ME, Jonker JM, De Rooij SE, Vos AG, Smorenburg CH, Van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol* 2012;13:e437-e44
2. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. *J Geriatr Oncol* 2016;7:346-353
3. Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *J Clin Oncol* 2015;33:1453-1459
4. Deliens C, Deliens G, Filleul O, Pepersack T, Awada A, Piccart M, et al. Drugs prescribed for patients hospitalized in a geriatric oncology unit: potentially inappropriate medications and impact of a clinical pharmacist. *J Geriatr Oncol* 2016;7:463-470
5. Paksoy C, Özkan Ö, Ustaalioğlu BB, Sancar M, Demirtunç R, Izzettin FV, et al. Evaluation of potentially inappropriate medication utilization in elderly patients with cancer at outpatient oncology unit. *J Oncol Pharm Pract* 2019;25:1321-1327
6. Chau SH, Jansen AP, Van de Ven PM, Hoogland P, Elders PJ, Hugtenburg JG. Clinical medication reviews in elderly patients with polypharmacy: a cross-sectional study on drug-related problems in the Netherlands. *Int J Clin Pharm* 2016;38:46-53
7. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging* 2013;30:285-307
8. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* 2014:CD008165
9. Onder G, Van der Cammen TJ, Petrovic M, Somers A, Rajkumar C. Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age Ageing* 2013;42:284-291
10. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther* 2013;38:360-372
11. Verdoorn S, Kwint HF, Faber A, Gussekloo J, Bouvy ML. Majority of drug-related problems identified during medication review are not associated with STOPP/START criteria. *Eur J Clin Pharmacol* 2015;71:1255-1262
12. Dutch College of General Practitioners. [Multidisciplinary guideline 'polypharmacy in the elderly' 2012]. Utrecht, 2012
13. Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. *J Geriatr Oncol* 2012;3:228-237
14. Feng X, Higa GM, Safarudin F, Sambamoorthi U, Tan X. Potentially inappropriate medication use and associated healthcare utilization and costs among older adults with colorectal, breast, and prostate cancers. *J Geriatr Oncol* 2019;10:698-704
15. Karuturi MS, Holmes HM, Lei X, Johnson M, Barcenas CH, Cantor SB, et al. Potentially inappropriate medications defined by STOPP criteria in older patients

with breast and colorectal cancer. *J Geriatr Oncol* 2019;10:705-708
16. Saarelainen LK, Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, et al. Potentially inappropriate medication use in older people with cancer: prevalence and correlates. *J Geriatr Oncol* 2014;5:439-446
17. Reis CM, Dos Santos AG, De Jesus Souza P, Reis AMM. Factors associated with the use of potentially inappropriate medications by older adults with cancer. *J Geriatr Oncol* 2017;8:303-307
18. Knol W, Verduijn MM, Lelie-Van der Zande AC, Van Marum RJ, Brouwers JR, Van der Cammen TJ, et al. [Detecting inappropriate medication in older people: the revised STOPP/START criteria]. *Ned Tijdschr Geneeskd* 2015;159:A8904
19. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2019. Accessed at https://www.whocc.no/atc_ddd_index/; 2019. Consulted on 22 March 2019
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383
21. Bo M, Gibello M, Brunetti E, Boietti E, Sappa M, Falcone Y, et al. Prevalence and predictors of inappropriate prescribing according to the Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment version 2 criteria in older patients discharged from geriatric and internal medicine wards: a prospective observational multicenter study. *Geriatr Gerontol Int* 2019;19:5-11
22. Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. *Drugs Aging* 2012;29:829-837
23. Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PR, et al. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. *Age Ageing* 2001;30:205-211
24. Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med* 2009;169:894-900

# Part 2

Metformin toxicity

# Chapter 4

## Metformin Associated Lactic Acidosis: Incidence and clinical correlation with metformin serum concentration measurements

*J Clin Pharm Ther. 2011; 36(3): 376-382*

Inge RF van Berlo – van de Laar
Cornelis G Vermeij
Cornelius J Doorenbos

# Abstract


## Background

The reported incidence of metformin associated lactic acidosis (MALA) in type 2 diabetes mellitus (DM) is 3 to 9 cases per 100,000 patient-years. In clinical practice, 22-94% of patients using metformin have contraindications to metformin, so the incidence of MALA may be higher than reported.

## Objectives

To estimate the incidence of MALA in type 2 DM patients by means of metformin serum concentration measurements and investigate the correlation of metformin serum concentration with the clinical outcome of MALA.

## Methods

MALA cases were identified by reviewing the medical records of patients with metformin serum concentrations measured between January 2000 and October 2008. MALA was defined as arterial pH <7.35 and lactate concentration >5.0 mmol/l in patients using metformin. Renal failure was defined as serum creatinine >132 µmol/l (men) and >124 µmol/l (women). The incidence of MALA was calculated from the number of cases and the at risk population. The correlation coefficient between the metformin and lactate concentration was calculated by linear regression. The relationship between metformin serum concentration, lactate concentration and outcome was examined by calculating the mean metformin and lactate concentration in patients who survived and those who died. The Student's t-test was used to compare groups.

## Results

In 29 patients metformin serum concentration was measured, 16 had MALA. 11 of the 16 MALA cases (69%) had risk factors for lactic acidosis in their medical history, 13 cases (81%) had renal failure on admission. The incidence of MALA was estimated at 47 per 100,000 patient-years, this is 5 to 16 times higher than previously reported. This may be explained by the use of metformin in the presence of risk factors for lactic acidosis. Survivors had a higher metformin serum concentration (18.9 mg/l) than non-survivors (2.9 mg/l, p=0.006) which can be explained by less severe underlying disease in patients who survived MALA, rather than an effect of metformin itself.

## Conclusion

The incidence of MALA estimated from metformin serum concentration measurements in type 2 DM patients is 5 to 16 times higher than reported in literature. MALA is probably caused by the frequent use of metformin in the presence of risk factors for lactic acidosis. Metformin serum concentration measurements may aid in the timely diagnosis and therapy of MALA. The outcome of MALA is determined by the severity of the underlying disease, rather than by metformin itself.

# Introduction

Metformin is a frequently used drug in the management of type 2 diabetes mellitus (DM). The UKPDS has shown that metformin use was associated with a lower mortality from cardiovascular diseases and all cause mortality than sulfonylureas or insulin in type 2 DM patients.[1] However, metformin has been associated with the risk of developing lactic acidosis.[2-4] Renal impairment, liver failure, heart failure and pulmonary disease increase the risk of lactic acidosis and are contraindications to metformin use. In clinical practice, metformin is used despite the presence of contraindications in 22-94% of the patients.[5-10] In literature, there is doubt whether metformin itself causes lactic acidosis in DM patients.[11-13] A Cochrane review found no increased risk of lactic acidosis for metformin compared with other antidiabetic drugs.[14] Estimates of the incidence of MALA range from 3 to 9 per 100,000 patient-years.[2-4, 15-17] In view of the frequent use of metformin in the presence of risk factors for lactic acidosis, the incidence of MALA may be higher than previously reported. Metformin serum concentrations often have not been measured in studies on MALA. Measurement of the metformin serum concentration may aid in the identification of MALA cases and estimation of the incidence of MALA. Furthermore, metformin serum concentration measurements may elucidate the correlation between metformin accumulation and clinical outcome. The aim of this study was to estimate the incidence of MALA in type 2 DM patients by means of metformin serum concentration measurements and investigate the correlation of metformin serum concentrations with the clinical outcome of MALA.



# Methods

The laboratory data of the Deventer Hospital were searched for patients with measured metformin serum concentrations in the period February 2000 to October 2008. The medical records of the selected patients were reviewed for data on age, sex, metformin dose, risk factors for lactic acidosis in the medical history and on admission, previous and admission creatinine concentration and MDRD estimated GFR, admission diagnosis, arterial pH, plasma lactate concentration, metformin serum concentration, treatment and outcome (30 days after admission). Renal failure was defined as creatinine concentration >132 μmol/l in men and >124 μmol/l in women (based on the FDA recommendation for metformin use). Impaired liver function was defined as serum ALAT concentration >3 times the upper limit of normal (40 U/l). MALA was defined as an arterial pH <7.35 and plasma lactate concentration >5.0 mmol/l. In the selected MALA cases, the correlation coefficient between metformin serum concentration and plasma lactate concentration was calculated. Linear regression analysis was applied to determine significance. The relationship between metformin serum concentration, lactate concentration and outcome was examined by

calculating the mean metformin serum concentration and lactate concentration in patients who survived and those who died. The Student's t-test was used to compare groups. A p-value <0.05 was considered statistically significant. The incidence of MALA was calculated from the number of cases and the number of patients using metformin in the observation period of the study. This calculation was based upon metformin prescription and DM prevalence data from 53 general practices in the hospital referral area, covering 91% of the population.

### Drug analysis

Metformin serum concentrations were determined by means of a high-performance liquid chromatography (HPLC) assay with UV detection. The HPLC analysis used a Chromspher Biomatrix column (particle size 5 µm, 150x4.6 mm) and a mobile phase consisting of acetonitril and phosphate-buffer solution with a pH of 5.0 in a ratio of 35:65. UV detection was set to 235 nm. Metformin was extracted from serum by protein precipitation with acetonitril.

## Results

29 patients with measured metformin serum concentration were identified in the hospital pharmacy laboratory database. Two patients were excluded, because they were treated in other hospitals. Ten patients were excluded because lactate was <5.0 mmol/l, one patient was excluded because the pH was exactly 7.35. This resulted in 16 patients fulfilling the criteria of MALA. Table 1 summarizes the demographic and laboratory data of the selected MALA cases. Arterial pH was 7.10±0.16 (mean±SD, range 6.77-7.33), lactate was 13.8±5.3 mmol/l (5.8-23.2) and metformin serum concentration was 13.9±14.9 mg/l (0.4-44.0). Creatinine was 178±174 µmol/l (64-731) and MDRD estimated GFR was 44±26 ml/min/1.73 $m^2$ (5-98) before admission and 477±333 µmol/l (86-1039) and 20±20 ml/min/1.73 $m^2$ (3-56) on admission. Seven patients (44%) had renal failure before admission and 13 patients (81%) had renal failure on admission. 11 Patients (69%) had risk factors for lactic acidosis in their medical history. The risk factors, admission diagnosis, treatment and outcome (30 days after admission) are summarized in table 2. Five out of the 16 patients with MALA died (mortality rate 31%).

**Table 1 Demographic and laboratory data of patients with MALA**

| Patient | Gender | Age (yr) | pH | Lactate (mmol/l) | Metformin (mg/l) | Metformin dose (mg/day) | Creatinine history (umol/l) | MDRD (ml/min/ 1.73m²) | Creatinine admission (umol/l) | MDRD (ml/min/1.73m²) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 67 | 7.05 | 19.0 | 2.9 | 1000 | 448 | 8 | 478 | 8 |
| 2 | F | 66 | 7.12 | 13.5 | 19.4 | 2550 | 236 | 18 | 640 | 6 |
| 3 | F | 75 | 7.03 | 16.5 | 5.0 | 1500 | 105 | 44 | 266 | 15 |
| 4 | F | 75 | 7.22 | 5.8 | 32.0 | 1700 | 159 | 27 | 813 | 4 |
| 5 | F | 88 | 7.30 | 11.0 | 2.3 | 850 | 94 | 49 | 126 | 35 |
| 6 | F | 78 | 6.85 | 10.2 | 4.0 | 2550 | 94 | 50 | 547 | 7 |
| 7 | M | 83 | 7.33 | 9.3 | 2.4 | 1700 | 67 | 98 | 158 | 37 |
| 8 | F | 72 | 7.16 | 14.0 | 2.3 | 2550 | 113 | 41 | 140 | 32 |
| 9 | M | 58 | 6.77 | 23.0 | 38.0 | 2550 | 114 | 57 | 1039 | 4 |
| 10 | F | 72 | 7.15 | 14.5 | 20.0 | 1700 | 731 | 5 | 814 | 4 |
| 11 | F | 77 | 7.18 | 11.1 | 25.4 | 1500 | 144 | 31 | 960 | 3 |
| 12 | F | 68 | 7.07 | 9.9 | 22.0 | 2550 | 126 | 37 | 706 | 5 |
| 13 | F | 78 | 6.94 | 20.3 | 44.0 | 1500 | 150 | 29 | 612 | 6 |
| 14 | M | 64 | 7.18 | 12.7 | 0.4 | 1700 | 82 | 82 | 123 | 51 |
| 15 | M | 70 | 6.95 | 23.2 | 0.7 | 1000 | 124 | 50 | 125 | 50 |
| 16 | F | 73 | 7.31 | 6.7 | 1.2 | 1000 | 64 | 79 | 86 | 56 |
| Average | | 73 | 7.10 | 13.8 | 13.9 | 1744 | 178 | 44 | 477 | 20 |
| Standard deviation | | 7.4 | 0.16 | 5.3 | 14.9 | 627 | 174 | 26 | 333 | 20 |
| Minimum | | 58 | 6.77 | 5.8 | 0.4 | 850 | 64 | 5 | 86 | 3 |
| Maximum | | 88 | 7.33 | 23.2 | 44.0 | 2550 | 731 | 98 | 1039 | 56 |





**Table 2 Risk factors, admission diagnosis, treatment and outcome of patients with MALA**

| Patient | Risk factors | Admission diagnosis | Treatment | Outcome |
|---|---|---|---|---|
| 1 | CRF | Hemorrhagic shock, liver failure | HD | Death |
| 2 | CRF | Dehydration by vomiting, acute renal failure | HD | Survival |
| 3 | - | Myocardial infarction, liver failure, acute renal failure | CVVHDF | Death |
| 4 | CRF, heart failure | Myocardial infarction, shock, acute renal failure | CVVHDF | Survival |
| 5 | Heart failure, COPD | Pneumonia, dehydration, liver failure | No dialysis | Survival |
| 6 | Heart failure | Dehydration, bradycardia, shock, acute renal failure, | No dialysis | Death |
| 7 | - | Myocardial infarction, shock, acute renal failure, liver failure | No dialysis | Survival |
| 8 | CRF | Myocardial infarction, shock, acute renal failure, liver failure | HD | Death |
| 9 | – | Dehydration, acute renal failure | HD | Survival |
| 10 | CRF | Metformin overdose | HD, CVVH | Survival |
| 11 | CRF | Dehydration by diarrhea, acute renal failure | HD | Survival |
| 12 | CRF | Dehydration, acute renal failure | HD | Survival |
| 13 | CRF, COPD | Dehydration by fever and diarrhea, acute renal failure | CVVH | Survival |
| 14 | Heart failure, COPD | Cardiogenic shock, liver failure, acute renal failure | No dialysis | Death |
| 15 | Alcohol abuses | Myocardial infarction, heart failure, acute renal failure | HD, CVVHDF | Survival |
| 16 | - | Anaphylactic shock | No dialysis | Survival |

CRF chronic renal failure

HD haemodialysis

CVVH continuous venovenous haemofiltration

CVVHDF continuous venovenous haemodiafiltration

## Incidence of MALA

The study period of observation was 8.7 years. In 2000 the hospital referral area had 160,357 and in 2008 180,226 inhabitants, so the average population in the study period was 171,483. In 2008 the studied 53 general practices in the hospital referral area had 156,458 registered patients, 7,619 of which had DM. As 90% of DM patients have type 2, we estimated there were 6,857 type 2 DM patients in the 53 general practices, yielding a type 2 DM prevalence of 4,38% of the population. In the hospital referral area this resulted in an estimated 7,515 type 2 DM patients in the study period. Analysis of the prescription data of the 53 general practices showed that 3,599 patients, this is 52% of the type 2 DM patients used metformin. Extrapolation of this prescription rate to the hospital area population indicates that there were 3,944 patients at risk of developing MALA each year. In the 8.7 year study period there were 34,316 patient-years at risk. With 16 MALA cases, the incidence of MALA was 16 per 34,316 patient-years, or 47 per 100,000 patient-years.



## Correlation between metformin serum concentration, lactate and outcome

The correlation coefficient between metformin serum concentration and lactate concentration in patients with MALA was 0.19 (p=0.47). In survivors, the mean metformin serum concentration was significantly higher (18.9 mg/l) than in non-survivors (2.9 mg/l, p=0.006, figure 1). The mean metformin dosage was 1,691 mg/day in survivors and 1,860 mg/day in non-survivors. There was no significant difference between the mean plasma lactate concentration in survivors (13.5±6.2 mmol/l) and non-survivors (14.5±3.4 mmol/l, p=0.68).

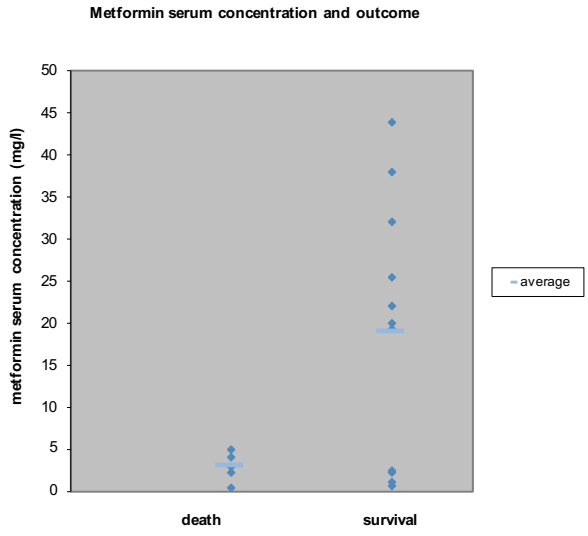


**Figure 1 Metformin serum concentration and outcome**

## Discussion

The incidence of metformin associated lactic acidosis (MALA) assessed by metformin serum concentrations in our study was 47 cases per 100,000 patient-years. This is 5 to 16 times higher than the incidence of 3 to 9 per 100,000 patient-years reported in previous studies.[2-4, 15-17] We used the same criteria for the diagnosis of MALA: arterial pH below 7.35 and lactate concentration above 5.0 mmol/l in patients using metformin. In our study, identification of MALA cases was based on metformin serum concentration measurements confirming the use of metformin in the patients with MALA. The incidence of MALA in our study was accurately calculated from the DM prevalence and metformin prescription data of 53 general practices covering 91% of the hospital referral area. Emslie-Smith et al.[8] found one MALA case in 4,600 patient-years (22 in 100,000 patient years). Nyirenda et al.[18] found 10 cases and an incidence of 30 per 100,000 patient-years. In the Fremantle Diabetes Study, the incidence of lactic acidosis was 57 per 100,000 patient-years in patients using metformin.[19] These studies and the present study demonstrate that the incidence of MALA is higher than previously reported. In studies reporting a low incidence of MALA, patients on metformin who developed lactic acidosis may not have been labeled as MALA cases, because concominant risk factors for lactic acidosis or comorbid conditions were held responsible for the lactic acidosis.[3,4,16,17] Similarly, in our study 69% of the MALA cases had at least one risk factor for lactic acidosis before admission and 81% of the patients had renal failure, a major potential risk factor for MALA, on admission. The frequent presence of risk factors for lactic acidosis in MALA cases raises the question to what extent metformin contributes to the development of lactic acidosis.[13] Findings against metformin as the only cause of lactic acidosis in type 2 DM are published data that the incidence of lactic acidosis in type 2 DM patients using metformin is not higher than with other oral antidiabetic agents or than before the introduction of metformin.[14,15,17,19,20] In our study, we found no significant correlation between the metformin serum concentration and the lactate concentration, which is in agreement with a previous reported study.[21] On the other hand, the numerous cases of metformin accumulation due to overdose or acute renal failure demonstrate that metformin can cause lactic acidosis in the absence of pre-existing risk factors for lactic acidosis or comorbid conditions.[22-30] Also in our study, six of the 16 patients had lactic acidosis due to metformin accumulation caused by renal failure (mean creatinine 795±175 µmol/l, MDRD GFR 4.7±1.2 ml/min/1.73 $m^2$) without cardiac or liver disease. These patients had a mean lactate concentration of 15.4±5.2 mmol/l and mean metformin serum concentration of 28.1±10.4 mg/l. Treatment consisted of rehydration and/or renal replacement therapy, resulting in survival in all six patients. The other 10 patients had more severe illnesses such as cardiogenic shock or

liver failure, but less severe renal failure (mean creatinine 286±245 μmol/l, MDRD GFR 30±20 ml/min/1.73 $m^2$), and therefore lower metformin concentrations (mean 5.3±9.5 mg/l). Their lactate levels were similarly elevated (mean 12.7±5.5 mmol/l), but this was probably caused by circulatory failure rather than by metformin. The severity of the underlying condition may have resulted in the high mortality rate in this group (five out of 10 patients). Apparently, the extent to which metformin contributes to lactic acidosis depends on the underlying disease. The difference in underlying disease also explains why metformin serum concentrations were much higher in survivors (18.9 mg/l) than non-survivors (2.9 mg/l), as previously described by Lalau.[21,31] It has been hypothesized that the higher metformin serum concentrations in survivors may reflect a beneficial effect of metformin in type 2 DM patients.[21] As the underlying diseases were different in survivors and non-survivors, this cannot be concluded from our study. An alternative explanation for the lack of correlation of the metformin serum concentration with lactate and the inverse relation with outcome may be that the metformin serum concentration does not reflect metformin's tissue effects. Metformin is regarded as an intracellular toxin, which may accumulate in erythrocytes and tissues, notably the mucosa of the human intestine.[32] On the other hand, the correlation between plasma and erythrocyte metformin concentrations was found to be high, so metformin serum concentration measurements do may adequately reflect its tissue effects.[33]



## Conclusion

The incidence of MALA estimated from metformin serum concentration measurements in type 2 DM patients is 5 to 16 times higher than reported in the literature. MALA is probably caused by the frequent use of metformin in the presence of risk factors for lactic acidosis. Metformin serum concentration measurements may aid in the timely diagnosis and therapy of MALA. The outcome of MALA is determined by the underlying disease, rather than by metformin itself.

## Acknowledgements

We thank Fokke Meima, general practitioner, for collecting the data on DM prevalence and metformin prescription and for critically reading the manuscript.

# References


1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKDPS 34). *Lancet* 1998;352:854-865
2. Bailey CJ, Nattrass M. Treatment-metformin. *Baillière's Clinical Endocrinology and Metabolism* 1988;2:455-476
3. Misbin RI, Green LR, Stadel BV et al. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998;338:265-266
4. Wilholm B-E, Myrhed M. Metformin-associated lactic acidosis in Sweden 1977-1991. *Eur J Clin Pharmacol* 1993;44:589-591
5. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 1997;20:925-928
6. Yap WS, Peterson GM, Vial JH et al. Review of management of type 2 diabetes mellitus. *J Clin Pharm Ther* 1998;23:457-465
7. Holstein A, Nahrwold D, Hinze S et al. Contra-indications to metformin therapy are largely disregarded. *Diabet Med* 1999;16:692-696
8. Emslie-Smith AM, Boyle DI, Evans JM et al. Contraindications to metformin therapy in patients with type 2 diabetes – a population-based study of adherence to prescribing guidelines. *Diabet Med* 2001;18:483-488
9. Horlen C, Malone R, Bryant B et al. Frequency of inappropriate metformin prescriptions. *JAMA* 2002;287:2504-2505
10. Calabrese AT, Coley KC, DaPos SV et al. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 2002;162:434-437
11. Lalau JD, Lacroix C, Compagnon P et al. Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 1995;18:779-784
12. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. *BMJ* 2003;326:4-5
13. Stades AME, Heikens JT, Erkelens DW et al. Metformin and lactic acidosis: cause or coincidence? A review of case reports. *Journal of Internal Medicine* 2004;255:179-187
14. Salpeter S, Greyber E, Pasternak G et al. Risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006;1:CD002967
15. Chan NN, Brain HP, Feher MD. Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabetic Med* 1999;16:273-281
16. Stang MR, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care* 1999;22:925-927
17. Bodmer M, Meier C, Krahenbuhl S et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycaemia *Diabetes Care* 2008;31:2086-2091
18. Nyirenda MJ, Sandeep T, Grant I et al. Severe acidosis in patients taking metformin: rapid reversal and survival despite high APACHE score. *Diabetic Medicine* 2006;23:432-435
19. Kamber N, Davis WA, Bruce DG et al. Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study. *Med J Aust* 2008;188:446-449
20. Brown JB, Pedula K, Barzilay J et al. Lactic acidosis rates in type 2 diabetes. Diabetes Care 1998;21:1659-1663
21. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic

value of arterial lactate levels and plasma metformin concentrations. *Drug Safety* 1999;20:377-384
22. Guo PYF, Storsley LJ, Finkle SN. Severe lactic acidosis treated with prolonged hemodialysis: recovery after massive overdoses of metformin. *Seminars in Dialysis* 2006;19:80-83
23. Pont de ACJM, Kerver ED, Jansen MEP et al. Een fatale auto-intoxicatie met metformine. *Ned Tijdschr Geneesk* 2007;151:981-984
24. Bruijstens LA, Luin van M, Buscher-Jungerhans PMM et al. Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. *The Netherlands Journal of Medicine 2008;*66:185-190
25. Runge S, Mayerle J, Warnke C et al. Metformin-associated lactic acidosis in patients with renal impairment solely due to drug accumulation? *Diabetes, Obesity and Metabolism 2008;*10:91-93
26. Prikis M, Mesler EL, Hood VL et al. When a friend can become an enemy! Recognition and management of metformin-associated lactic acidosis. *Kidney International* 2007;72:1157-1160
27. Brassøe R, Elkmann T, Hempel M et al. Fulminant lactic acidosis in two patients with type 2 diabetes treated with metformin. *Diabetic Medicine* 2005;22:1451-1453
28. Harvey B, Hickman C, Hinson G. et al. Severe lactic acidosis complicating metformin overdose successfully treated with high-volume venovenous hemofiltration and aggressive alkalinization. *Pediatr Crit Care Med* 2005;6:598-601
29. Lacher M, Hermanns-Clausen M, Haeffner K et al. Severe metformin intoxication with lactic acidosis in an adolescent. *Eur J Pediatr* 2005;164:362-365
30. Chang CT, Chen YC, Fang JT et al. High anion gap metabolic acidosis in suicide: don't forget metformin intoxication-two patient's experiences. *Renal Failure* 2002;4:671-675
31. Lalau JD, Race JM. Metformin and lactic acidosis in diabetic humans. *Diabetes, Obesity and Metabolism* 2000;2:131-137
32. Bailey CJ, Wilcock C, Scarpello JHB. Metformin and the intestine. *Diabetologia* 2008;51:1552-1553
33. Lalau JD, Lacroix C. Measurement of metformin concentration in erythrocytes: clinical implications. Diabetes, Obesity and Metabolism 2003;5:93-98

# Chapter 5

## Identifying patients with Metformin Associated Lactic Acidosis in the Emergency Department

*Int J Clin Pharm. 2020; 42(5): 1286-1292*

Inge RF van Berlo – van de Laar*
Asiye Gedik*
Arthur de Meijer
Esther van 't Riet
Katja Taxis
Frank GA Jansman

*Both authors contributed equally to the manuscript

# Abstract


## Background

Metformin associated lactic acidosis (MALA) is a serious adverse event with a high mortality rate of 30-50%. Early recognition of MALA and timely starting treatment may reduce its morbidity and mortality.

## Objective

The aim of this study was to explore clinical parameters to identify patients with MALA in patients with suspected sepsis induced lactic acidosis in the emergency department (ED).

## Setting

A retrospective single centre study was conducted at the Deventer Teaching Hospital in the Netherlands.

## Method

Patients with lactate concentration > 4.0 mmol/l admitted at the ED between 2010 and 2017 with suspected sepsis or confirmed MALA and referred to the Intensive Care Unit were included. Baseline characteristics (pH, lactate, creatinine and CRP) of MALA patients were compared with patients with suspected sepsis induced lactic acidosis. Creatinine and lactate concentration were selected as potential relevant parameters.

## Main outcome measure

Sensitivity and specificity of the highest tertiles of the creatinine and the lactate concentrations separately, in combination, and both combined with metformin use, were calculated.

## Results

Thirteen MALA and 90 suspected sepsis induced lactic acidosis patients were included. Lactate (14.7 vs 5.9 mmol/l, $p<0.01$) and creatinine concentration (642 vs 174 umol/l, $p<0.01$) were significantly higher in the MALA group and arterial pH (7.04 vs 7.38, $p<0.01$) and CRP (90 vs 185 mg/l, $p<0.01$) were significantly lower. The combined parameters lactate ≥ 8.4 mmol/l, creatinine ≥ 256 umol/l had a sensitivity of 85% and a specificity of 95% for identifying MALA in suspected sepsis induced lactic acidosis patients in the ED. When combined with metformin use the specificity increased to 99%.

## Conclusion

When managing lactic acidosis in the ED the diagnosis MALA should be considered in patients with a creatinine concentration ≥ 256 umol/l and lactate concentration ≥ 8.4 mmol/l.

# Introduction

Metformin is recommended as the treatment of choice in patients with type 2 diabetes mellitus because it decreases cardiovascular morbidity and mortality.[1,2] Metformin associated lactic acidosis (MALA) is a serious adverse event with a high mortality rate of 30-50%.[3] The reported incidence of MALA varies from 0-138 per 100.000 patient years but this may be increasing the coming years due to the increase in the number of type 2 diabetes mellitus patients and the use of metformin.[3-5] In addition, the guidelines for prescribing metformin have been changed: metformin use is not contraindicated any more in patients with more severe renal failure (eGFR < 45 ml/min).[6]

The clinical symptoms of MALA and sepsis are similar, but the treatment is different. As in sepsis, MALA is often accompanied by organ dysfunction e.g. renal failure and hypotension.[7] Furthermore, in sepsis, lactate concentrations are frequently increased.[8,9] Several studies suggest that starting timely treatment of MALA might reduce MALA-related morbidity and mortality.[5,10-15] Identifying MALA patients in an early stage may also avoid unnecessary expensive and high risk diagnostic tests as e.g. CT-abdomen at the ED. Information about metformin use is not always known or fast available on admission at the ED. Measuring metformin serum concentrations can be helpful in diagnosing MALA but this is not routinely available in most hospitals.[16-18]

In the treatment of MALA, extracorporeal treatment (ECTR) may be necessary to remove metformin, clear lactate and correct acid-base abnormalities.[19] The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) group formulated recommendations for ECTR in the treatment of metformin poisoning.[19,20] Clinical criteria to identify sepsis and septic shock are described by Singer et al.[21] The management of the septic patient is described in the Surviving Sepsis Campaign International Guidelines 2016.[8] Lactate is the most common serologic test used in the ED for risk stratification in suspected sepsis patients to optimize treatment but hyperlactatemia may be caused by conditions other than sepsis.[8,21,22] The differentiation between different origins of hyperlactatemia can be very difficult in clinical practice and there is a risk of misclassification.[23] In sepsis lactate is formed under hypoxic conditions and in MALA there is no evidence of a hypoxic condition.[23] The most widely accepted and established mechanism of hyperlactatemia and metabolic acidosis of metformin is partial inhibition of oxidative phosphorylation complex 1 of the mitochondrial electron transport chain. Another possible mechanism in which metformin may elevate plasma lactate levels is through inhibition of pyruvate carboxylase which results in both accelerated lactate production and reduced lactate metabolism.[24,25]

## Aim of the study

Early recognition of MALA and timely starting treatment may reduce morbidity and mortality. Therefore, the aim of this study was to explore clinical parameters that could be used to identify MALA patients in patients with suspected sepsis induced lactic acidosis in the ED intended for use in further research.

## Ethics approval

This study was performed after written consent of the institutional review board and board director of the Deventer Teaching Hospital. Due to the retrospective nature of the study in which patient data were used anonymously, no informed consent of patients was needed.

# Methods

A retrospective single centre study was conducted at the Deventer Teaching Hospital in the Netherlands. Laboratory data were searched for patients admitted at the ED with lactate levels > 4.0 mmol/l between January 2010 and January 2017. Patients with the diagnosis suspected sepsis or a confirmed diagnosis of MALA and who were admitted at the ICU were included. Patients who were not admitted at the ICU, who had a diagnosis other than suspected sepsis or MALA, who died within 24 hours after admittance and all patients with an intentional overdose with metformin were excluded.

The following data were extracted from the medical records: age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II), treatment (supportive care or extracorporeal treatment ECTR), mortality and laboratory results on admission: serum concentrations of creatinine, lactate, C-reactive protein (CRP) and metformin and blood pH. The APACHE II score is a common ICU scoring system to classify disease state and to predict mortality risk and prognosis.

The diagnosis suspected sepsis was extracted from the medical records and was based on quick Sequential Organ failure Assessment (qSOFA) and or Systemic Inflammatory Response Syndrome (SIRS) criteria.

The included patients were divided into 2 groups: MALA and suspected sepsis induced lactic acidosis. MALA was confirmed by a pH < 7.35 and lactate concentration > 5.0 mmol/l and a metformin serum concentration > 5 mg/l, simultaneously measured at admission.[3] In the Deventer Teaching Hospital the metformin assay is routinely available 24 hours a day. Results are available for clinical decisions within 4 hours.

Baseline characteristics between groups were compared using the Mann Whitney test because of non-normal distributed data. Based on clinical experience and previous studies, creatinine and lactate concentration were selected as potential diagnostic clinical parameters and were categorized into tertiles.[4,5,7,11-13,15,18,26-29] The sensitivity and

specificity of the highest tertiles of these concentrations were calculated separately, in combination and both combined with metformin use respectively. The sensitivity was calculated by dividing the number of MALA patients with the specified clinical parameter(s) by the total number of MALA patients. The specificity was calculated by dividing the number of patients without MALA not having the specified clinical parameter(s) by the total number of patients without MALA.
In all tests, a p-value < 0.05 was considered statistically significant. Data analysis was performed with SPSS version 24.0.

## Results

In total 103 patients were included: 13 MALA patients and 90 suspected sepsis induced lactic acidosis patients. Patient characteristics of both groups are depicted in table 1. There was no difference in age and APACHE II score between groups. The MALA group consisted of significantly more women compared to the suspected sepsis induced lactic acidosis group (85% versus 40%). Lactate and creatinine concentration were significantly higher in the MALA group and arterial pH and CRP were significantly lower. The treatment modality ECTR was more frequently used and mortality was higher in the MALA group. Twenty-six percent of the suspected sepsis induced lactic acidosis patients used metformin but did not comply with the definition of MALA. Four patients in the MALA group had positive urine cultures but none of them had positive blood cultures.

**Table 1 Patient characteristics**

| Parameter | Suspected sepsis induced lactic acidosis | MALA | Statistical analysis (p-value) |
|---|---|---|---|
| N (%) | 90 (87) | 13 (13) | |
| Age (years) (median, percentiles 25-75) | 70 (64-80) | 72 (63-81) | 0.74 |
| Gender Male (%) | 54 (60) | 2 (15) | < 0.01 |
| Creatinine (umol/l) (median, percentiles 25-75) | 174 (118-258) | 642 (260-801) | < 0.01 |
| Lactate (mmol/l) (median, percentiles 25-75) | 5.9 (4.8-8.3) | 14.7 (11.0-22.5) | < 0.01 |
| pH (median, percentiles 25-75) | 7.38 (7.28-7.43) | 7.04 (6.83-7.18) | < 0.01 |
| CRP (mg/l) (median, percentiles 25-75) | 185 (90-305) | 90 (34-145) | < 0.01 |
| Metformin use (%) | 23 (26) | 13 (100) | |
| Metformin (mg/l) (mean ± sd) | * | 27.5 ± 15.3 | |
| APACHE II** (median, percentiles 25-75) | 26.5 (21.0-32.3) | 26.0 (23.0-33.0) | 0.53 |
| ECTR yes (% ) | 9 (10) | 10 (77) | < 0.01 |
| Mortality (%) | 19 (21) | 6 (46) | 0.049 |

MALA: Metformin Associated Lactic Acidosis; CRP: C-reactive protein; APACHE: Acute Physiology and Chronic Health Evaluation II; ECTR: extracorporeal treatment

* Metformin serum concentration in metformin users is not measured or below 5 mg/l

** APACHE II scores and mortality prediction as percentage death rate:

| | | |
|---|---|---|
| 0-4 ≅ 1-4% | 15-19 ≅ 12-24% | 30-34 ≅ 75% |
| 5-9 ≅ 3-8% | 20-24 ≅ 30-40% | > 34 ≅ 85% |
| 10-14 ≅ 7-15% | 25-29 ≅ 35-55% | |

Lactate and creatinine concentration were selected as potential relevant clinical parameters.

Lactate concentration was categorized into tertiles resulting in the groups: ≤ 5,5 mmol/l; 5,6 – 8,3 mmol/l and ≥ 8.4 mmol/l. The creatinine concentration tertiles resulted in the groups: ≤ 142 umol/l; 143- 255 umol/l and ≥ 256 umol/l. A scatterplot in figure 1 shows the relationship between lactate and creatinine concentrations of all patients in relation to the highest tertiles.

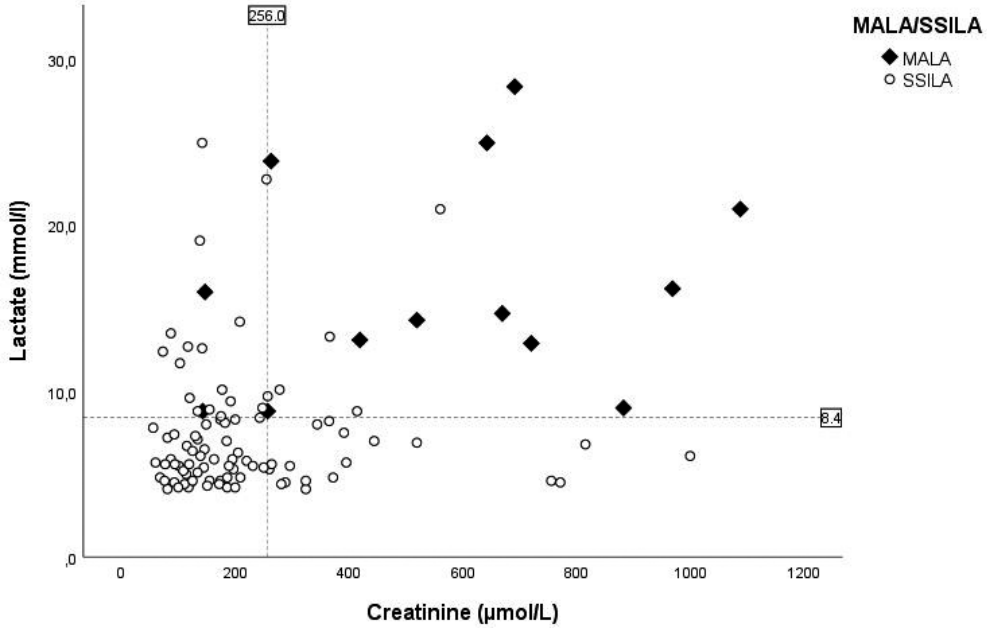


**Figure 1 Scatterplot of creatinine and lactate concentrations from the MALA and suspected sepsis induced lactic acidosis patients**

SSILA: suspected sepsis induced lactic acidosis

Dotted lines present the highest tertiles lactate and creatinine concentration

The sensitivity and specificity of the highest tertiles of lactate and creatinine concentration are depicted in table 2. Sensitivity and specificity are presented in relation to lactate and creatinine concentration separately, in combination and both in combination with metformin use. Among these, the combined parameters lactate ≥ 8.4 mmol/l, creatinine ≥ 256 umol/l and metformin use showed the highest combination of sensitivity (85%) and specificity (99%) in identifying MALA patients from patients with suspected sepsis induced lactic acidosis in the ED.

**Table 2 Sensitivity and specificity of parameters for identifying MALA patients in patients with suspected sepsis induced lactic acidosis**

| Clinical parameter | MALA N=13 | Patients without MALA N=90 |
|---|---|---|
| Lactate ≥ 8.4 mmol/l (N) | 13 | 21 |
| Lactate < 8.4 mmol/l (N) | 0 | 69 |
| **Sensitivity (%) / Specificity (%)** | **100** | **76.6** |
| Creatinine ≥ 256 umol/l (N) | 11 | 23 |
| Creatinine < 256 umol/l (N) | 2 | 67 |
| **Sensitivity (%) / Specificity (%)** | **84.6** | **74.4** |
| Metformin use (yes) | 13 | 23 |
| Metformin use (no) | 0 | 67 |
| **Sensitivity (%) / Specificity (%)** | **100** | **74.4** |
| Lactate ≥ 8.4 mmol/l and creatinine ≥ 256 umol (N) | 11 | 5 |
| Lactate < 8.4 mmol/l and/or creatinine < 256 umol (N) | 2 | 85 |
| **Sensitivity (%) / Specificity (%)** | **84.6** | **94.4** |
| Lactate ≥ 8.4 mmol/l and creatinine ≥ 256 umol and metformine use (yes) (N) | 11 | 1 |
| Lactate < 8.4 mmol/l and/or creatinine < 256 umol and/or metformin use (no) (N) | 2 | 89 |
| **Sensitivity (%) / Specificity (%)** | **84.6** | **99.0** |

MALA: Metformin Associated Lactic Acidosis

# Discussion

The aim of this study was to explore clinical parameters to identify MALA patients in patients with suspected sepsis induced lactic acidosis in the ED. This is important because early recognition of MALA may improve treatment and reduce morbidity and mortality. The results show that the combined parameters lactate ≥ 8.4 mmol/l and creatinine ≥ 256 umol/l have a sensitivity and specificity of 85% and 95% respectively for identifying MALA in suspected sepsis induced lactic acidosis in the ED. The specificity is increased to 99% when combining this with metformin use.

The MALA group in this study had more severe metabolic acidosis (higher lactate and lower

pH) and more severe renal dysfunction (higher creatinine concentration) compared to the suspected sepsis induced lactic acidosis group. The clinical parameters (lactate, pH, creatinine, metformin serum concentration) of the MALA group in this study are in line with previous literature.[4,5,7,11-13,15,18,26-29] To our knowledge, this is the first study comparing MALA and suspected sepsis induced lactic acidosis patients. Three related studies were found.[7,10,22] Semely et al.[10] have shown that an early MALA diagnosis procedure in all patients with metformin admitted at the ED tends to decrease mortality, especially for serious MALA cases. Friesecke et al.[7] have compared MALA patients with patients with lactic acidosis of other origin (LAOO). They found, as in our study, a significantly higher lactate concentration and significantly lower blood pH in MALA patients. Green et al.[22] have shown in adult ED patients with suspected sepsis that metformin users had slightly higher lactate concentrations and hyperlactatemia but this was not associated with a higher mortality risk.

If MALA was not considered as a cause of the hyperlactatemia in this study, 13% of the patients would have received sepsis treatment and adequate MALA treatment was possibly started too late or not at all leading to a higher mortality. The mortality in our MALA group of 46% is in accordance with results presented in previous literature, i.e. 30-50%.[5,19] In addition, the measured mean APACHE II scores of 26.5 matches the mortality in this study. APACHE II scores of 25-29 are associated with an approximated in-hospital mortality of 35-55%.[30] However, the mortality in the sepsis group of 21% is, relatively low compared to literature and the measured APACHE II score of 26.0.[8,30] Not all our sepsis patients had a confirmed sepsis diagnosis, which could be an explanation of the low mortality seen in this group. Patients were included with the diagnosis suspected sepsis based on SIRS or qSOFA scores in the medical files. We did not evaluate if the diagnosis sepsis of these patients was confirmed with microbiological data or otherwise because this study concerned the prediction of the identification of MALA patients in patients with suspected sepsis induced lactic acidosis in the ED. We selected lactate and creatinine as potential relevant parameters to identify MALA patients in patients with suspected sepsis induced lactic acidosis in the ED. C-reactive protein (CRP) was significantly lower in the MALA patients but adding CRP did not improve the predictive value (data not shown). We chose not to select pH as a relevant parameter because pH is also dependent of carbondioxide.

A sensitivity of 85% is not optimal and a higher sensitivity is desirable. In this study, 2 out of 13 MALA patients are not identified using this approach. Both patients had a lactate concentration exceeding 8.4 mmol/l but their creatinine concentration was less than 256 umol/l. MALA is often preceded by gastrointestinal symptoms e.g nausea, vomiting and diarrhoea prior to admittance.[4,5,7,26] The gastrointestinal problems lead to acute renal failure which subsequently leads to metformin accumulation causing lactic acidosis. Possibly, by taking gastrointestinal symptoms prior to admission into account, sensitivity could be improved.

The specificity of the combined parameters lactate and creatinine concentration is 95%. In figure 1 is shown that four sepsis patients have a lactate ≥ 8.4 mmol/l and a creatinine ≥ 256 umol/l and are therefore falsely identified as MALA patients using these two parameters. These patients did not use metformin and the specificity can be increased to 99% by adding metformin use as clinical parameter. However, metformin use may not always be directly available at the ED.

A strength of this study is that we defined MALA based on simultaneously measurement of lactate, pH and metformin serum concentration at admission. Lalau et al.[3] identified the lack of these combined data as one of the methodological flaws in most studies about MALA. Another strength is our selection of MALA patients. To minimize the discussion if metformin or comorbidity is causing lactic acidosis in patients using metformin we added the criterion metformin serum concentration > 5 mg/l to the generally accepted criteria of MALA pH < 7.35 and lactate > 5 mmol/l as suggested by Lalau et al.[3]

A limitation of the study is that comorbidity was not extracted separately from the medical records because this was divers in the study population and difficult to quantify and to extract form the electronic patient files. However, we did extract the APACHE II scores, which is a common ICU scoring system for classifying disease state and predicting mortality and prognosis. There was no significant difference in APACHE II scores between the MALA and the suspected sepsis induced lactic acidosis group, reflecting comparable disease states and mortality risks. Another limitation of our study regards to the retrospective single centre study design. In addition, the number of MALA patients (N=13) was very low which makes drawing conclusions on clinical implications from this study difficult. Because of the relatively low patient number, it was also not possible to perform multivariate regression analysis, which is the method of first choice in prediction research, so we had to calculate the sensitivity and specificity of the selected parameters manually. With multivariate regression analysis, it is possible to estimate statistically significant relations between multiple independent clinical variables and outcome simultaneously. This would have made the results more accurate and robust. Furthermore, selection bias cannot be excluded in our study. We selected patients based on lactate concentrations > 4.0 mmol/l. There is no hard criterion defined for the lactate concentration to identify sepsis or septic shock. However, lactate levels exceeding 4 mmol/l correlate highly with underlying pathology and increased morbidity.[22,23,31] Therefore we selected patients with lactate > 4.0 mmol/l. However, patients with suspected sepsis and lactate < 4.0 mmol/l could have been missed. This also counts for MALA patients with no measured metformin concentrations. Finally, we divided the patients into two groups, i.e. MALA and suspected sepsis induced lactic acidosis based on the inclusion and exclusion criteria. However, possibly, there were combined diagnoses and other comorbidity contributing to hyperlactatemia. Twenty-six percent of the sepsis group used metformin but did not comply with the definition of MALA. Four patients in the

MALA group had positive urine cultures but none of them had positive blood cultures.
Our findings are of important clinical relevance because of the high mortality of MALA and the necessity of starting the right treatment immediately. The number of diabetes mellitus type 2 patients will increase the coming years and so is the use of metformin, thereby probably increasing the incidence of MALA.[5] Clinical symptoms of MALA and sepsis are similar and metformin serum concentration measurement is not routinely available in most hospitals. In addition, sepsis confirmation by microbiologically testing takes days. In the treatment of MALA, ECTR is often necessary to remove metformin, clear lactate and correct acid-base abnormalitie.[19] Therefore, a simple diagnostic approach identifying MALA patients in patients with suspected sepsis induced lactic acidosis in the ED is of high clinical relevance. Lactate and creatinine are standard laboratory tests which are performed immediately at the ED when sepsis is suspected.[8,14,22,23,31] This study presents specific readily available clinical parameters in order to identify MALA patients, which gives direction in starting fast the right treatment, possibly leading to a better outcome. However, further research is necessary to improve the sensitivity of this approach and to validate the distinctive value in a prospective, multicentre design.
For clinical practice, we recommend that clinicians be alert to MALA in the Emergency Department when patients are admitted with severe lactic acidosis and renal failure. Knowledge of the metformin serum concentrations may be a valuable additional parameter for the diagnosis and management of MALA, despite the uncertainty concerning the prognostic value and the lack of a specific threshold for metformin to initiate ECTR.[16-18] Therefore, we recommend clinical pharmacists to organise access to a 24 hour available metformin assay for hospitals treating MALA patients. Also, pharmacists can play an important role in preventing MALA by performing adequate medication surveillance in patients using metformin and having renal failure and educating patients to temporarily stop metformin when they have symptoms of diarrhoea and vomiting.[4,26]



## Conclusion

In case of lactic acidosis in the ED, besides sepsis, the diagnosis MALA should be considered in patients with a creatinine concentration ≥ 256 umol/l and lactate concentration ≥ 8.4 mmol/l. The sensitivity and specificity of these parameters combined with metformin use to identify MALA patients in patients with suspected sepsis induced lactic acidosis were 85% and 99% respectively. As early recognition of MALA is essential for initiating the appropriate treatment in order to reduce morbidity and mortality and to avoid expensive and high risk diagnostic tests, these parameters should be considered in managing lactic acidosis in the ED. A prospective, multicentre design validating the distinctiveness of these set of parameters is recommended to confirm these results.

# References


1. UK Prospective Diabetes Study (UKPDS) group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854-865
2. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41(12): 2669-2701
3. Lalau JD, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): Moving towards a new paradigm. *Diabetes Obes Metab* 2017; 19(11): 1502-1512
4. Berlo van - Laar van de IRF, Vermeij CG, Doorenbos CJ. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. *J Clin Pharm Ther* 2011; 36(3): 376-382
5. Boucaud-Maitre D, Ropers J, Porokhov B, Altman J-J, Bouhanick B, Doucet J, et al. Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. *Diabet Med* 2016; 33: 1536-1543
6. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* 2015; 30: ii1–142.
7. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care* 2010; 14: R226
8. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; 45(3): 486-552
9. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock; 2012. *Crit Care Med* 2013; 41(2): 580-636
10. Semely D, Bennett E, Vallejo C, Saint-Marcoux F, Merle L, Nouaille Y, et al. Can an early diagnostic procedure of metformin-associated lactic acidosis in an emergency unit reduce mortality? *Therap* 2016: 71(6): 605-612
11. Mariano F, Pozzato M, Inguaggiato P, Guarena C, Turello E, Manes M, et al. Metformin-Associated Lactic Acidosis Undergoing Renal Replacement Therapy in Intensive Care Units: A Five Million Population-Based Study in the North-West of Italy. *Blood Purif* 2017; 44(3): 198-205
12. Angioi A, Cabiddu G, Conti M, Pili G, Atzeni A, Matta V, et al. Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long term follow up. *BMC Nephrol* 2018; 19(1): 77
13. Corchia A, Wynckel A, Journet J, Frances JM, Skandrani N, Lautrette A. et al. Metformin-related lactic acidosis with acute kidney injury: results of a French observational multicentre study. *Clin Toxicol* 2019; aug 6: 1-8
14. Jung B, Martinez M, Claessens YE, Darmon M, Klouche K, Lautrette A. et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care* 2019; 9: 92
15. Moioli A, Maresca B, Manzione A, Napoletana AM, Coclite D, Pirozzi N, et al. Metformin associated lactic acidosis (MALA): Clinical profiling and management. *J. Nephrol* 2016; 29(6): 783-789

16. Kajbaf F, De Broe ME, Lalau JD. Therapeutic Concentrations of Metformin: a Systematic Review. *Clin Pharmacokinet* 2016; 55(4): 439-459
17. Kajbaf F, Lalau JD. The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. *BMC Pharmacol Toxicol* 2013; 14: 22
18. Duong JK, Furlong TJ, Roberts DM, Graham GG, Greenfield JR, Williams KM, et al. The role of metformin in metformin-associated lactic acidosis (MALA): case series and formulation of a model of pathogenesis. *Drug Saf* 2013; 36: 733-746
19. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med* 2015; 43(8): 1716-1730
20. EXTRIP-workgroup. Metformin [internet]: accessed February 12, 2019. Available from: https://www.extrip-workgroup.org/metformin
21. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315(8): 801-810
22. Green JP, Berger TB, Garg N, Suarez A, Hagar y, Radeos MS, et al. Impact of metformin use on the prognostic value of lactate in sepsis. *Am J Emerg Med* 2012: 30: 1667-1673
23. Nouland van den DPA, Brouwers MCG, Stassen PM. Prognostic value of plasma lactate levels in a retrospective cohort presenting at a university hospital emergency department. *BMJ Open* 2017; 7: e011450
24. Wang GS, Hoyte C. Review of biguanide (metformin) toxicity. *J Intensive Care* 2018; doi: 10.1177/0885066618793385
25. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risks. *Metabolism* 2016; 65(2): 20-29
26. Vecchio S, Giampretti A, Petrolini M, Lonati D, Protti A, Papa P et al. Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. *Clin Toxicol* 2014; 52: 129-135
27. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: A prognostic and therapeutic study. *Crit Care Med* 2009; 37(7): 2191-2196
28. Greco P, Reolisti G, Maggiore U, Feriolo E, Fani F, Loratelli C et al. Sustained low-efficiency dialysis for metformin associated lactic acidosis in patients with acute kidney injury. *J Nephrol* 2019; 32(2): 297-306
29. Peters N, Jay N, Barraud D, Cravoisy A, Nace L, Bollaer PE, et al. Metformin-associated lactic acidosis in an intensive care unit. *Crit Care* 2008; 12(6): R149
30. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13(10): 819-829
31. Kjelland CB, Djogovic D. The role of serum lactate in the acute care setting. *J Intensive Care Med* 2010; 25(5): 286-300

# Chapter 6

## Extracorporeal treatment of Metformin Associated Lactic Acidosis in clinical practice: a retrospective cohort study

*Eur J Clin Pharmacol. 2020; 76(6): 815-820*

Inge RF van Berlo – van de Laar
Cornelis G Vermeij
Marjo van den Elsen-Hutten
Arthur de Meijer
Katja Taxis
Frank GA Jansman

# Abstract


## Objectives

To assess whether extracorporeal treatment (ECTR) improves outcome of patients with metformin associated lactic acidosis (MALA) and to evaluate the clinical applicability of the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) criteria for starting ECTR in metformin poisoning.

## Methods

Patients with metformin serum concentrations above 2 mg/l who were admitted in the Deventer Teaching Hospital between January 2000 and July 2019 and complied with the definition of MALA (pH < 7.35 and lactate concentration > 5 mmol/l) were included. Mortality and clinical parameters of patients treated with ECTR or not were compared. In addition, treatment of MALA in clinical practice was verified against the criteria of EXTRIP.

## Results

Forty-two patients were included. Lactate (13.8 versus 10.5 mmol/l, $p = 0.01$), creatinine (575 versus 254 umol/l, $p < 0.01$)), metformin (29.4 versus 8.6 mg/l, $p < 0.01$) concentrations and vasopressor requirement (72% versus 23%, $p<0.01$) were significantly higher in the ECTR-group. Blood pH (7.05 versus 7.19, $p = 0.03$) and bicarbonate (6 versus 11 mmol/l, $p < 0.01$) were significantly lower. Mortality, length of hospital stay and mechanical ventilation requirement were not statistically different. In 83% of patients, treatment of MALA was in accordance with the EXTRIP criteria.

## Conclusion

Although there was no statistical benefit in mortality shown from ECTR, ECTR might be lifesaving in MALA, considering the ECTR-group was significantly sicker than the non-ECTR-group.

The majority of patients were treated in line with the EXTRIP criteria. Severity of lactic acidosis and renal impairment were the main indications for initiating ECTR.

# Introduction

Metformin is the most commonly prescribed oral antidiabetic drug in non-insulin dependent type 2 diabetes mellitus (NIDDM). Metformin inhibits gluconeogenesis, facilitates cellular glucose uptake and decreases insulin resistance.[1] Metformin treatment is associated with a lower incidence of cardiovascular events and mortality in NIDDM.[2] Although metformin is considered to be a safe and well tolerated drug, its use may rarely be complicated by lactic acidosis.[1,3,4-6] The most widely accepted mechanism how metformin causes hyperlactatemia and metabolic acidosis is by partial inhibition of oxidative phosphorylation complex 1 of the mitochondrial electron transport chain. Another possible mechanism in which metformin may elevate plasma lactate levels is through inhibition of pyruvate carboxylase which results in both accelerated lactate production and reduced lactate metabolism.[1,3-5] There appears to be a clear relationship between metformin accumulation and lactic acidosis, although some authors have pointed out that several such patients had other confounding risk factors for lactic acidosis.[3,4,5,7]
Metformin associated lactic acidosis (MALA) is a serious adverse event with a high mortality rate of up to 50%.[1,4] The incidence of MALA varies from 0-138 per 100.000 patient years and may increase in the coming years due to the increase in the number of type 2 diabetes mellitus patients and the use of metformin.[4,6,8,9] Several studies suggest that starting timely treatment might reduce MALA-related morbidity and mortality.[8-14] Extracorporeal treatments (ECTRs) may be necessary to remove metformin, clear lactate and correct acid-base abnormalities.[1,11] Calello et al.[1] formulated specific recommendations for starting ECTR in metformin poisoning based on a systematic literature search: the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) criteria[15] which have been included in the treatment guidelines for metformin intoxication by the Dutch Poisons Information Centre (DPIC).[16] However, the evidence levels of the EXTRIP criteria are low and their validity in clinical practice has not been assessed yet. We therefore evaluated the treatment of MALA patients in clinical practice. The aim of this study was firstly to assess whether ECTR improves outcome of MALA patients. Secondly, we aimed to evaluate whether the EXTRIP criteria for starting ECTR in MALA are applicable in clinical practice, i.e. to what extent patients who received ECTR and those who did not fulfilled the EXTRIP criteria for starting ECTR.[1]

# Methods

A retrospective single centre cohort study was conducted at the Deventer Teaching Hospital in the Netherlands. Laboratory data were searched for patients who had their metformin serum concentrations measured between January 2000 and July 2019. In these patients, serum metformin concentration measurement had been requested

because of a clinical suspicion of MALA, based on documented metformin use and concurrent illness leading to an Emergency Department visit. In the Deventer Teaching Hospital the metformin assay is routinely available 24 hours a day. Results are available for clinical decisions within 4 hours. Patients were included if they met the MALA definition: pH < 7.35 and lactate > 5.0 mmol/l in association with metformin exposure.[1] Only patients with serum metformin concentrations above the lower limit of quantification of our analysis method, i.e. 2 mg/l, were included. The following patient data were extracted from the medical records: age, gender, admission diagnosis, ECTR treatment (or not), reasons for initiating ECTR (or not), decreased consciousness, vasopressor requirement, mechanical ventilation requirement, length of hospital stay, mortality (defined as in-hospital mortality) and laboratory results on admission: serum concentrations of creatinine, lactate, bicarbonate and metformin and blood pH. In the Deventer Teaching Hospital ECTR is readily and unrestrictedly available for treatment of MALA patients.

Patients were divided into an ECTR and non-ECTR group and the concentrations of lactate, creatinine, bicarbonate and metformin, blood pH, decreased consciousness, vasopressor and mechanical ventilation requirement, length of hospital stay and mortality were compared. In case of normal distribution of continuous data, the independent sample t-test was used. The non-parametric Mann Whitney test was used for not normally distributed and ordinal data. The Chi square test was used to compare nominal data between groups. In all tests, a p-value < 0.05 was considered statistically significant. Data analysis was performed with SPSS version 24.0.

In the ECTR and non-ECTR group, we assessed whether patients met the EXTRIP criteria for starting ECTR depicted in table 1. Impaired kidney function is defined by the EXTRIP nephrology sub-committee as 1) Advanced stage G3b, G4 or G5 chronic kidney disease (i.e. eGFR < 45 mL/min/1.73 m2), 2) Kidney Disease: Improving Global Outcomes (KDIGO) Stage 2 or 3 acute kidney injury, 3) In the absence of a baseline serum creatinine, 176 µmol/L in adults and 132 µmol/L in elderly/low muscle mass patients, 4) the presence of oligo/anuria regardless of serum creatinine concentration. In those patients who were not treated according to the EXTRIP criteria the reasons for initiating ECTR or not were evaluated.

**Table 1 EXTRIP criteria for starting ECTR in metformin poisoning[1]**

| **Indications** |
|---|
| ECTR is recommended if: |
| • Lactate concentration greater than 20 mmol/l<br>• Blood pH less than or equal to 7.0<br>• Standard therapy (supportive measures, bicarbonate etc.) fails |
| ECTR is suggested if: |
| • Lactate concentration is 15-20 mmol/l<br>• Blood pH 7.0 – 7.1 |
| Comorbid conditions that lower the treshold for initiating ECTR: |
| • Impaired kidney function<br>• Shock<br>• Decreased level of consciousness<br>• Liver failure |

EXTRIP: Extracorporeal Treatments in Poisoning Workgroup

ECTR: Extracorporeal treatment

# Results

In our hospital pharmacy laboratory database, we identified 160 patients who had serum metformin concentrations measured. Of these, 42 patients met the inclusion criteria of MALA and were included in the study. Forty patients (95%) had renal impairment on admission and 29 patients (69%) were treated with ECTR. ECTR was conducted in the intensive care unit. ECTR modalities used were continuous veno venous hemofiltration (CVVH) (19 patients), hemodialysis (HD) (7 patients) or a sequential combination of CVVH and HD (3 patients). The patient characteristics and the results of the comparison between the ECTR and non-ECTR groups are listed in table 2. The main admission diagnoses were dehydration, sepsis, shock and myocardial infarction. Detailed information of the patient characteristics per patient is given in supplementary table 1 (ECTR-group) and supplementary table 2 (non-ECTR-group).

**Table 2 Results: patient characteristics and comparison clinical parameters ECTR versus non-ECTR group**

| Patient characteristics | ECTR N=29 Mean ± sd (range) | Non-ECTR N=13 Mean ± sd (range) | Statistical analysis |
|---|---|---|---|
| Gender | 6M 23F | 5M 8F | |
| Age (years) | 71 ± 9 (52-87) | 77 ± 11 (58-89) | |
| pH | 7.05 ± 0.18 (6.61-7.34) | 7.19 ± 0.18 (6.85-7.33) | p = 0.027 |
| Lactate (mmol/l) | 13.8 ± 4.9 (5.8-23.2) | 10.5 ± 2.8 (6.7-18) | p = 0.033 |
| Bicarbonate (mmol/l) | 6 ± 3 (2-13) | 11 ± 4 (2-17) | p < 0.01 |
| Metformin concentration (mg/l) | 29.4 ± 20.3 (2.3-100) | 8.6 ± 11.2 (2.2-37) | p < 0.01 |
| Creatinine (umol/l) | 575 ± 268 (113-1039) | 254 ± 192 (70-720) | p < 0.01 |
| Decreased consciousness N (%) | 9 (31%) | 3 (23%) | p=0.699 |
| Vassopressor requirement N (%) | 21 (72%) | 3 (23%) | p < 0.01 |
| Mechanical ventilation requirement N (%) | 6 (21%) | 1 (8%) | p=0.296 |
| Length of stay (days) | 17.3 ± 23.6 (2-120) | 7.8 ± 9.0 (1-32) | p=0.067 |
| Mortality N (%) | 11 (38%) | 6 (46%) | p=0.616 |

ECTR: Extracorporeal treatment

Thirty-five of the 42 (83%) patients were treated in line with the EXTRIP criteria.
Of the 29 patients in the ECTR-group, 28 (97%) fulfilled the EXTRIP criteria to receive ECTR. Clinical reasons for starting ECTR in these patients were severe metabolic acidosis, renal failure, hyperkalaemia and high metformin concentrations. Ninety-seven percent of the ECTR group met the criterion of impaired renal function of Calello et al.[1] in which the threshold for initiating ECTR could be lowered. One patient (patient No. 27, supplementary table 1) did not fulfil the EXTRIP criteria. This patient was admitted because of an intentional overdose and did not meet the criterion of impaired renal function of Calello et al.[1] ECTR was started because of the combination high serum metformin concentration and lactic acidosis in order to eliminate metformin and to correct the acidosis.
Of the 13 patients in the non-ECTR group, in 7 (54%) of the patients treatment (non-ECTR) was in line with the EXTRIP criteria. One patient (patient No. 6, supplementary table 2) did not fulfil the EXTRIP criteria for starting ECTR and in 6 patients ECTR was not

necessary because they recovered after starting supportive care.
For the other 6 (46%) patients, ECTR should have been considered according to the EXTRIP criteria. Supportive care was started in these patients but they died shortly after start of the treatment. Four patients died within one day from cardiac arrest. In one patient, a conservative policy was started because of the very bad prognosis due to comorbidity and she died one day after admittance. One patient (patient No.10, supplementary table 2) did not recover with supportive care and died one month after admission probably from sepsis. There were no data available in this patients' medical record whether ECTR was considered.

## Discussion

This retrospective cohort study shows a lower but not statistically different mortality in MALA patients treated with ECTR compared to those who were not. The overall mortality of 40% in our study is in line with the mortality reported in previous studies, ranging from 20-50%.[7,8,12-14,17-21] Blood pH, lactate, creatinine and serum metformin concentration in the ECTR group in this study are similar to that reported in the literature.[9,13,20-22] The significantly higher lactate and creatinine concentrations in the ECTR group compared to the non-ECTR group have also been reported in other studies.[9,12,19]
Patients in the ECTR group were sicker than patients in the non-ECTR group considering the degree of lactic acidosis, kidney function and vasopressor requirement while having a lower but not statistically different, mortality. As hyperlactatemia in general and in MALA patients is associated with increased mortality, this at least comparable outcome suggests there might be a benefit for ECTR.[8,11,23-25] This is also suggested by Peters et al.[19] Our study was probably underpowered to show a statistical difference. We also compared the length of hospital stay (17.3 versus 7.8 days, p=0.067) but in this study this parameter is less suitable as outcome measure compared to mortality because of the large range in the ECTR group (2-120 days) and the high percentage patients who died within 1-2 days in the non-ECTR group.

To evaluate whether the EXTRIP criteria for initiating ECTR in patients with MALA are applicable in clinical practice we compared the indications for starting ECTR in this study with the recommendations of Calello et al.[1] Overall, 83% of our patients were treated in line with the EXTRIP criteria. In the ECTR group, 97% and in the non-ECTR group 54% of the patients fulfilled the EXTRIP criteria. Severity of lactic acidosis and kidney function were the main indications for initiating ECTR in this study. This is also shown in the EXTRIP criteria and the study of Corcia et al.[1,9,15] Moreover, in accordance with Corchia et al.[9], we identified hyperkalaemia as a reason for starting ECTR. In contrast, hemodynamic instability and shock, as proposed by Corcia et al.[9] and EXTRIP[1,15] for initiating

ECTR, were not recorded in the patients' medical records in this study. Calello et al.[1] have not formulated a threshold for metformin serum concentration because at the time of formulation of these recommendations, there was much uncertainty regarding the value of metformin concentrations in relation to the prognosis and the limited availability of the metformin assays. Some studies have shown a correlation between metformin concentration and mortality[8,9,20] while others have not.[17,21,25,26] Despite the uncertainty concerning its prognostic value, measuring metformin serum concentrations could be of diagnostic value in MALA and may assist in its management.[9,22,26] However, establishing a specific threshold for metformin serum concentrations is not possible based on the results of this study.

The EXTRIP criteria include lowering thresholds of pH and lactate for initiating ECTR in impaired kidney function, shock, decreased level of consciousness and liver failure but this is not quantified. The majority of the ECTR group in this study had impaired renal function and the mean pH and lactate concentration were 7.05 and 13.8 mmol/l respectively. In clinical practice, comorbidity is common and it is not always clear whether there is metformin accumulation, showing the heterogeneity regarding the EXTRIP criteria and real-life scenarios. Because of this heterogeneity, formulating more concise criteria for initiating ECTR in MALA patients is very difficult. The main reasons for not initiating ECTR in this study were recovery after starting supportive care or death shortly after admission. Six patients who met the EXTRIP criteria were not treated with ECTR and died. At the time of admission of these patients, the EXTRIP criteria were not implemented in our hospital. Four out of these six patients died within 1 day from cardiac arrest and there was no renal indication for starting ECTR. Additionally, in the non-ECTR group, 54% of patients had serum metformin concentrations lower than 5 mg/l which is in line with the 'normal' value of serum metformin concentrations in therapeutic use.[4,27] Therefore, it is debatable whether metformin was the cause of MALA in these patients. Lalau et al.[4] suggested adding serum metformin concentration higher than 5 mg/l as criterion to MALA to distinguish it from metformin unrelated lactic acidosis (MULA). However, we used the definition of MALA pH < 7.35 and lactate > 5 mmol/l in association with metformin exposure as formulated by Calello et al.[1] because we wanted to evaluate Calello's recommendations in clinical practice. In addition, we validated metformin exposure by only including patients with verifiable serum metformin concentrations to avoid discussion about metformin exposure.

The present study is one of the largest cohort studies regarding the management of MALA. The strength of our study is that metformin concentrations, lactate, blood pH and kidney function were measured simultaneously on admission and during subsequent treatment. Furthermore, only patients with verified metformin serum concentrations

were included. Lalau et al.[4] presented the lack of these combined data as major methodological flaw in most studies on MALA. However, we did not measure metformin concentrations in erythrocytes, which probably better reflects metformin tissue effects, and we have no information on last intake so we cannot refer to peak versus trough concentrations.[4] A limitation of our study is that other causes of lactic acidosis were not ruled out which could have influenced the mortality in this study. Other limitations include the retrospective and monocentric design and selection bias. We selected patients based on serum metformin concentration measurement. MALA patients without serum metformin concentration measurement could have been missed. Finally, as presented in the EXTRIP guidelines, metformin and lactate clearance are lower with continuous renal replacement therapy (CRRT) than with intermittent HD. As such, the predominant use of CVVH in our study might have weakened the results in favor for ECTR.

For clinical practice, we recommend that clinicians be alert to MALA in the Emergency Department when patients are admitted with lactic acidosis in combination with metformin use. ECTR might be lifesaving in the treatment of MALA and should therefore be considered at an early stage. The EXTRIP-criteria are a good starting point for the decision to start ECTR but each individual patient needs to be evaluated separately. Severity of lactic acidosis and renal impairment are the main indications for initiating ECTR. Knowledge of the metformin concentrations may be a valuable additional parameter for the diagnosis and management of MALA. Therefore, we recommend implementing metformin assays as routine investigation with 24-hour availability in hospitals treating MALA patients.



## Conclusion

Although there was no statistical difference in mortality between the treatment with or without ECTR, ECTR might be lifesaving in treating MALA. Patients in the ECTR group were sicker compared to the non-ECTR group considering the degree of lactic acidosis, kidney function and vasopressor requirement and had at least a comparable mortality. In 83% of the patients, treatment was in line with the EXTRIP criteria. Severity of lactic acidosis and renal impairment were the main indications for initiating ECTR. Measuring serum metformin concentrations may assist in the diagnosis and management of MALA.

## Ethics approval

This study was assessed by the Medical Ethical Committee of Isala Hospital (Zwolle, the Netherlands) and approved as a non-interventional study.

# References


1. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med* 2015;43(8):1716-1730
2. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-865
3. Wang GS, Hoyte C. Review of biguanide (metformin) toxicity. *J Intensive Care* 2018; doi: 10.1177/0885066618793385
4. Lalau JD, Kajbaf F, Protti A, Christensen MM, De Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): Moving towards a new paradigm. *Diabetes Obes Metab* 2017;19(11):1502-1512
5. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risks. *Metabolism* 2016;65(2):20-29
6. Berlo van - Laar van de IRF, Vermeij CG, Doorenbos CJ. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. *J Clin Pharm Ther* 2011;36(3):376-382
7. Kuan HIS, Savage RL, Dufull SB, Walker RJ, Wright DFB. The association between metformin therapy and lactic acidosis. *Drug Saf* 2019; aug 1
8. Boucaud-Maitre D, Ropers J, Porokhov B, Altman JJ, Bouhanick B, Doucet. J et al. Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. *Diabet Med* 2016;33:1536-1543
9. Corchia A, Wynckel A, Journet J, Frances JM, Skandrani N, Lautrette A. et al. Metformin-related lactic acidosis with acute kidney injury: results of a French observational multicentre study. *Clin Toxicol* 2019;aug 6:1-8
10. Semely D, Bennett E, Vallejo C, Saint-Marcoux F, Merle L, Nouaille Y et al. Can an early diagnostic procedure of metformin-associated lactic acidosis in an emergency unit reduce mortality? *Therap* 2016;71(6):605-612
11. Jung B, Martinez M, Claessens YE, Darmon M, Klouche K, Lautrette A. et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care* 2019;9:92
12. Moioli A, Maresca B, Manzione A, Napoletano AM, Coclite D, Pirozzi N, et al. Metformin associated lactic acidosis (MALA): clinical profiling and management. *J. Nephrol* 2016;29(6):783-789
13. Mariano F, Pozzato M, Inguaggiato P, Guarena C, Turello E, Manes M, et al. Metformin-Associated Lactic Acidosis Undergoing Renal Replacement Therapy in Intensive Care Units: A Five Million Population-Based Study in the North-West of Italy. *Blood Purif* 2017;44(3):198-205
14. Angioi A, Cabiddu G, Conti M, Pili G, Atzeni A, Matta V, et al. Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long term follow up. *BMC Nephrol* 2018;19(1):77
15. EXTRIP-workgroup. Metformin [internet]: accessed February 12, 2019. Available from: https://www.extrip-workgroup.org/metformin
16. UMC Utrecht Nationaal Vergiftigingen Informatie Centrum. Metformine [internet]. Utrecht: UMC Utrecht Nationaal Vergiftigingen Informatie Centrum; Accessed June 1, 2019. Available from: https://www.vergiftigingen.

info/f?p=300:STOFMONOGRAFIE:10568776339678::NO:::
17. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: A prognostic and therapeutic study. *Crit Care Med* 2009;37(7):2191-2196
18. Greco P, Reolisti G, Maggiore U, Feriolo E, Fani F, Loratelli C et al. Sustained low-efficiency dialysis for metformin associated lactic acidosis in patients with acute kidney injury. *J Nephrol* 2019;32(2):297-306
19. Peters N, Jay N, Barraud D, Cravoisy A, Nace L, Bollaer PE, et al. Metformin-associated lactic acidosis in an intensive care unit. *Crit Care* 2008;12(6):R149
20. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care* 2010;14:R226
21. Vecchio S, Giampretti A, Petrolini M, Lonati D, Protti A, Papa P et al. Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. *Clin Toxicol* 2014;52:129-135
22. Duong JK, Furlong TJ, Roberts DM, Graham GG, Greenfield JR, Williams KM, Day RO. The role of metformin in metformin-associated lactic acidosis (MALA): case series and formulation of a model of pathogenesis. *Drug Saf* 2013;36:733-746
23. Nouland van den DPA, Brouwers MCG, Stassen PM. Prognostic value of plasma lactate levels in a retrospective cohort presenting at a university hospital emergency department. *BMJ Open* 2017;7:e011450
24. Kjelland CB, Djogovic D. The role of serum lactate in the acute care setting. *J Intensive Care Med* 2010;25(5):286-300
25. Yeh HC, Ting IW, Tsai CW, Wu JY, Kuo CC. Serum lactate level and mortality in metformin associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. *BMC Nephrol* 2017;18(1):229
26. Kajbaf F, Lalau JD. The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. *BMC Pharmacol Toxicol* 2013;14:22
27. Kajbaf F, De Broe ME, Lalau JD. Therapeutic Concentrations of Metformin: a Systematic Review. *Clin Pharmacokinet* 2016;55(4):439-459

**Supplementary table 1 Patient characteristics ECTR group**

| Nr | Sex | Age (years) | pH | Lactate (mmol/l) | Bic (mmol/l) | Metformin (mg/l) | Creatinine (umol/l) | Diagnosis | DC | VR | MVR | LoS (days) | Out-come | Reason ECTR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 67 | 7.05 | 19.0 | 8 | 2.9 | 478 | Hemorrhagic shock | Y | N | N | 34 | D | Renal failure |
| 2 | F | 66 | 7.12 | 13.5 | 7 | 19.4 | 640 | Dehydration | Y | Y | N | 120 | S | Severe metabolic acidosis and renal failure with metformin use |
| 3 | F | 75 | 7.03 | 16.5 | 7 | 5.0 | 266 | Myocardial infarction | Y | Y | N | 2 | D | Severe metabolic acidosis and renal failure with metformin use |
| 4 | F | 75 | 7.22 | 5.8 | 12 | 32 | 813 | Myocardial infarction | N | N | N | 18 | S | Renal failure |
| 5 | M | 58 | 6.77 | 23 | 2 | 38 | 1039 | Dehydration | N | Y | Y | 19 | S | Severe metabolic acidosis and renal failure with metformin use |
| 6 | F | 72 | 7.15 | 14.5 | 8 | 20 | 814 | Renal failure | N | N | N | 38 | S | Severe metabolic acidosis and renal failure with metformin use |
| 7 | F | 77 | 7.18 | 11.1 | 7 | 25.4 | 960 | Dehydration | N | N | N | 22 | S | Renal failure, hyperkalaemia, MALA |
| 8 | F | 68 | 7.07 | 9.9 | 10 | 22 | 706 | Dehydration | N | N | N | 2 | S | Renal failure, hyperkalaemia |
| 9 | F | 78 | 6.94 | 20.3 | 4 | 44 | 612 | Dehydration | N | Y | N | 2 | S | Severe metabolic acidosis and renal failure with metformin use |
| 10 | F | 62 | 6.9 | 13.8 | 2 | 34 | 590 | Dehydration | Y | Y | N | 14 | S | Severe metabolic acidosis and renal failure with metformin use |
| 11 | F | 82 | 6.82 | 23.2 | 2 | 47 | 691 | Dehydration | N | Y | N | 15 | S | Severe metabolic acidosis and high metformin serum concen-tration |
| 12 | F | 56 | 7.12 | 8.8 | 7 | 31 | 882 | Dehydration | Y | Y | N | 7 | S | Severe metabolic acidosis and renal failure with metformin use, hyperkalaemia |
| 13 | F | 67 | 7.25 | 6.6 | 12 | 22.8 | 519 | Pneumonia | N | Y | N | 18 | D | Lactic acidosis and high met-formin serum concentration |
| 14 | F | 62 | 6.61 | 15.6 | 4 | 45 | 808 | Septic shock | Y | Y | Y | 2 | D | Failure supportive care, severe metabolic acidosis and high metformin serum concentration |
| 15 | F | 76 | 7.12 | 8.0 | 3 | 27.5 | 669 | Urosepsis | N | Y | N | 14 | S | Failure supportive care, high metformin serum concentration |
| 16 | F | 72 | 6.82 | 11.2 | 4 | 45 | 1004 | Dehydration | N | Y | N | 2 | D | Severe metabolic acidosis and renal failure with metformin use |
| 17 | M | 82 | 7.12 | 8.8 | 8 | 4.1 | 414 | Urosepsis | N | N | N | 25 | S | Renal failure, hyperkalaemia |
| 18 | M | 87 | 7.34 | 11.7 | 9 | 8.2 | 263 | Urosepsis | N | Y | N | 2 | D | MALA |
| 19 | F | 79 | 6.94 | 13.5 | 2 | 46 | 642 | Dehydration | N | Y | N | 8 | S | Failure supportive care, se-vere metabolic acidosis |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | F | 78 | 7.22 | 14.3 | 8 | 12.6 | 147 | Heart failure | N | N | N | 11 | D | MALA |
| 21 | F | 70 | 6.98 | 12.8 | 8 | 42.4 | 419 | Septic shock | Y | Y | Y | 5 | D | Severe metabolic acidosis, high metformin serum concentration |
| 22 | F | 69 | 7.22 | 19 | 7 | 23.4 | 523 | Dehydration | N | Y | N | 9 | S | Failure supportive care, lactic acidosis, renal failure, high metformin serum concentration |
| 23 | F | 82 | 6.66 | 10.6 | 2 | 44.5 | 574 | Septic shock | Y | Y | Y | 60 | S | Renal failure, severe metabolic acidosis |
| 24 | F | 72 | 7.14 | 6.5 | 8 | 30.4 | 841 | Sepsis | N | Y | Y | 17 | D | Failure supportive care |
| 25 | F | 72 | 7.16 | 14 | 4 | 2.3 | 140 | Heart failure | Y | N | N | 11 | D | MALA |
| 26 | M | 58 | 7.00 | 21.6 | 6 | 100 | 208 | Intentional overdose | N | Y | Y | 10 | S | Severe metformin intoxication, lactic acidosis |
| 27 | M | 52 | 7.26 | 11.4 | 13 | 50 | 113 | Intentional overdose | N | Y | N | 5 | S | Severe metformin intoxication, lactic acidosis |
| 28 | M | 69 | 7.17 | 16 | 5 | 4.6 | 255 | Hemorrhagic shock | N | Y | N | 3 | D | Renal failure, MALA |
| 29 | F | 65 | 6.97 | 18 | 4 | 23.3 | 645 | Dehydration | N | Y | N | 8 | S | Renal failure, hyperkalaemia, MALA |

DC = decreased conciousness: Y= yes, N = no, U = unknown

VR = Vassopressor requirement: Y= yes, N = no

MVR = mechanical ventilation requirement: Y= yes, N = no

LoS = Length of Stay

Outcome: D = died, S = survived

MALA = metformin associated lactic acidosis





**Supplementary table 2 Patient characteristics non-ECTR group**

| Nr | Sex | Age (years) | pH | Lactate (mmol/l) | Bic (mmol/l) | Metformin (mg/l) | Creatinine (umol/l) | Diagnosis | DC | VR | MVR | LoS (days) | Outcome | Reason ECTR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 78 | 6.85 | 10.2 | 2 | 4 | 547 | Dehydration | N | N | N | 1 | D | Supportive care but cardiac arrest and passed away the same night |
| 2 | F | 87 | 7.24 | 9.4 | 10 | 2.5 | 146 | Cardiogenic shock, myocardial infarction | N | N | N | 2 | D | Supportive care but passed away within 1 day after admittance |
| 3 | F | 85 | 7.33 | 8.8 | 13 | 6.8 | 257 | Hypovolemic shock by bleeding | N | N | N | 10 | S | Recovery with supportive care |
| 4 | F | 58 | 7.04 | 12.6 | 7 | 37 | 720 | Sepsis | N | N | N | 6 | S | Recovery with supportive care |
| 5 | M | 89 | 7.3 | 9.4 | 12 | 6.1 | 136 | Hypovolemic shock by bleeding | N | N | N | 12 | S | Recovery with supportive care |
| 6 | M | 63 | 7.31 | 9 | 14 | 3 | 73 | MALA | N | N | N | 3 | S | Recovery with supportive care |
| 7 | F | 80 | 7.14 | 13.3 | 12 | 3 | 366 | Pneumosepsis | Y | N | N | 2 | D | No recovery with supportive care, conservative policy because of bad prognosis, passed away within 1 day after admittance |
| 8 | M | 58 | 7.08 | 8.8 | 11 | 7.9 | 207 | Myocardial infarction | N | Y | Y | 1 | D | No recovery with supportive care, passed away within 1 day after admittance from cardiac arrest |
| 9 | F | 77 | 7.32 | 10.4 | 11 | 29.3 | 70 | MALA | Y | N | N | 3 | S | Recovery with supportive care |
| 10 | F | 88 | 7.3 | 11 | 14 | 2.3 | 126 | Pneumonia, 3rd grade AV-block | N | Y | N | 32 | D | No recovery with supportive care, passed away probably from sepsis |
| 11 | M | 83 | 7.33 | 9.3 | 7 | 2.4 | 158 | Cardiogenic shock | U | N | N | 17 | S | Recovery with supportive care |
| 12 | F | 78 | 7.33 | 6.7 | 17 | 2.2 | 200 | Dehydration | N | N | N | 12 | S | Recovery with supportive care |
| 13 | M | 77 | 6.86 | 18 | 6 | 5.5 | 301 | Myocardial infarction | Y | Y | N | 1 | D | Passed away after cardiopulmonary resuscitation (CPR) |

DC = decreased conciousness; Y= yes, N = no, U = unknown
VR = Vassopressor requirement: Y= yes, N = no
MVR = mechanical ventilation requirement: Y= yes, N = no
LoS = Length of Stay
Outcome: D = died, S = survived
MALA = metformin associated lactic acidosis





# Part 3

Binding interactions

# Chapter 7

## Subtherapeutic quetiapine serum concentrations after absorption inhibition by binding resins: a case report

*J Clin Pharm Ther. 2015; 40(3): 355-357*

Rien HL Hoge
Maurits EL Arbouw
Steven DWS Radstake
Inge RF van Berlo – van de Laar

# Abstract

We describe a patient with unexplainable low serum quetiapine concentrations. Our hypothesis was that this could be caused by a potential drug-drug interaction between quetiapine and the binding resins polysterene sulfonate and sevelamer. First, we performed an *In vitro* binding assay which showed pH-independent absorbance inhibition of quetiapine by polystyrene sulfonate and pH-dependent absorbance inhibition by sevelamer. Second, the time of ingestion of quetiapine, polysterene sulfonate and sevelamer was separated, where after serum quetiapine concentrations rose from <20 µg/L to 345 µg/L (therapeutic $C_{min}$ range 100 - 500 µg/L). Our observations were complicated by the start of concurrent haemodialysis treatment. However this led to another observation: a substantial amount of quetiapine is probably extracted during haemodialysis. Psychiatrists and other clinical physicians should be aware of this potential drug-drug interaction as this could lead to treatment failure with quetiapine.

# Introduction

Quetiapine is a second generation antipsychotic drug that is being used in the first-line treatment of several mental disorders such as psychosis, bipolar disorder and depression.[1,2] Low serum quetiapine concentrations can lead to therapy failure.

Sodium polystyrene sulfonate (Resonium A®) is a potassium-binding resin used for the treatment of hyperkalemia in a dosage of 15 grams qd-qid.[3] Polystyrene sulfonate is not absorbed from the gastro-intestinal tract and is completely excreted in the faeces.[4] Binding drug interactions with sodium polystyrene sulfonate which may result in lower plasma levels of the bound drugs are known following simultaneous oral use of either lithium or thyroxine.[4] Sevelamer carbonate (Renvela®) is a potent phosphate binder which is most effective if taken with meal to bind dietary phosphate in the treatment of hyperphosphatemia. Sevelamer is not absorbed from the gastrointestinal tract.[11] Bio-availability of ciprofloxacin is significantly reduced when co-ingested with sevelamer.[5] There are also reports of reduced serum concentrations of several immunosuppressive drugs during concurrent use with sevelamer.[6,7] This case report describes a patient with unexplained low serum quetiapine serum concentrations, possibly due to co-treatment with polystyrene sulfonate and sevelamer.

# Case description

A 45-year-old female with bipolar disorder and diabetic nephropathy was treated with quetiapine, polystyrene sulfonate, sevelamer, furosemide, insulin, atorvastatin, ipratropium, irbesartan and sodium hydrogen carbonate. In January 2014 she was admitted to our hospital for diabetic disregulation. A serum quetiapine concentration was determined because of a suspicion of adverse effects. The serum quetiapine concentration revealed to be < 20 µg/L (therapeutic range through levels between 100 - 500 µg/L). The dose quetiapine was Seroquel XR 800 mg qd. This low concentration could be caused by non compliance, however, after 7 days of hospitalisation and administration of quetiapine by a nurse the serum quetiapine concentration was 40 µg /L, still subtherapeutic.

Another explanation could be enhanced metabolism of quetiapine by CYP3A5*1 polymorphism.[8] However the patient was genotyped as being wild type homozygous CYP3A5*3, so the low serum concentration could not be explained by this pharmacogenetic marker. Evaluation of the co-medication did not reveal any known drug-drug interactions, but she used polystyrene sulfonate and sevelamer for which binding interactions are known.[4-7] The polystyrene sulfonate 15 g qd was co-ingested with quetiapine at 8 AM. Sevelamer was dosed as 2,4 g at 8 AM, 12 PM, and 10 PM, and 4,8 g at 5 PM. We suspected these drugs to bind quetiapine analogous to other drugs, causing absorption inhibition of quetiapine resulting in low serum concentrations.

## In-vitro binding assay

In order to investigate possible binding of polystyrene sulfonate or sevelamer to quetiapine, a binding assay was performed in twofold. Therefore 800 mg quetiapine fumarate was dissolved in 600 ml water alone and together with either 15 g polysterene sulfonate and 2,4 g sevelamer. The intraluminal pH of the gastro-intestinal tract fluctuates from pH < 3 in the stomach to 7.4 in the terminal ileum and drops to 5.7 in the caecum.[9] In order to simulate the different pH environments of the gastro-intestinal tract, which may affect binding, the assays were executed at pH 1.5, 5.0 and 7.4, adjusted with either sodium hydroxide or hydrochloric acid. Twenty-five ml of the assay solution was incubated at 37°C for 1 hour under gently shaking conditions after which it was centrifuged and the quetiapine concentration of the supernatant was analysed by HPLC-DAD. The results of the binding assays are depicted in figure 1. Nearly all quetiapine was bound to polystyrene sulfonate (99,1%) independent of the tested pH. Quetiapine was partly bound to sevelamer (62% and 70% at respectively pH 5.0 and 7.4). Under very acidic conditions (pH 1.5) no binding to sevelamer was observed. In the control samples binding percentages of quetiapine were found of about 10% independent of pH, which is probably explained by recovery loss of the assay. These results support the hypothesis that quetiapine could be bound by polystyrene sulphonate and dependent on the pH partly by sevelamer.

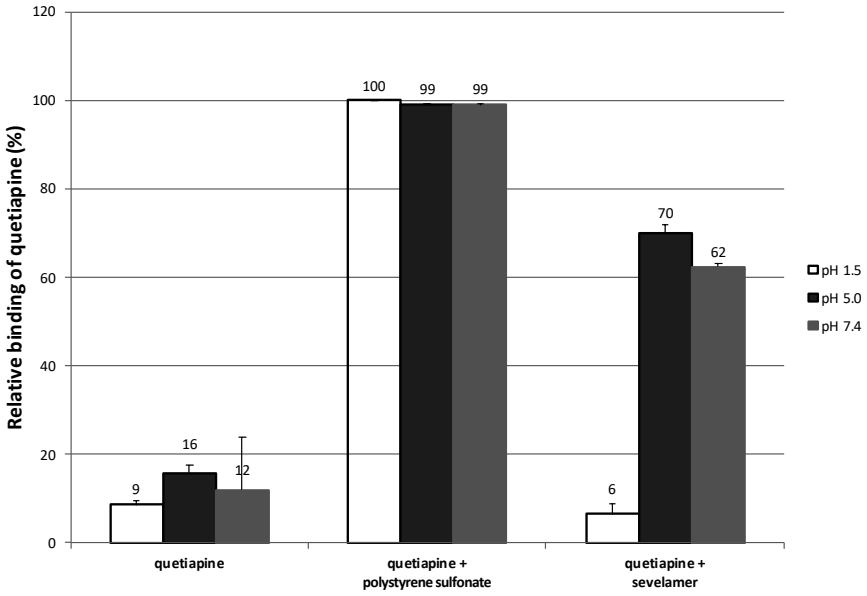


**Figure 1 Relative binding of quetiapine fumarate in vitro experiment with polystyrene sulfonate or sevelamer at different pH.**

Error bars represent standard deviation of two independent measurements

## Separating administration of quetiapine and the resins

In order to further investigate the results from the *in-vitro* experiment in our patient, we changed the time of the quetiapine dose to 10 PM, the polystyrene sulfonate dose to 8 AM and the sevelamer doses to 8 AM, 12 PM and 5 PM. Meanwhile haemodialysis was started in this patient because of further decline of her kidney function. Renal insufficiency should not affect serum quetiapine concentrations but the effect of haemodialysis on serum quetiapine concentrations is unknown.[12,13] Therefore the serum quetiapine concentration was determined before dialysis and after dialysis (duration of the dialysis was 4 hours). The results were 345 µg/L and 145 µg/L respectively.

## Discussion

Both polysterene sulfonate and sevelamer are important medicines in the binding of potassium and phosphate respectively. However, little is known about the drug-drug interactions between these resins and quetiapine.

We demonstrated with the *in-vitro* test that quetiapine binds to polystyrene sulfonate and sevelamer. Separating the administration of quetiapine, polystyrene sulphonate and sevelamer resulted in significantly higher serum quetiapine concentrations, from subtherapeutic to therapeutic concentrations. The interpretation of the serum concentrations was however complicated by the start of haemodialysis treatment. In order to examine the influence of haemodialysis serum quetiapine concentrations were measured before and after 4 hours of dialysis. The concentration dropped from 345 µg/L to 145 µg/L indicating that a substantial amount of quetiapine is extracted. Based on these observations we therefore conclude that the absorption of quetiapine improved by separating the co-ingestion of quetiapine with either polystyrene sulfonate and sevelamer. However, our case report has several shortcomings as our *in-vivo* data is limited to one patient. We separated the ingestion times of quetiapine, polystyrene sulfonate and sevelamer but quetiapine was administered as an extended-release formulation which gradually releases the active substance over a period of 20 hours.[10] How long polysterene sulfonate is present in the intestinal tract in unknown. For sevelamer the manufacturer recommends to ingest co-medication 1 hour before or 3 hours after sevelamer intake to avoid possible interactions.[11] Because of the extended-release formulation of quetiapine it is possible that separating the ingestion times not entirely led to elimination of binding of quetiapine to sevelamer or polystyrene sulfonate. Quetiapine immediate release tablets are maybe a better alternative.

During the observation period, our patient started with haemodialysis, which complicated the interpretation of the results, however renal insufficiency should not influence quetiapine serum concentrations. Nevertheless, we think that the *in-vitro* and *in-vivo*

results give a strong indication of a possible quetiapine absorbance inhibition by polysterene sulfonate and sevelamer which needs further investigation. Also, this is the first report that shows that quetiapine is being extracted during haemodialysis which also justifies further research.

Psychiatrists, clinical physicians and pharmacists should be aware of this potential drug-drug interaction as this could lead to treatment failure with quetiapine. We recommend to separate the ingestion times, use quetiapine immediate release tablets and monitor clinical response and serum quetiapine concentrations when patients are treated with quetiapine together with either two of these resins.

# References


1. Asmal L, Flegar SJ, Wang J, Rummel-Kluge C, Komossa K, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia (Review). *Cochrane Database Syst Re*v 2013;11:CD006625
2. Adityanjee, Schulz SC. Clinical use of quetiapine in disease states other than schizophrenia. *J Clin Psychiatry* 2002;63 Suppl 13:32-38
3. Chaaban A, Abouchacra S, Gebran N, Abayechi F, Hussain Q, Al Nuaimi N, Hassan ME. Potassium Binders in Hemodialysis Patients: A Friend or Foe? *Ren Fail* 2013;35(2):185-188
4. Summary of product characteristics, Resonium A, Dutch Medicines Evaluation Board, 2 may 1990
5. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of Sevelamer Hydrochloride and Calcium Acetate on the Oral Bioavailability of Ciprofloxacin. *Am J Kidney Dis* 2003;42(6):1253-1259
6. Pieper AK, Buhle F, Bauer S, Mai I, Budde K, Haffner D, Neumayer HH, Querfeld U. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004;19(10):2630-2633
7. Merkle M, Wornle M, Rupprecht HD. The effect of sevelamer on tacrolimus target levels. *Transplantation* 2005;80(5):707
8. Kim KA, Joo HJ, Lee HM, Park JY. Influence of ABCB1 and CYP3A5 genetic polymorphisms on the pharmacokinetics of quetiapine in healthy volunteers. *Pharmacogenet Genomics* 2014;24(1):35-42
9. Fallingborg J. Intraluminal pH of the human gastrointestinal tract. *Dan Med Bull* 1999;46(3):183-196
10. Bui K, Earley W, Nyberg S. Pharmacokinetic profile of the extended-release formulation of quetiapine fumarate (quetiapine XR): clinical implications. *Curr Med Res Opin* 2013;29(7):813-825
11. Summary of product characteristics, Renvela, European Medicines Agency, 10 June 2009
12. Summary of product characteristics, Seroquel, European Medicines Agency, August 2013
13. The Renal Drug Handbook (Third Edition), edited by Ashley C & Currie A, 2009, monograph Quetiapine, p.626

# Chapter 8

## Exploring co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential novel binding interactions: a cross sectional in silico study

*Submitted*

Inge RF van Berlo – van de Laar*
Ilona Prins - Can*
Nyncke CM Schuiling - Veninga
Katja Taxis
Frank GA Jansman

*Both authors contributed equally to the manuscript

# Abstract


## Background

Sevelamer and polystyrene sulfonate are used for treating hyperphosphatemia and hyperkalaemia in chronic kidney disease patients. Because of their binding properties, these resins potentially bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness.

## Aim

The aim of this study was to explore co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential novel binding interactions.

## Method

In this *in silico* study, the 100 drugs most frequently co-dispensed with sevelamer/polystyrene sulfonate in the period 2000-2018 from the University Groningen IADB.nl database were extracted. Drugs dispensed to < 5% of patients, drugs not orally administered, drugs administered once daily before bedtime and drugs for which information on binding interactions with sevelamer or polystyrene was already available were excluded. The likelihood of an interaction (yes or no) of the included drugs was assessed based on pKa- and Log P values. For sevelamer, drugs with a pKa (acid) between 1.5 and 7.4 and or a Log P value > 2.0 were identified as potential interacting drug. For polystyrene sulfonate, drugs with a pKa (base) > 1.5 were identified as potential interacting drug.

## Results

Of the top 100 drugs most frequently co-dispensed with sevelamer/polystyrene sulfonate, 22 and 27 potentially clinically relevant new interacting drugs were identified for sevelamer and polystyrene sulfonate respectively.

## Conclusion

Several potentially relevant novel binding interactions for sevelamer and polystyrene sulfonate were identified based on dispensing data and assessment of chemical properties for which further interaction research is warranted.

# Introduction

Resins, such as sevelamer and polystyrene sulfonate, are often used for binding phosphate and potassium to treat hyperphosphatemia and hyperkaliemia which can cause serious complications in patients with Chronic Kidney Disease (CKD).[1,2] Because of their binding properties, these resins potentially bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. CKD patients often use many different drugs, due to comorbidities such as cardiovascular diseases, diabetes mellitus, metabolic disorders, gout and anaemia. Most often prescribed drug groups are cardiovascular drugs, antidiabetic agents, drugs for acid related gastro-intestinal disorders, anti-gout preparations and agents for the treatment of mineral bone disorder.[3,4] Due to the high number of prescribed drugs, the prevalence of potential drug-drug interactions in CKD patients is high, varying from 75 to 91%.[5-9] For instance phosphate binders, used by 85% of haemodialysis patients, show several drug-drug interactions in clinical practice.[10,11] Sevelamer is the phosphate binder of first choice because it reduces mortality when used as an alternative or addition to calcium containing phosphate binders.[10,12] Furthermore, the use of calcium containing phosphate binders needs to be restricted due to an increased risk of metastatic and vascular calcifications.[2] Sevelamer is a non-absorbed polymer, free of metal and calcium. It contains several amines separated by one carbon from the polymer backbone. The amines become partially protonated in the gastro-intestinal tract and interact with phosphate molecules through ionic and hydrogen binding. This binding decreases the bioavailability of phosphate and thereby decreases elevated serum phosphate concentrations. In addition to its phosphate-binding properties, sevelamer acts as a bile acid sequestrant and significantly reduces low-densitiy lipoprotein (LDL) cholesterol levels.[13]

Polystyrene sulfonate (available as sodium or calcium salt) is a cation-exchanging resin that has been widely used for several decades as first-line therapy of mild chronic hyperkaliemia in patients with CKD.[1,2] It lowers the plasma potassium concentration through exchange of potassium and sodium/calcium ions in the gastro-intestinal tract, mainly in the colon and partly in the small intestine. Polystyrene sulfonate itself is not absorbed from the gastro-intestinal tract.[14,15]

Studies and case reports investigating binding interactions of sevelamer show that sevelamer binds to levothyroxine, ciprofloxacin, mycophenolic acid, tacrolimus, cyclosporine, vitamin D analoga, lipid soluble vitamins like vitamin A, E and K, folic acid, quetiapine and furosemide.[11,13-23] For polystyrene sulfonate, binding interactions have been described with lithium, quetiapine and levothyroxine.[22,24,25] Based on the chemical mechanism of the known binding interactions there are possibly many more drugs that bind to sevelamer and/or polystyrene sulfonate. The Summary of Product Characteristics (SmPC) of

polystyrene sulfonate underlines this by discouraging taking other oral medication three hours before or after polystyrene sulfonate intake.[26] In the Netherlands, only the known binding interactions are included in the electronic medication surveillance systems with the advice for staggered dosing between drugs. However, this advice is difficult to accomplish in a patient group using on average 8 different drugs per day.[3,4] In addition, nephrologists may not be aware of binding interactions of these resins with comedication and their clinical implications.[11] Therefore, more knowledge about potential binding interactions with sevelamer and polystyrene sulfonate is relevant for tailored management in clinical practice. To be able to identify clinically relevant binding interactions, co-dispensed drug use of patients using sevelamer and or polystyrene sulfonate should be investigated.

# Aim

The aim of the present study was to explore co-dispensed drug use of patients on sevelamer or polystyrene sulfonate to identify drugs for which further interaction research is warranted based on their chemical properties.

# Ethics approval

No ethics committee approval is needed for research using anonymous medical records. This study was conducted in accordance with the Declaration of Helsinki.

# Methods

## Design and setting

This study used an *in silico* strategy to detect potential novel drug-drug interactions. In a cross sectional study, we used pharmacy dispensing data from the population-based University Groningen, IADB.nl prescription database.[27,28] The database comprises prescription drug dispensing data from more than 70 community pharmacies in the northern and eastern part of the Netherlands since 1994, covering a population of approximately 700,000 people. Prescription rates among this database population have been found to be representative for the Netherlands as a whole and the database is widely used in research.[27] The database includes demographic information such as date of birth and gender and medication information with Anatomical Therapeutic Chemical (ATC) codes, dispensing date, amount and dose dispensed, number of defined daily doses dispensed and period of drug coverage, i.e. the period of time in days for which the patient had drugs dispensed.[27] Due to a high patient pharmacy commitment in the Netherlands and sophisticated software, the medication records for each patient are virtually complete, except for over-the-counter drugs and medicines dispensed during hospitalization.

## Study population and Outcome definition

From the IADB database all patients using sevelamer (ATC-code V03AE02) and/or polystyrene sulfonate (ATC-code V03AE01) for at least 90 days in a period of 12 months between 1st January 2000 to 31st December 2018 were selected. The different options for identification of co-dispensed drugs are graphically depicted in figure 1 using drugs A, B, C and D as examples. Drugs were identified as 'co-dispensed' when they were dispensed before the first/follow up date of dispensing sevelamer/polystyrene sulfonate and the use covered a period ending after the dispensing date of sevelamer/polystyrene sulfonate (drug A and B). Furthermore, all drugs, which were dispensed after the first/follow up dispensing date of sevelamer/polystyrene sulfonate, but before the last day of coverage with sevelamer/polystyrene sulfonate, were included (drug C and D).

The number of patients who received a drug which was co-dispensed with sevelamer/polystyrene sulfonate during the study period was extracted from the database. A co-dispensed drug in combination with sevelamer or polystyrene sulfonate was counted only once for every individual patient. Therefore, this number is further referred to as 'unique drug-sevelamer/polystyrene sulfonate combination'.

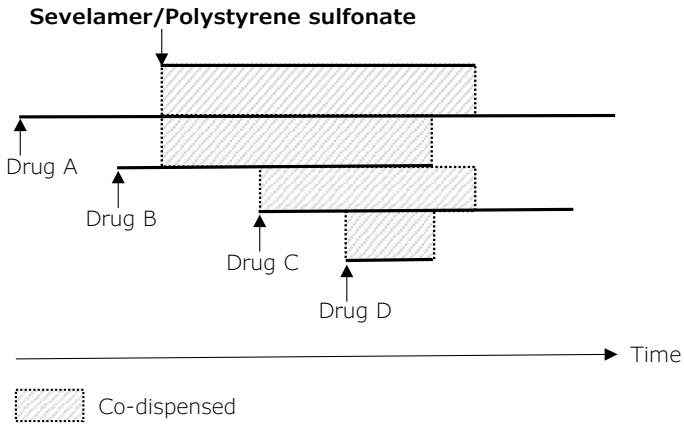


**Figure 1 Graphic presentation of the identification of drugs A, B, C and D which were co-dispensed with sevelamer or polystyrene sulfonate**

## Analysis

*Patient characteristics*

We determined the mean age (including standard deviation and range) of sevelamer/polystyrene sulfonate users on July first of each study year from 2000 to 2018. Because there were no relevant differences between these results, we only reported the age data of 2009, the middle of the study period, in the results section.

*Top 100 co-dispensed drugs - first level of ATC classification*
The 100 drugs most frequently co-dispensed with sevelamer or polystyrene sulfonate during the study period were categorized in the first ATC-class level. Therefore, we combined the number of unique drug-sevelamer/polystyrene sulfonate combinations within the defined ATC-class first level. Subsequently, we calculated the percentage by dividing this number by the total number of unique drug-sevelamer/polystyrene sulfonate combinations in the top 100.

*Top 100 co-dispensed drugs*
We determined the percentage of sevelamer/polystyrene sulfonate users who received each drug from the top 100 during the study period, by dividing the number of unique drug-sevelamer/polystyrene sulfonate combinations by the total number of patients using sevelamer/polystyrene sulfonate.

*Drugs for which further interaction research is warranted*
From the list of 100 most frequently co-dispensed drugs we excluded all drugs, which were registered in duplicate. For example, calcium carbonate and cholecalciferol were amongst the top 100 drugs included as mono-preparations as well as a combination product. In this case, we excluded the combination product. We also excluded drugs dispensed to < 5% of the patients and drugs not orally administered. Furthermore, we excluded drugs usually administered once daily at bedtime, since for this dosage regimen an interaction with sevelamer or polystyrene sulfonate is unlikely. Finally, all the drugs for which there is evidence for an interaction or evidence that there is no interaction based on literature were excluded (supplementary data).[14-26,30,31] This resulted in a list of drugs co-dispensed with sevelamer or polystyrene sulfonate, the number of unique drug-sevelamer/polystyrene sulfonate combinations and the percentage of patients having received the combination during the study period.
Thereafter the likelihood of an interaction with sevelamer was assessed based on the pKa (acid) and Log P value of the drugs.[31] Drugs with a pKa (acid) between 1.5 and 7.4 and/or a Log P > 2.0 were identified as potentially binding to sevelamer. Drugs with a pKa (acid) between 1.5 and 7.4 are at least 50% negatively charged in the gastrointestinal pH range of 1.5 to 7.4. Drugs with a Log P value > 2.0 are associated with potential binding to colesevelam and because sevelamer also acts as a bile sequestrant a Log P value > 2.0 was used as parameter for identifying potential binding to sevelamer.[34] Drugs with a pKa (base) > 1.5 were identified as potentially binding to polystyrene sulfonate because these drugs are at least 50% positively charged in the gastrointestinal pH range of 1.5 to 7.4. The drugs were categorized as 'Yes' (binding interaction expected) or 'No' (binding interaction not expected).

# Results

From the IADB-data base, 1,083 patients using sevelamer and 716 patients using polystyrene sulfonate for at least 90 days in a period of 12 months between January 2000 and December 2018 were identified. The patient characteristics are depicted in table 1.

**Table 1 Patient characteristics**

| | **Sevelamer N =1,083** | **Polystyrene sulfonate N=716** |
|---|---|---|
| Age*, years (mean (sd) [range]) | 62 (17) [1-89] | 58 (20) [10-95] |
| Gender (N (%)) | | |
| Male | 619 (57) | 471 (66) |
| Female | 464 (43) | 245 (34) |
| Duration S / PSP use, days (mean (sd) [range]) | 840 (759) [90-5247] | 576 (628) [90-3813] |
| Unique drug-S/PSP combinations (N (%)) | | |
| < 10 | 278 (25.7) | 293 (40.9) |
| 11-20 | 403 (37.2) | 275 (38.4) |
| 21-30 | 226 (20.9) | 95 (13.3) |
| 31-40 | 115 (10.6) | 41 (5.7) |
| 41-50 | 37 (3.4) | 10 (1.4) |
| > 50 | 24 (2.2) | 2 (0.3) |

* Age measured on 1th July 2009

sd: standard deviation
S: sevelamer
PSP: polystyrene sulfonate

Seven hundred and fifty-five different drugs were dispensed to the sevelamer users during this study period, which resulted in 20,801 unique drug-sevelamer combinations; 654 different drugs were dispensed to the polystyrene sulfonate users, which resulted in 10,311 unique drug-polystyrene sulfonate combinations.
We selected the 100 most frequently co-dispensed drugs with sevelamer and with polystyrene sulfonate. For these 100 drugs, 14,739 unique drug-sevelamer combinations and 7,123 unique drug-polystyrene sulfonate combinations were extracted from the database, which covered about 70% of the total unique drug-sevelamer/polystyrene sulfonate combinations.

Table 2 shows the categorization of these 100 drugs in ATC-class first level.
In sevelamer users, 58.6% of the co-dispensed drugs were from ATC-classes A, B and C and in polystyrene sulfonate users this was 66.8%. These included proton pump inhibitors,

laxatives, vitamin D analoga, antidiabetic agents as insulins, drugs for treating renal anaemia, antiplatelet coagulation drugs, antithrombotics, antihypertensive drugs, heart failure treatment and lipid lowering treatment. Other frequently co-dispensed drugs were dermatologicals (indifferent dermatological products, dermal corticosteroids, anti-infective treatment), ATC class H (prednisolon, cincacalcet, levothyroxine) ATC class L (mycophenolic acid, tacrolimus), ATC class M (allopurinol, colchicine), and ATC-class N (pain medication, benzodiazepines). The individual top 10 drugs co-dispensed with sevelamer (with the percentage of patients who received the combination during the study period) were alfacalcidol (59.4%), metoprolol (50.0%), omeprazole (43.5%), calcium carbonate (39.6%), furosemide (38.9%), acetylsalicylic acid (36.3%), amlodipine (33.1%), macrogol (31.5%), ferrofumarate (28.3%) and prednisolone (26.8%). For polystyrene sulfonate the individual top 10 included alfacalcidol (45.4%), metoprolol (43.4%), omeprazole (35.5%), furosemide (32.5%), amlodipine (30.7%), calcium carbonate (29.6%), ferrofumarate (27.9%), acetylsalicylic acid (26.3%), simvastatin (24.4%) and prednisolone (22.9%).

**Table 2: One hundred most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate, by ATC-class first level**

| Drug category (ATC-first level) | Sevelamer (N*, (%)) Ntotal =14,739 | Polystyrene sulfonate (N*, (%)) Ntotal = 7,123 |
|---|---|---|
| A. Alimentary tract and metabolism | 3,597 (24.4) | 1,660 (23.3) |
| B. Blood and blood forming organs | 1,806 (12.3) | 1,026 (14.4) |
| C. Cardiovascular system | 3,231 (21.9) | 2,074 (29.1) |
| D. Dermatologicals | 958 (6.5) | 416 (5.8) |
| G. Genito-urinary system and sex hormones | 50 (0.3) | 34 (0.5) |
| H. Systemic hormonal preparations, excluding sex hormones and insulines | 541 (3.7) | 259 (3.6) |
| J. Antiinfectives for systemic use | 1,378 (9.3) | 579 (8.1) |
| L. Antineoplastic and immunomodulating agents | 66 (0.4) | 72 (1.0) |
| M. Musculo-skeletal system | 374 (2.5) | 207 (2.9) |
| N. Nervous system | 1,408 (9.6) | 455 (6.4) |
| R. Respiratory system | 474 (3.2) | 156 (2.2) |
| S. Sensory organs | 293 (2.0) | 120 (1.7) |
| V. Various | 563 (3.8) | 65 (0.9) |

* number of unique drug-sevelamer/polystyrene sulfonate combinations

After application of the described exclusion criteria, a list of 39 drugs co-dispensed with sevelamer and 47 drugs co-dispensed with polystyrene sulfonate was compiled for further exploration of interaction potential (figure 2).

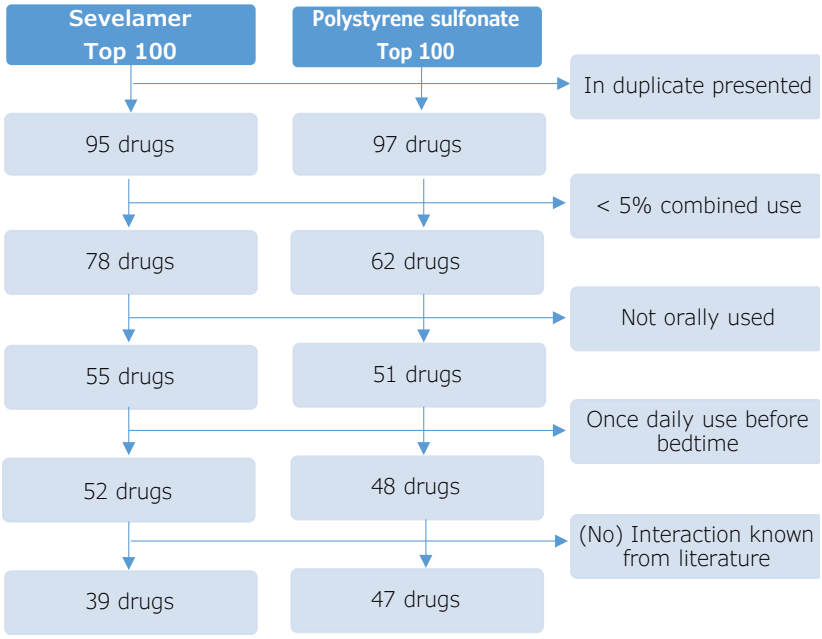


**Figure 2 Selection of co-dispensed drugs with sevelamer or polystyrene sulfonate for further interaction research**

Table 3 presents the selected drugs, the number of unique drug-sevelamer/polystyrene sulfonate combinations, the percentage of sevelamer/polystyrene sulfonate users having received these drugs and the results of the analysis of potential new binding interactions based on pKa- and Log P values. We identified 22 and 27 potentially clinically relevant new binding interactions for sevelamer and polystyrene sulfonate, respectively.

**Table 3 Most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate and assessment of potential binding interactions**

| | Sevelamer (N=1,083) | | | | | Polystyrene sulfonate (N=716) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Drug** | **pKa (acid)[31]** | **Log P[31]** | **Unique drug combination (N)** | **Patients (%)** | **Potential new binding interaction (Yes/No)** | **Drug** | **pKa (base)[31]** | **Unique drug acombina- tion (N)** | **Patients (%)** | **Potential new binding interaction (Yes/No)** |
| Calcium carbonate | 6.1 | 0.3 | 429 | 39.6 | No[a] | Alfacalcidol | -2.8 | 325 | 45.4 | No |
| Acetylsalicylic acid | 3.4 | 1.2 | 393 | 36.3 | Yes | Metoprolol | 9.7 | 311 | 43.4 | Yes |
| Amlodipine | 19.1 | 1.6 | 358 | 33.0 | No | Omeprazol | 4.8 | 254 | 35.5 | Yes |
| Macrogol | - | - | 341 | 31.5 | No | Furosemide | -1.5 | 233 | 32.5 | No |
| Ferrofumarate | 3.4 | < 0 | 307 | 28.3 | No[a] | Amlodipine | 9.5 | 220 | 30.7 | Yes |
| Prednisolone | 12.6 | 1.27 | 290 | 26.8 | No | Calcium carbonate | - | 212 | 29.6 | No[b] |
| Amoxicillin/clavulanic acid | 3.2/3.3 | < 0 | 285 | 26.3 | Yes / Yes | Ferrofumarate | - | 200 | 27.9 | Yes[c] |
| Acenocoumarol | 5.8 | 2.7 | 272 | 25.1 | Yes | Acetylsalicylic acid | -7.1 | 188 | 26.3 | No |
| Lanthanum carbonate | 6.1 | 0.3 | 259 | 23.9 | No[a] | Prednisolone | -2.9 | 164 | 22.9 | No |
| Polystyrene sulfonate | - | - | 245 | 22.6 | No | Macrogol | - | 157 | 21.9 | No |
| Acetaminophen | 9.5 | 0.9 | 214 | 19.8 | No | Acenocoumarol | -6.8 | 149 | 20.8 | No |
| Lactulose | 10.3 | < 0 | 213 | 19.7 | No | Enalapril | 5.2 | 138 | 19.3 | Yes |
| Tramadol | 13.8 | 2.5 | 212 | 19.6 | Yes | Pantoprazol | 3.6 | 121 | 16.9 | Yes |
| Cinacalcet | - | 6.3 | 184 | 17.0 | Yes | Amoxicillin/clavulanic acid | 7.4/ -2.6 | 111 | 15.5 | Yes / No |
| Bumetanide | 4.7 | 2.4 | 165 | 15.2 | Yes | Acetaminophen | -4.4 | 102 | 14.2 | No |
| Doxycycline | 3.3 | < 0 | 156 | 14.4 | Yes | Ciprofloxacin | 8.7 | 95 | 13.3 | Yes |
| Doxazosin | 12.7 | 2.1 | 145 | 13.4 | Yes | Allopurinol | 1.3 | 88 | 12.3 | No |
| Flucloxacillin | 3.8 | 2.4 | 125 | 11.5 | Yes | Bumetanide | 2.7 | 86 | 12.0 | Yes |
| Allopurinol | 8.5 | 0 | 125 | 11.5 | No | Doxazosin | 7.2 | 84 | 11.7 | Yes |
| Metoclopramide | 14.5 | 1.4 | 121 | 11.2 | No | Colecalciferol | -1.3 | 81 | 11.3 | No |
| Oxazepam | 10.6 | 2.9 | 121 | 11.2 | Yes | Lactulose | -3.0 | 78 | 10.9 | No |
| Codeine | 13.8 | 1.3 | 121 | 11.2 | No | Bisoprolol | 9.7 | 75 | 10.5 | Yes |
| Oxycodone | 13.6 | 1.0 | 120 | 11.1 | No | Tramadol | 9.2 | 74 | 10.3 | Yes |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nifedipine | - | 1.8 | 116 | 10.7 | No | Isosorbide mononitrate | -3.5 | 72 | 10.0 | No |
| Colchicine | 15.1 | 1.5 | 116 | 10.7 | No | Colchicine | 0 | 70 | 9.8 | No |
| Bisoprolol | 14.1 | 2.2 | 112 | 10.3 | Yes | Doxycyclin | 8.3 | 69 | 9.6 | Yes |
| Isosorbide mononitrate | 13.3 | < 0 | 105 | 9.7 | No | Hydrochlorothiazide | -2.7 | 69 | 9.6 | No |
| Lisinopril | 3.2 | < 0 | 103 | 9.5 | Yes | Lanthanum carbonate | - | 65 | 9.1 | Yes[b] |
| Clopidogrel | - | 4.0 | 101 | 9.3 | Yes | Nifedipine | 5.3 | 65 | 9.1 | Yes |
| Clindamycin | 12.4 | 1.0 | 97 | 9.0 | No | Lisinopril | 10.2 | 64 | 8.9 | Yes |
| Amitriptyline | - | 4.8 | 88 | 8.1 | Yes | Oxazepam | -1.5 | 62 | 8.7 | No |
| Sulfamethoxazol/trimethoprim | 6.2/17.3 | 0.8/1.3 | 88 | 8.1 | Yes / No | Oxycodone | 8.8 | 58 | 8.1 | Yes |
| Losartan | 7.4 | 5.1 | 85 | 7.8 | Yes | Flucloxacillin | -0.9 | 52 | 7.3 | No |
| Diclofenac | 4.0 | 4.3 | 84 | 7.8 | Yes | Irbesartan | 4.1 | 52 | 7.3 | Yes |
| Irbesartan | 7.4 | 5.5 | 81 | 7.5 | Yes | Spironolactone | -4.9 | 50 | 7.0 | No |
| Hydrochlorothiazide | 9.1 | < 0 | 71 | 6.6 | No | Diclofenac | -2.1 | 49 | 6.8 | No |
| Loperamide | 14.0 | 4.8 | 71 | 6.6 | Yes | Clopidogrel | 5.1 | 48 | 6.7 | Yes |
| Vitamin B complex/vitamin C | 15.5/4.4 | <0 /< 0 | 64 | 5.9 | No / Yes | Cinacalcet | 10.3 | 48 | 6.7 | Yes |
| Bisacodyl | - | 3.6 | 55 | 5.1 | Yes | Perindopril | 5.5 | 48 | 6.7 | Yes |
| | | | | | | Mycophenolic acid | -4.1 | 46 | 6.4 | No |
| | | | | | | Codeine | 9.2 | 44 | 6.1 | Yes |
| | | | | | | Amitriptyline | 9.8 | 43 | 6.0 | Yes |
| | | | | | | Gliclazide | 1.4 | 43 | 6.0 | No |
| | | | | | | Esomeprazole | 4.8 | 43 | 6.0 | Yes |
| | | | | | | Losartan | 4.1 | 37 | 5.2 | Yes |
| | | | | | | Dipyridamole | 6.6 | 36 | 5.0 | Yes |
| | | | | | | Metformin | 12.3 | 36 | 5.0 | Yes |

[a] Sevelamer may bind carbonate or fumarate but not the clinically effective ions calcium, iron and lanthanum

[b] Although theoretically polystyrene sulfonate could bind the positively charged calcium, this would not lead to a binding interaction in clinical practice, considering the availability of a polystyrene sulfonate product as a calcium-salt

[c] Polystyrene sulfonate may bind the positively charged iron and lanthanum ions

## Discussion

This study identified several novel potential binding interactions for sevelamer and polystyrene sulfonate using an *in silico* approach.

The 100 most frequently co-dispensed drugs with sevelamer or polystyrene sulfonate found in this study are in line with other drug utilization studies done in patients with CKD and haemodialysis patients.[2-7,9] Cardiovascular drugs, antidiabetic agents, drugs for the treatment of metabolic disorders, proton pump inhibitors, laxatives, anaemia-, anticoagulation-, gout treatment, anti-infectives, dermatological products and pain medication were the main drug categories reported in those studies.[2-7,9] This confirms the suitability of the IADB database for this research.[27]

The high number of unique drug-sevelamer/polystyrene sulfonate combinations found in this study can be explained by polypharmacy of this population, switching of drugs because of inefficacy or adverse effects, prescription of drugs for short duration, for example antibiotics and the long study period of 19 years.

In several studies the prevalence of drug-drug interactions in CKD patients is reported to be high, i.e. 75-91%, and is associated with the number of prescribed drugs, age, the stage of CKD, as well as comorbidities as diabetes mellitus, hypertension and obesity.[5-9] However, these studies did not report binding interactions among the top 10 drug-drug interactions, despite the fact that several binding interactions with sevelamer and polystyrene sulfonate are already known and both drugs are widely used by patients with CKD stage 4 or 5.[10,11,16-25,31] The lack of reporting of binding interactions may be because previous studies included patients with all stages of CKD instead of only patients with CKD stage 4 and 5. In addition, different (software) methods for identifying drug-drug interactions are used in these studies. Furthermore, the study of Sommer et al. focused on pharmacodynamic interactions instead of pharmacokinetic interactions.[8]

We identified 22 and 27 potentially relevant binding interaction candidates for sevelamer and polystyrene sulfonate respectively for further interaction research. We suggest performing *in vitro* experiments for those drugs to gather knowledge on clinically relevant binding interactions by simulating gastro-intestinal conditions in the laboratory in the presence and absence of sevelamer or polystyrene sulfonate. Walker et al. showed that *in vitro* binding studies using colesevelam are very sensitive but have a low specificity for identifying compounds binding to the drug.[34] No binding *in vitro* meant that the likelihood for binding *in vivo* was very small. On the other hand, when there is binding *in vitro* this will not automatically imply there is binding *in vivo*. This is because drug absorption from the gastro-intestinal tract is affected by many different factors as absorptive surface area, pH, food effects, intestinal transit time, passive intestinal permeability, intestinal transporters and enzymes, which are not all accounted for in *in*

*vitro* experiments.[35] So confirmatory *in vivo* studies are necessary to assess the clinical relevance of *in vitro* binding findings. *In vitro* screening is however, a valuable tool to test a large number of drugs, to limit the number of candidates for subsequent clinical drug interaction studies.

Strengths of this study are extracting the most frequently co-dispensed drugs with sevelamer and polystyrene sulfonate from a large, up-to-date and representative database and analysing these for their interaction potential based on pKa and Log P values. The analysed top 100 co-dispensed drugs covered about 70% of the unique drug-sevelamer/polystyrene sulfonate combinations. However, we considered combinations received by less than 5% of the sevelamer/polystyrene sulfonate users as clinically less relevant to assess for potential interaction potential and the analysed top 100 covered all drugs used by more than 5% of the sevelamer/polystyrene users.

The interaction potential was assessed based on a minimum of 50% negatively or positively charged availability of the drugs at gastrointestinal pH levels based on pKa-values. For sevelamer also lipophilicity was assessed by taking into account Log P values. Computational approaches have also been developed to identify novel drug-drug interactions *in silico*.[36] Which approach is most successful in determining clinically relevant drug-drug interactions has not been determined yet. A limitation of our study is that prescribing in this patient group may be different in other regions of the world or in other health care systems, so we may have missed clinically relevant drugs with potential to interact, which are infrequently prescribed in the Netherlands.

## Conclusion

In conclusion, we identified several candidates for potential novel binding interactions with sevelamer and polystyrene sulfonate from data on co-dispensed drugs and through an assessment of the chemical properties of these drugs. Further *in vitro* studies should be performed with those candidates.



## Acknowledgements

We thank Rita Nasee, Frederike Simonis, Aliesa de Lange and Jens Bos for performing the database research.

# References


1. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management. *JAMA* 2019;322(13):1294-1304
2. KDIGO. 2012 Clinical Practice Guidelines for the Evaluation and management of Chronic Kidney Disease. Accessed at www.kdigo.org. Consulted on 11 November 2019
3. Schmidt IM, Hubner S, Nadal J, Titze S, Schmid M, Barthlein B et al. Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: the german Chronic Kidney Disease study. *Clinical Kidney Journal* 2019; 12(5): 663-672
4. Laville SM, Metzger M, Stengel B, Jacquelinet C, Combe C, Fouque D et al. Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort. *Br J Clin Pharmacol* 2018;84:2811-2823
5. Al-Ramahi R, Raddad AR, Rashed AO, Bsharat A, Abu-Ghazaleh D, Yasin E et al. Evaluation of potential drug-drug interactions among Palestinian hemodialysis patients. *BMC Nephrology* 2016;17:96-101
6. Fasipe OJ, Akhideno PE, Nwaiwu O, Adelosoye AA. Assessment of prescribed medications and pattern of distribution for potential drug-drug interactions among chronic kidney disease patients attending the Nephrology Clinic of lagos University Teaching Hospital in Sub-Saharan West Africa. *Clinical Pharmacology: Advances and Applications* 2017;9:125-132
7. Marquito AB, Da Silva Fernandes NM, Colugnati FAB, Baumgratz de Paula R. Identifying potential drug interactions in chronic kidney disease patients. *J Brass Nefrol* 2014;36(1):26-34
8. Sommer J, Seeling A, Rupprecht H. Adverse Drug Events in patients with Chronic Kidney Disease Associated with Multiple Drug Interactions and Polypharmacy. *Drugs & Aging* 2020;37:359-372
9. Santos-Diaz G, Perez-Pico AM, Suarez-Santisteban MA, Garcia-Bernalt V, Mayordomo R, Dorado P. Prevalence of potential drug-drug interaction risk among chronic kidney disease patients in a Spanish hospital. *Pharmaceutics* 2020;12:713-724
10. Cannata-Andia JB, Fernandez-Martin JL, Locatelli F, London G, Gorriz JL, Floege J et al. Use of phosphate binding agents is associated with a lower risk of mortality. *Kidney International* 2013;84:998-1008
11. Sanjuan JB, Navarro-Gonzalez JF, Arenas MD, Torregrosa J-V, Menendez JT, de Francisco ALM et al. Pharmacological interactions of phosphate binders. *Nefrologia* 2018;38(6):573–578
12. Komaba H, Wang M, Taniguchi M, Yamamoto S, Nomura T, Schaubel DE et al. Initiation of Sevelamer and Mortality among Hemodialysis Patients treated with Calcium-based Phosphate Binders. *Clin J Am Soc Nephrol* 2017;12:1489-1497
13. Summary of Product Characteristics: Renagel. Accessed at www.cbg-meb.nl. Consulted on 11 November 2019
14. Summary of product Characteristics: Sorbisterit. Accessed at www.cbg-meb.nl. Consulted on 11 November 2019
15. Summary of Product Characteristics: Resonium A. Accessed at www.cbg-meb.nl. Consulted on 11 November 2019
16. Cataldo E, Columbano V, Nielsen L, Gendrot L, Covella B, Picolli GB. Phosphate

binders as a cause of hypothyroidism in dialysis patients: practical indications from a review of the literature. *BMC Nephrol* 2018;19(1):155
17. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailibility of ciprofloxacin. *Am J Kidney Dis* 2003:;42(6):1253-1259
18. Sprague SM, Covic AC, Floege J, Ketteler M, Botha J, Chong EM, Rastogi A. Pharmacodynamic effects of sucroferric oxyhydroxide and sevelmaer carbonate on vitamin D receptor agonist bioactivity in dialysis patients. *Am J Nephrol* 2016;44(2): 104-112
19. Pierce D, Hossack S, Poole L, Robinson A, Heusen van H, Martin P, Smyth M. The effect of sevelamer carbonate and lanthanum carbonate on the pharmacokinetics of oral calcitriol. *Nephrol Dial Transplant* 2011;26(5):1615-1621
20. Merkle M, Wornle M, Rupprecht HD. The Effect of Sevelamer on Tacrolimus Target Levels. *Transplantation* 2005;80:707
21. Pieper AK, Buhle F, Bauer S, Mai I, Budde K, Hafner D, Neumayer HH, Querfeld U. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004;19(10):2630–2633
22. Hoge RHL, Arbouw MEL, Radstake DWS, van Berlo-van de Laar IRF. Subtherapeutic serum quetiapine concentrations after absorption inhibition by binding resins: a case report. *J Clin Pharm Ther* 2015;40(3):355-357
23. Fleuren HWHA, Kho Y, Schuurmans MMJ, Vollaard EJ. Drug interaction between sevelamer and furosemide. *Nephrol Dial Transplant* 2005;20:2288-2289
24. Bélanger DR, Tierney MG, Dickinson G. Effect of sodium polystyrene sulfonate on lithium bioavailability. *Ann Emerg Med* 1992:21(11):1312-1315
25. McLean M, Kirkwood I, Epstein M, Jones B, Hall C. Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* 1993:341(8855):1286
26. U.S. Food and Drug Administration. Accessed at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-recommends-separating-dosing-potassium-lowering-drug-sodium. Consulted on 11 November 2019
27. Visser ST, Schuiling-Veninga CM, Bos JHJ, Jong de-Berg van den LTW, Postma MJ. The population-based prescription database IADB.nl: its development, usefulness in outcomes and research and challenges. *Expert rev. Pharmacoecon. Outcomes Res* 2013;13(3):285-292
28. Sediq R, Schans van der J, Dotinga A, Aligh RA, Wilfert B, Bos JHJ, Schuiling-Veninga CMC, Hak E. Concordance assessment of self-reported medication use in the Netherlands three-generation Lifelines Cohort study with the pharmacy database iaDB.nl: the Pharmlines initiative. *Clin Epidemiol* 2018; 10: 981-989
29. Burke S, Amin N, Incerti C, Plone M, Watson N. Sevelamer Hydrochloride (Renagel), a Nonabsorbed Phosphate-Binding Polymer, Does Not Interfere with Digoxin or Warfarin Pharmacokinetics. *J Clin Pharmacol* 2001;41:93-198
30. Burke SK, Amin NS, Incerti C, Plone MA, Lee JW. Sevelamer Hydrochloride (Renagel®), a Phosphate-Binding Polymer, Does Not Alter the Pharmacokinetics of Two Commonly Used Antihypertensives in Healthy Volunteers. *J Clin Pharmacol* 2001;41:199-205
31. Drugbank. Accessed at www.drugbank.ca/. Consulted on 1 June 2020
32. Summary of product Characteristics: Colestyramine. Accessed at www.cbg-meb.nl. Consulted on 1 June 2020
33. Berlo van – Laar van de IRF, Sluiter HE, Riet van 't E, Taxis K, Jansman FGA. Pharmacist-led medication reviews in predialysis and dialysis patients. *Res Social*

*Adm Pharm* 2020; Feb 22;S1551-7411(20)30112-1
34. Walker JR, Brown K, Rohatagi S, Bathala MS, Xu C, Wickremasingha PK, Salazar DE, Mager DE. Quantitative Structure-Property Relationships Modeling to Predict in Vitro and in Vivo Binding of Drugs to the Bile Sequestrant, Colesevelam (Welchol). *J Clin Pharmacol* 2009;49(10):1185-1195
35. Usansky HH, Sinko PJ. Estimating Human Drug Oral Absorption Kinetics From Caco-2 Permeability Using an Absorption-Disposition Model: Model Development and Evaluation and Derivation of Analytical Solutions for K(a) and F(a). *J Pharmacol Exp Ther* 2005;314(1):391-399
36. Ferdousi R, Safdari R, Omidi Y. Computational prediction of drug-drug interactions based on drugs functional similarities. *J Biomed Inform* 2017; 70: 54-64

# Supplementary Data

Drugs excluded from the top 100 co-dispensed drugs for which there is evidence for an interaction or evidence that there is no interaction based on literature were excluded.[10-24]

## Sevelamer

Interaction: Levothyroxine, Ciprofloxacin, Mycophenolic acid, Vitamin D analoga, Folic acid, Furosemide, Proton pump inhibitors
*No interaction:* Metoprolol, Enalapril, Digoxine

## Polystyrene sulfonate

Interaction: Levothyroxine

# Chapter 9

## Binding interactions with sevelamer and polystyrene sulfonate *in vitro*

*Pharmacol Res Perspect. 2021; Aug 9(4): e00834*

Inge RF van Berlo – van de Laar*
Ilona Prins - Can*
Aliesa A de Lange
Katja Taxis
Frank GA Jansman

* Both authors contributed equally

# Abstract

This study explored the binding of 28 drugs, which were selected based on frequency of concomitant use and chemical properties, to sevelamer and polystyrene sulfonate *in vitro*. The relative binding was determined by dissolving the investigated drugs alone (= control), together with 800mg sevelamer and together with 15g polystyrene sulfonate at different pH levels (1.5, 5.5 and 7.4), respectively. After incubation at 37°C and shaking for 60 minutes, the solutions were diluted, centrifuged and the drug concentrations were quantified with validated analytical assays. The binding assays were performed in three-fold. The mean relative binding (MRB) at each pH level was calculated, with a MRB > 20% for at least one pH level to be considered as relevant binding. Fourteen and 23 potentially new binding interactions were identified with sevelamer and polystyrene sulfonate, respectively. These potentially new binding interactions have to be studied *in vivo* to assess their clinical relevance.

# Introduction

Resins, such as sevelamer and polystyrene sulfonate, are used to treat hyperphosphatemia and hyperkaliaemia in patients with Chronic Kidney Disease (CKD).[1,2] Sevelamer and polystyrene sulfonate bind phosphate and potassium in the gastrointestinal tract, respectively, preventing their absorption and thereby reducing elevated phosphate and potassium levels, which may cause serious complications in CKD patients.[3-5] In addition to its phosphate binding properties, sevelamer acts as a bile acid sequestrant and significantly reduces low-density lipoprotein (LDL) cholesterol levels.[3] Because of their binding properties, resins are known to bind other drugs in the gastrointestinal tract, decreasing their bioavailability and clinical effectiveness.

Clinical studies and case reports have shown that sevelamer binds to levothyroxine, ciprofloxacin, mycophenolic acid, tacrolimus, cyclosporine, vitamin D analogues, lipid soluble vitamins like vitamin A, E and K, folic acid, quetiapine, furosemide and levetiracetam.[6-21] For polystyrene sulfonate, binding interactions have been described with lithium, quetiapine and levothyroxine.[21-23] CKD patients often use many different drugs (average of 8 drugs a day) and the prevalence of potential drug-drug interactions in CKD patients is high (75-91%).[24-30] Therefore, probably more drug binding interactions with sevelamer and/or polystyrene sulfonate than already described in literature may be of clinical relevance.

Previously, we performed an *in silico* study, analysing drug utilization data and chemical properties of these co-dispensed drugs, and identified various drugs which potentially may bind to sevelamer or polystyrene sulfonate.[31] A next step to study binding interactions is performing *in vitro* experiments in which gastro-intestinal conditions are simulated in the laboratory and binding of different drugs is tested by determining drug concentrations with and without the presence of sevelamer or polystyrene sulfonate. *In vitro* testing provides a valuable tool whereby numerous drugs can be tested relatively quickly to limit the number of candidates taken forward into clinical drug interaction studies.[32]

The aim of this study was to identify potential new binding interactions with sevelamer and with polystyrene sulfonate by assessing the relative *in vitro* binding of different drugs to these resins.



# Methods

## Selection of the investigated drugs

We used the list of drugs co-dispensed in patients using sevelamer/polystyrene sulfonate from our previous study.[31] Assessment of the chemical properties, pKa- and log

P-values of these drugs, in combination with the available validated analytical methods to quantify these drugs in the laboratory of the Deventer Teaching Hospital, led to the selection of 28 drugs for the current study, depicted in table 1.[33] Salicylic acid was used to represent acetylic salicylic acid because *in vivo* exposure to acetylic salicylic acid is measured by measuring salicylic acid and therefore the available analytical method was for quantifying salicylic acid and not acetylic salicylic acid. This was justified because the potential binding is based on the carboxylic acid group and not the acetylic group.

## Prediction of binding

Drugs negatively charged at gastro-intestinal pH levels based on the pKa value potentially bind to sevelamer. In addition, drugs with log P value ≥ 2.0 potentially bind to sevelamer.[3,32,33] For polystyrene sulfonate, drugs potentially bind when positively charged at gastro-intestinal pH levels based on pKa value.[4,5,33] In table 1, the predicted binding of the investigated drugs to sevelamer/polystyrene sulfonate is presented.

## Experimental procedure

The relative binding of 28 drugs (table 1) to sevelamer and polystyrene sulfonate was determined by performing *in vitro* binding experiments at simulated gastrointestinal environment conditions.

**Table 1 Investigated drugs and predicted binding to sevelamer and polystyrene sulfonate**

| Drug | Product | Binding prediction sevelamer pKa | Binding prediction sevelamer Log P | Binding prediction polystyrene sulfonate pKa |
|---|---|---|---|---|
| Amiodaron | Amiodarone HCl TEVA 200mg | No | Yes | Yes |
| Amitriptyline | Amitriptyline HCl CF 50mg | No | Yes | Yes |
| Aripiprazole | Aripiprazole DMB 2.5mg | No | Yes | Yes |
| Carbamazepine | Carbamazepine CF 200mg | No | Yes | No |
| Citalopram | Citalopram CF 10mg | No | Yes | Yes |
| Clomipramine | Clomipramine Sandoz 25mg | No | Yes | Yes |
| Clonazepam | Rivotril® 0.5mg | No | Yes | No |
| Clozapine | Clozapine Sandoz 25mg | No | Yes | Yes |
| Duloxetine | Duloxetine CF 30mg MSR | No | Yes | Yes |
| Flucloxacillin | Flucloxacillin Mylan 500 mg | Yes | Yes | No |
| Fluoxetine | Fluoxetine CF 20mg | No | Yes | Yes |
| Fluvoxamine | Fluvoxamine maleaat CF 50mg | No | Yes | Yes |
| Haloperidol | Haloperidol PCH 1mg | No | Yes | Yes |
| Imipramine | Imipramine CF 25mg | No | Yes | Yes |
| Lamotrigine | Lamictal® dispers 50mg | No | No | Yes |
| Metformin | Metformin TEVA 500mg | No | No | Yes |
| Mirtazapine | Mirtazapine Mylan 15mg | No | Yes | Yes |
| Nortriptyline | Nortrilen® 25mg | No | Yes | Yes |
| Paroxetine | Paroxetine PCH 10mg | No | Yes | Yes |
| Phenytoin | Diphantoine-Z-75® | No | Yes | No |
| Pipamperone | Dipiperon® 40mg | No | No | Yes |
| Risperidone | Risperidone PCH 0.5mg | No | Yes | Yes |
| Salicylic acid | Acidum salicylicum (90) Fagron BV | Yes | No | No |
| Sertraline | Sertraline PCH 50mg | No | Yes | Yes |
| Sulfamethoxazole | Cotrimoxazol 480mg | Yes | No | Yes |
| Trimethoprim | Cotrimoxazol 480mg | No | No | Yes |
| Valproic acid | Depakine Enteric® 150mg | Yes | Yes | No |
| Venlafaxine | Venlafaxine PCH 37.5mg retard | No | Yes | Yes |

The intraluminal pH of the gastrointestinal tract varies from pH < 3 in the stomach to 7.4 in the terminal ileum. To simulate the different pH environments of the gastrointestinal tract, which may affect binding, the assays were executed at pH 1.5, 5.5 and 7.4. pH adjusted aqueous solutions were prepared by adjusting the pH of Milli-Q®-water with sodium hydroxide 2M and hydrochloric acid 2M. The investigated drugs (table 1) were disintegrated/dissolved in 50.0 ml pH adjusted aqueous solution alone (control), in 50.0 ml pH adjusted aqueous solution together with 800 mg sevelamer (Renvela® sachet 2.4 grams) and in 100.0 ml pH adjusted aqueous solution together with 15 grams of polystyrene sulfonate sodium (Resonium A®). These solutions were incubated at 37°C and shaken for 60 minutes. The solutions of the investigated drugs were further diluted in 10.0 ml of the corresponding pH adjusted aqueous solution. Each diluted solution was centrifuged at 4000 rpm for 5 minutes. Finally, the concentrations of the investigated drugs were measured with validated analytical assays that are routinely used in the laboratory of the Deventer Teaching Hospital for therapeutic drug monitoring and clinical toxicology. The used analytical techniques were liquid chromatography tandem mass-spectrometry and liquid chromatography with diode array detection. For each drug, the binding assays were performed in three-fold at each pH level. The experimental procedure is graphically depicted in figure 1.

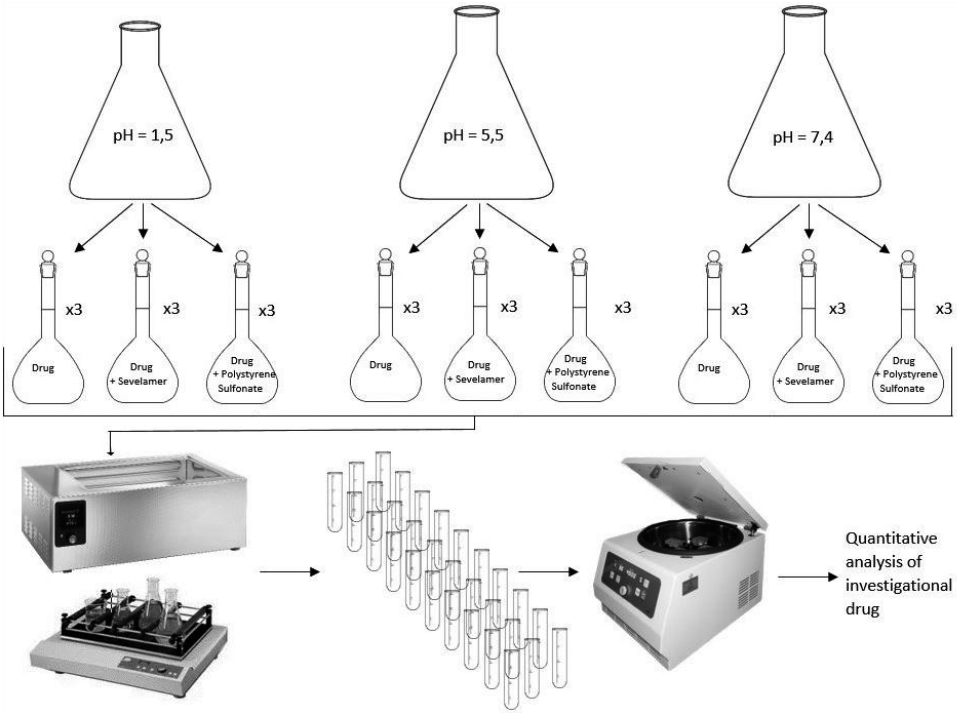


**Figure 1 Experimental procedure**

### Data analysis

The relative binding (RB) is calculated as follows:
RB = 100% * (U - T) / U

where U is the mean measured concentration of the investigated drug in the control solution and T is the measured concentration of the investigated drug combined with sevelamer / polystyrene sulfonate. The mean relative binding (MRB) and the standard deviations were calculated for each drug-resin combination, for each pH value. A MRB > 20% for at least one pH level was considered as relevant binding. This cut off was chosen by analogy with requirements in bioequivalence studies in which an exposure of less than 80% or more than 125% is considered not bio-equivalent. An exposure < 80% may result in clinically relevant less effectiveness and an exposure > 125% may result in clinically relevant more adverse effects. Because binding to resins in the gastro-intestinal tract will result in less exposure, the lower cut off level of 20% was used.

## Results

The results of the drugs with relevant binding (MRB > 20% for at least one pH level) are presented in table 2. The drugs in this table are ordered from the highest MRB to the lowest MRB.

**Table 2 Mean relative binding to sevelamer/polystyrene sulfonate**

| | RB to sevelamer (mean (%) ± sd) | | | | RB to polystyrene sulfonate (mean (%) ± sd) | | |
|---|---|---|---|---|---|---|---|
| **Drug / pH** | **1.5** | **5.5** | **7.4** | **Drug / pH** | **1.5** | **5.5** | **7.4** |
| Salicylic acid | NB[1] | 85 ± 2 | 73 ± 2 | Duloxetine | 100±0 | 100±0 | 100±0 |
| Flucloxacillin | NA[2] | 65 ± 3 | 74 ± 6 | Sertraline | 99 ± 0 | 99 ± 1 | 100±0 |
| Amiodarone | NB | NA | 58 ± 20 | Amitriptyline | 96 ± 1 | 99 ±0 | 98 ± 1 |
| Sulfamethoxazole | NB[1] | 54 ± 3 | 48 ± 4 | Aripiprazole | 99 ± 0 | 69 ± 7 | 76 ± 9 |
| Trimethoprim | 53±4 | NB | NB | Citalopram | 99 ± 0 | 99 ± 0 | 99 ± 0 |
| Sertraline | 45±22 | 14 ± 3 | NB | Clomipramine | 99 ± 0 | 99 ± 0 | 99 ± 0 |
| Amitriptyline | 43±24 | 37 ± 5 | 44±14 | Clozapine | 99 ± 0 | 80 ± 0 | 72 ± 0 |
| Imipramine | 38 ± 7 | 12±10 | NB | Imipramine | 99 ± 0 | 99 ± 0 | 99 ± 0 |
| Mirtazapine | 11±40 | 38 ± 1 | NB | Nortriptyline | 99 ± 0 | 99 ± 0 | 99 ± 0 |
| Clomipramine | 9 ± 11 | 31±13 | 6 ± 12 | Risperidone | 99 ± 0 | 99 ± 0 | 99 ± 0 |
| Duloxetine | 7 ± 8 | 29±12 | 21 ± 3 | Venlafaxine | 96 ± 1 | 99 ± 0 | 99 ± 0 |
| Haloperidol | 20 ± 7 | 24 ± 6 | 24±40 | Fluoxetine | 98 ± 0 | 98 ± 0 | 98 ± 0 |
| Fluvoxamine | NB | 22 ±6 | 8 ± 7 | Fluvoxamine | 97 ± 0 | 98 ± 0 | 98 ± 0 |
| Phenytoin | 21±10 | NB | NB | Haloperidol | 98 ± 0 | 97 ± 0 | 98 ± 0 |
| | | | | Mirtazapine | 98 ± 0 | 98 ± 0 | 96 ± 1 |
| | | | | Pipamperone | 98 ± 0 | 98 ± 0 | 98 ± 0 |
| | | | | Lamotrigine | 97 ± 0 | 52 ± 4 | 48 ± 5 |
| | | | | Clonazepam | 96 ± 0 | 74 ± 2 | 72 ± 3 |
| | | | | Metformin | 96 ± 0 | 96 ± 0 | 86±17 |
| | | | | Paroxetine | 93 ± 2 | 94 ± 2 | 95 ± 2 |
| | | | | Trimethoprim | 89 ± 0 | 94 ± 0 | 94 ± 0 |
| | | | | Amiodarone | 57 ± 0 | 71 ± 3 | 87 ± 4 |
| | | | | Sulfamethoxazole | 86 ± 4 | NB[3] | NB[3] |

*Abbreviations*
sd: standard deviation
NA: not available
NB: no binding
RB: relative binding

*Remarks*
[1] Salicylic acid and sulfamethoxazole are negatively charged at pH 5.5 and 7.4 but not at pH 1.5
[2] Flucloxacillin was not stable at pH 1.5
[3] Sulfamethoxazole is positively charged at pH 1.5 but not at pH 5.5 and 7.4

### Sevelamer

Salicylic acid, flucloxacillin and sulfamethoxazole showed relevant binding to sevelamer as predicted based on pKa value at pH levels 5.5 and 7.4. In contrast, valproic acid, showed no relevant binding. Amitriptyline and haloperidol had a MRB of about 40% and 22% at all pH levels, respectively. Binding of these drugs to sevelamer was predicted based on log P value. This also counts for amiodarone, sertraline, imipramine, mirtazapine, clomipramine, duloxetine, fluvoxamine and phenytoin. These drugs showed a MRB > 20% at one pH level but not at the other two pH levels. In some of these drugs the standard deviation of the MRB was high (table 2). The MRB of trimethoprim of 53% at pH level 1.5 was not predicted. For the investigated drugs (table 1) not mentioned in table 2 the MRB to sevelamer was ≤ 20% at all three pH levels. Carbamazepine, citalopram, clonazepam, clozapine, fluoxetine, nortriptyline, paroxetine, risperidone, valproic acid and venlafaxine, predicted to bind based on log P value, showed no relevant binding. For amiodarone, aripiprazole and flucloxacillin not all results were available due to solubility or stability issues.

### Polystyrene sulfonate

All investigated drugs predicted to bind to polystyrene sulfonate based on pKa value showed relevant bindings of 48-100% at all three pH levels. The drugs not predicted to bind to polystyrene sulfonate (table 1) showed MRBs ≤ 20% at all three pH levels with the exception of clonazepam, that showed a MRB > 70% independent of pH level. For carbamazepine there were no results due to solubility issues.

## Discussion

In this study, 14 and 23 relevant candidates were identified for binding interactions with sevelamer and polystyrene sulfonate respectively, based on *in vitro* binding.

*In vitro* experiments, to assess binding to resins, have been described in literature before. [21,23,32,34-43] The sensitivity of *in vitro* studies for identifying compounds binding to resins is high but the specificity may be low.[32] Studies confirming that *in vitro* binding is also clinically relevant *in vivo* have been described for different drug-resin combinations.[21,22,32,39,40,42,43] However, there are also several studies in which *in vitro* binding could not be confirmed *in vivo* to the same extent.[32,34,36,41,44-46] This can be explained by the fact that drug absorption from the gastro-intestinal tract is affected by many different factors such as absorptive surface area, pH, food effects, co-medication, intestinal transit time, passive intestinal permeability, intestinal transporters and enzymes that are not accounted for *in vitro*.[47]

To select candidates for confirmatory *in vivo* studies, drugs with the highest *in vitro* binding should be given priority. For polystyrene sulfonate, all candidates showed high MRBs of 48-100% at all three pH levels, while for sevelamer, flucloxacillin, acetylic salicylic

acid, amiodarone and sulfamethoxazole showed the highest binding. However, also the therapeutic window of the drug and the absence of a clinical effect parameter, determine the clinical relevance of a binding interaction.
For polystyrene sulfonate, binding results with investigated drugs were in accordance with predictions based on pKa values, with the exception of clonazepam, that unexpectedly showed binding to polystyrene sulfonate. Polystyrene sulfonate lowers the plasma potassium concentration through exchange of potassium and sodium/calcium ions in the gastrointestinal tract which explains the binding with positively charged drugs at gastrointestinal pH levels.[4,5] Sevelamer is a polymer containing several amines that become partially protonated in the gastro-intestinal tract and interact with phosphate molecules through ionic and hydrogen binding.[3] Compounds negatively charged in the gastro-intestinal tract may bind to sevelamer, indicating that pKa values may be predictive for binding capacity. In this study, this was confirmed in 3 out of 4 of the investigated drugs. Flucloxacillin, salicylic acid and sulfamethozazole showed a MRB of 80, 70 and 50%, respectively, where as the MRB of valproic acid was ≤ 20% at all pH levels. In addition, sevelamer acts as a bile sequestrant and may also bind lipophilic compounds.[3] Prediction of binding based on log P value was less accurate, i.e. only 50% of the investigated drugs predicted to bind to sevelamer, showed a MRB of > 20% for at least one pH level. These findings were not consistent at all pH levels and variation in MRB was high. Furthermore, the high trimethoprim MRB of 53% to sevelamer at pH level 1.5 cannot be explained by pKa or log P value. Possibly there is an interaction based on hydrogen binding.

A strength of this study is the selection of the investigated drugs from a large database study of co-dispensed drugs in patients using sevelamer/polystyrene sulfonate. We selected drugs regularly used in patients with CKD, taking into account their chemical properties (pKa and Log P), as potential binding candidates for performing these *in vitro* experiments. We have shown that *in vitro* experiments represent a relative quick and simple tool to identify many potential novel drug binding interactions. This study has resulted in 37 potentially new binding interactions and also provides information on drugs not binding to these resins. The latter is also clinically relevant information when establishing dosing regimens for patients. The well-described design of the study, mimicking gastro-intestinal environment, is easy to reproduce in clinical pharmacy laboratories performing routine Therapeutic Drug Monitoring. However, this design does not reflect all physiological factors influencing absorbance of drugs which is a limitation of this study. More sophisticated *in vitro* and computational designs have been described to study drug binding and drug absorbance, that are worthwhile to investigate, because they may reduce the necessity of confirmatory *in vivo* studies.[47,48] However, the facilities needed for these designs are mostly not available in routine daily practice of clinical pharmacists. Another limitation

of our study was low recovery found for some of the investigated drugs, i.e. amiodarone. This may be due to low water solubility of some of the lipophilic investigated drugs because we measured lower concentrations in the aqueous solutions than theoretically calculated. Additionally, instability may be a cause for the low recovery found as we observed for flucloxacilline in solution pH 1.5. We believe these results are still valid because we measured relevant decreased concentrations incubated together with the resins compared to control. However, the results that show high variation in binding within the triplicate should be interpreted more cautiously.

CKD patients, the main users of sevelamer and polystyrene sulfonate, use many different drugs for comorbidities such as cardiovascular disease, diabetes mellitus, metabolic disorders, gout and anaemia.[24,25] Binding interactions with sevelamer or polystyrene sulfonate may lead to ineffective treatment of these comorbidities. In the Netherlands, electronic medication surveillance systems containing information about known drug interactions are used by physicians and pharmacists during prescribing and dispensing. In general, for binding interactions the advice is to stagger dosing between the drugs.[24,25] More knowledge of new binding interactions with sevelamer and polystyrene sulfonate will improve treatment of CKD patients significantly. Therefore, the potentially new binding interactions which were identified in the current study should be further studied *in vivo* to assess the clinical relevance. We suggest to perform prospective cross-over studies in healthy volunteers in which participants ingest the investigated drug alone on one day and simultaneously with sevelamer of polystyrene sulfonate on another day, after which bloodsamples are taken on different time points during both days. The effect of combined intake on exposure of the investigated drug can be measured by comparing the maximum concentration (Cmax) and the area under the curve (AUC) for the investigated drug taken together with the resin and the investigated drug taken alone. The advantage of healthy volunteers is that variation in binding can be minimized by exclusion of co-medication and standardization of food intake. A disadvantage is that the effect of CKD itself or other comorbidities on exposure of the investigated drug is not accounted for.

## Conclusion

This study identified 14 and 23 potentially new binding interactions with sevelamer and polystyrene sulfonate, respectively, in *in vitro* experiments. Further research *in vivo* is necessary to assess the clinical relevance of these results.



## Acknowledgements

We thank the analysts of the laboratory of the Deventer Teaching Hospital for performing the assays.

# References


1. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management. *JAMA* 2019;322(13):1294-1304
2. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD). Accessed at www.kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf. Consulted on 28 May 2021
3. Summary of Product Characteristics: Renagel. Accessed at www.cbg-meb.nl. Consulted on 1 December 2020
4. Summary of product Characteristics: Sorbisterit. Accessed at www.cbg-meb.nl. Consulted on 1 December 2020
5. Summary of Product Characteristics: Resonium A. Accessed at www.cbg-meb.nl. Consulted on 1 December 2020
6. Sanjuan JB, Navarro-Gonzalez JF, Arenas MD, Torregrosa J-V, Menendez JT, de Francisco ALM et al. Pharmacological interactions of phosphate binders. *Nefrologia* 2018;38(6):573–578
7. Cataldo E, Columbano V, Nielsen L, Gendrot L, Covella B, Picolli GB. Phosphate binders as a cause of hypothyroidism in dialysis patients: practical indications from a review of the literature. *BMC Nephrol* 2018;19(1):155
8. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis* 2003;42(6):1253-1259
9. Sprague SM, Covic AC, Floege J, Ketteler M, Botha J, Chong EM, Rastogi A. Pharmacodynamic effects of sucroferric oxyhydroxide and sevelamer carbonate on vitamin D receptor agonist bioactivity in dialysis patients. *Am J Nephrol* 2016;44(2):104-112
10. Pierce D, Hossack S, Poole L, Robinson A, Heusen van H, Martin P, Smyth M. The effect of sevelamer carbonate and lanthanum carbonate on the pharmacokinetics of oral calcitriol. *Nephrol Dial Transplant* 2011;26(5):1615-1621
11. Merkle M, Wornle M, Rupprecht HD. The Effect of Sevelamer on Tacrolimus Target Levels. *Transplantation* 2005;80:707
12. Pieper AK, Buhle F, Bauer S, Mai I, Budde K, Hafner D, Neumayer HH, Querfeld U. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004;19(10):2630–2633
13. Fleuren HWHA, Kho Y, Schuurmans MMJ, Vollaard EJ. Drug interaction between sevelamer and furosemide. *Nephrol Dial Transplant* 2005;20:2288-2289
14. Inayat F, Bokhari SRA, Almas T, Rosen RM. Drug interaction between sevelamer and levetiracetam: The first clinical experience. *Am J Ther* 2020;Aug 14
15. Wauters JP, Uehlinger D, Marti HP. Drug interaction between sevelamer and cyclosporine. *Nephrol Dial Transplant* 2004;19(7):1939-1940
16. Susantitaphong P, Jaber BL. Potential interaction between sevelamer and fat-soluble vitamins: a hypothesis. *Am J Kidney Dis* 2012;59(2):165-167
17. Guillen-Anaya MA, Jadoul M. Drug interaction between sevelamer and cyclosporine. *Nephrol Dial transplant* 2004;19(2):515
18. Uehlinger D, Marti HP, Jadoul M, Wauters JP. Sevelamer and pharmacokinetics of cyclosporine A after kidney transplantation. *Nephrol Dial Transplant* 2005;20(3):661

19. Granata A, Floccari F, Gallieni M. Levothyroxine and sevelamer: listen to the patient. *Endocr Pract* 2011;17(6):961-962
20. Lovino M, Lovine N, Petrosino A, Giagulli VA, Licchelli B, Guastamacchia E et al. Sevelamer carbonate markedly reduces levothyroxine absorption. *Endocr metab Immune Disord Drug Targets* 2014;14(3):206-209
21. Hoge RHL, Arbouw MEL, Radstake DWS, van Berlo-van de Laar IRF. Subtherapeutic serum quetiapine concentrations after absorption inhibition by binding resins: a case report. *J Clin Pharm Ther* 2015;40(3):355-357
22. Bélanger DR, Tierney MG, Dickinson G. Effect of sodium polystyrene sulfonate on lithium bioavailability. *Ann Emerg Med* 1992;21(11):1312-1315
23. McLean M, Kirkwood I, Epstein M, Jones B, Hall C. Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* 1993;341(8855):1286
24. Schmidt IM, Hubner S, Nadal J, Titze S, Schmid M, Barthlein B et al. Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: the German Chronic Kidney Disease study. *Clinical Kidney Journal* 2019;12(5):663-672
25. Laville SM, Metzger M, Stengel B, Jacquelinet C, Combe C, Fouque D et al. Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort. *Br J Clin Pharmacol* 2018;84:2811-2823
26. Al-Ramahi R, Raddad AR, Rashed AO, Bsharat A, Abu-Ghazaleh D, Yasin E et al. Evaluation of potential drug-drug interactions among Palestinian hemodialysis patients. *BMC Nephrology* 2016;17:96-101
27. Fasipe OJ, Akhideno PE, Nwaiwu O, Adelosoye AA. Assessment of prescribed medications and pattern of distribution for potential drug-drug interactions among chronic kidney disease patients attending the Nephrology Clinic of Lagos University Teaching Hospital in Sub-Saharan West Africa. Clinical Pharmacology: *Advances and Applications* 2017;9:125-132
28. Marquito AB, Da Silva Fernandes NM, Colugnati FAB, Baumgratz de Paula R. Identifying potential drug interactions in chronic kidney disease patients. *J Brass Nefrol* 2014;36(1):26-34
29. Sommer J, Seeling A, Rupprecht H. Adverse Drug Events in patients with Chronic Kidney Disease Associated with Multiple Drug Interactions and Polypharmacy. *Drugs & Aging* 2020;37:359-372
30. Santos-Diaz G, Perez-Pico AM, Suarez-Santisteban MA, Garcia-Bernalt V, Mayordomo R, Dorado P. Prevalence of potential drug-drug interaction risk among chronic kidney disease patients in a Spanish hospital. *Pharmaceutics* 2020;12:713-724
31. Berlo van – Laar van de IRF, Prins-Can I, Schuiling-Veninga CCM, Taxis K, Jansman FGA. Exploring co-dispensed drug use in patients on sevelamer or polystyrene sulfonate to identify potential new binding interactions. *Basic Clin Pharmacol Toxicol* 2021;submitted
32. Walker JR, Brown K, Rohatagi S, Bathala MS, Xu C, Wickremasingha PK, Salazar DE, Mager DE. Quantitative Structure-Property Relationships Modeling to Predict in Vitro and in Vivo Binding of Drugs to the Bile Sequestrant, Colesevelam (Welchol). *J Clin Pharmacol* 2009;49(10):1185-1195
33. Drugbank. Accessed at www.drugbank.ca/. Consulted on 1 December 2020
34. Johansson S, Leonsson-Zachrisson M, Knutson M, Specer AG, Labonte ED, Deshpande D et al. Preclinical and healthy volunteer studies of potential drug-drug interactions between tenapanor and phosphate binders. *Clin Pharmacol Drug Dev* 2017;6(5):448-456

35. Bailey ND, Coffee JJ, Anderson B, Manoguerra S. Interaction of tricyclic antidepressants with colestyramine in vitro. *Ther Drug Monit* 1992;14(4):339-342
36. Nakai A, Nishikata M, Matsuyama K, Ichikawa M. Drug interaction between simvastatine and cholestyramine in vitro and *in vivo*. *Biol Pharm Bull* 1996;19(9):1231-1233
37. Neradova A, Schumacher SP, Hubeek I, Lux P, Schurgers LJ, Vervloet MG. Phosphate binders affect vitamin K concentration by undesired binding, an in vitro study. *BMC Nephrol* 2017;18(1):149
38. Takagi K, Masuda K, Yamazaki M, Kiyohara C, Wasaki M, Inoue H. Metal ion and vitamin adsorption profiles of phosphate binder ion exchange resins. *Clin Nephrol* 2010;73(1):30-35
39. King CY, Barriere SL. Analysis of the in vitro interaction between vancomycin and cholestyramine. *Antimicrob Agents Chemother* 1981;19(2):326-327
40. Muzeeb S, Venkatesh P, Mullangi R, Srinivas NR. Influence of cholestyramine on the pharmacokinetics of rosiglitazone and its metabolite desemthylrosiglitazone, after oral ans intravenous dosing of rosiglitazone: impact on oral bioavailability, absorption, and metabolic disposition in rats. *Xenobiotica* 2006;36(9):838-856
41. Muck W, Ritter W, Frey R, Wetzelsberger N, Lucker PW, Kuhlmann J. Influence of cholestyramine on the pharmacokinetics of cerivastatin. *Int J Clin Pharmacol Ther* 1997;35(6):250-254
42. Johansson C, Adamsson U, Stiemer U, Lindsten T. Interaction by cholestyramine on the uptake of hydrocortisone in the gastrointestinal tract. *Acta Med Scan* 1978;204(6):509-512
43. Young MA, Lettis S, Eastmond R. Concomitant administration of cholestyramine influences the absorption of trioglitazone. *Br J Clin Pharmacol* 1998;45(1):37-40
44. Geeze DS, Wise MG, Stigelman WH. Doxepin-cholestyramine interaction. *Psychosomatics* 1988;29(2):233-236
45. Burke S, Amin N, Incerti C, Plone M, Watson N. Sevelamer Hydrochloride (Renagel), a Nonabsorbed Phosphate-Binding Polymer, Does Not Interfere with Digoxin or Warfarin Pharmacokinetics. *J Clin Pharmacol* 2001;41:193-198
46. Burke SK, Amin NS, Incerti C, Plone MA, Lee JW. Sevelamer Hydrochloride (Renagel®), a Phosphate-Binding Polymer, Does Not Alter the Pharmacokinetics of Two Commonly Used Antihypertensives in Healthy Volunteers. *J Clin Pharmacol* 2001;41:199-205
47. Usansky HH, Sinko PJ. Estimating Human Drug Oral Absorption Kinetics From Caco-2 Permeability Using an Absorption-Disposition Model: Model Development and Evaluation and Derivation of Analytical Solutions for K(a) and F(a). *J Pharmacol Exp Ther* 2005;314(1):391-399
48. Ferdousi R, Safdari R, Omidi Y. Computational prediction of drug-drug interactions based on drugs functional similarities. *J Biomed* Inform 2017;70:54-64

# Chapter 10

## Assessing The Binding Interaction Of Polystyrene Sulfonate With Amitriptyline In Healthy Volunteers: A Cross-Over Design The BIND-study

*Submitted*

Ilona Prins - Can*
Inge RF van Berlo – van de Laar*
Marieke Zeeman
Cornelis G Vermeij
Esther van 't Riet
Katja Taxis
Frank GA Jansman

* Both authors contributed equally to the manuscript

# Abstract


## Background

Polystyrene sulfonate is used for binding potassium in patients with chronic kidney disease (CKD). Because of its binding properties, it can potentially bind other medications before absorption and thereby decrease their bioavailability and efficacy. Amitriptyline, which may be used by CKD patients for neuropathic pain, shows significant binding to polystyrene sulfonate *in vitro. In vivo* information about this interaction is needed to assess its clinical relevance.

## Objective

To determine the effect of polystyrene sulfonate on the exposure of amitriptyline when taken concomitantly in healthy volunteers.

## Methods

We performed a prospective cross-over study in nine healthy volunteers. Participants were 18 years of age or older, did not use any medication and had no known allergy to amitriptyline or polystyrene sulfonate. Participants visited Deventer Teaching Hospital twice. Once they received a single dose of amitriptyline 50 milligrams and once they received a single dose of both polystyrene sulfonate 15 grams and amitriptyline 50 milligrams. After intake of the medication six blood samples were collected, at 2, 3, 4, 5, 6, and 8 hours. Blood samples were analysed to determine maximum concentration (Cmax) and area under the curve 0-8 hours after intake ($AUC_{0\text{-}8h}$). Difference in Cmax and $AUC_{0\text{-}8h}$ was analysed with a Wilcoxon signed rank test, a p-value $<0.05$ was considered statistically significant.

## Results

Of the nine participants included, eight participants completed both visits to the hospital. Mean maximum concentration (Cmax) of amitriptyline was 35.61µg/l (±9.23µg/l) when taken alone, compared to 9.25µg/l (±3.19µg/l) when taken with polystyrene sulfonate ($p=0.012$). Mean $AUC_{0\text{-}8h}$ of amitriptyline was 168.20h*µg/l (±33.79h*µg/l) when taken alone and 45.78h*µg/l (±18.64h*µg/l) when taken with polystyrene sulfonate ($p=0.012$).

## Conclusion

These results show a significant decrease in exposure of amitriptyline of approximately 75% when taken concomitantly with polystyrene sulfonate, thereby probably compromising therapy efficacy. Patients using both amitriptyline and polystyrene sulfonate should be informed to separate intake of these medications.

# Introduction

Polystyrene sulfonate is a resin that is used to bind potassium for the treatment of hyperkalaemia. It is often used by patients with chronic kidney disease (CKD), who may also undergo haemodialysis, when dietary restrictions are not sufficient.[1,2] Polystyrene sulfonate is a non-absorbed cation exchange resin that lowers the plasma potassium concentration through exchange of potassium and sodium- or calcium-ions in the gastro-intestinal tract. The effect mainly occurs in the colon and partly in the small intestine.[3] Because of its binding properties, polystyrene sulfonate may potentially bind to other medications before absorption and thereby decrease their bioavailability and clinical efficacy.

Binding of polystyrene sulfonate to other medications has been investigated to a limited extent for a few medications in clinical studies or case reports.[4-6] An FDA Drug Safety Communication from 2017 discourages simultaneous use of polystyrene sulfonate with all other orally taken medication.[7] However, practically this is often difficult for patients with CKD and haemodialysis who have comorbidities and need several other medications.[8] Additionally, the prevalence of potential drug-drug interactions in this population is high, indicating that more drug binding interactions with polystyrene sulfonate may be of clinical relevance than already described in literature.[8,9-14] Therefore, it is necessary to gather more knowledge on drug binding interactions with polystyrene sulfonate.

A previous study of our research group identified several new potential binding interactions with polystyrene sulfonate, based on their chemical structure, one of which was the tricyclic antidepressant amitriptyline [unpublished]. Amitriptyline is usually used as an analgesic for neuropathic pain in patients with CKD and haemodialysis.[15,16]

We performed an *in vitro* screening of the binding capacity of polystyrene sulfonate to amitriptyline and found that amitriptyline is almost completely bound to polystyrene sulfonate [unpublished]. *In vitro* experiments in order to assess binding have a high sensitivity but specificity may be low.[17] In some studies *in vitro* binding of drug-resin combinations was also found *in vivo*, but in other studies *in vitro* binding could not be confirmed *in vivo.*[4,5,17-27]

Therefore, assessment of the clinical relevance of the *in vitro* binding between amitriptyline and polystyrene sulfonate *in vivo* is warranted. The aim of this study was to determine the effect of polystyrene sulfonate on the exposure of amitriptyline when taken simultaneously, in healthy volunteers.

# Methods

We performed a prospective cross-over trial in healthy volunteers. Eligible participants were aged 18 years or older. Participants were excluded from the trial if they met one

of the following criteria: known allergy to amitriptyline or polystyrene sulfonate, known renal or hepatic impairment, pregnancy, breast feeding, use of other medication within 24 hours of the study period (oral contraceptives within 12 hours of the study period), contra-indication for one of the investigated substances (such as recent myocardial infarction, cardiac arrhythmias, hypokalaemia and obstructive bowl disease) or history of a gastro-intestinal condition that may interfere with the absorption of amitriptyline. All participants gave written informed consent before study entry.

Participants visited the Deventer Teaching Hospital on two separate days. On day one they received a single dose of amitriptyline 50 milligrams and on day two a single dose of amitriptyline 50 milligrams in combination with a single dose of sodium polystyrene sulfonate 15 grams. Participants were given the same snack on both occasions before intake of the medication, as polystyrene sulfonate is usually taken with meals. After intake of the medication, six blood samples were collected, at 2, 3, 4, 5, 6, and 8 hours. Side effects of amitriptyline and polystyrene sulfonate were registered. There was a wash out period between the first and second visit of at least one week, to ensure all amitriptyline was removed from the body before the second visit, based on the half-life of amitriptyline of 25 hours.[28]

The primary objective was to determine whether polystyrene sulfonate has a significant effect on exposure of amitriptyline, when taken simultaneously, compared to amitriptyline taken alone. This was expressed as Cmax and area under the curve 0-8 hours after intake ($AUC_{0\text{-}8h}$). The assay used to quantify amitriptyline serum concentrations was developed and validated in our laboratory.

The number of participants needed was based on the mean maximum concentration (Cmax) after a single dose of amitriptyline 50 milligrams (30.95µg/l) and an expected reduction of 50% in Cmax of amitriptyline when taken concomitantly with polystyrene sulfonate.[28] The expected reduction was based on results of our previous *in vitro* study [unpublished]. The probability is 93% that we detect a difference in Cmax at a one-sided 0.025 significance level, if the true difference between treatments is 16µg/l (50%), based on the assumption that the standard deviation of the difference in Cmax is 9µg/l.[28] As a result, to compensate for possible loss-of-follow-up, nine persons were included in the trial in order to be able to evaluate six participants.

Amitriptyline concentrations were quantified using a LC/MSMS method (Shimadzu LCMS-8050). A kinetex 1.7 um 30x2.1mm UPLC column was used combined with a binary gradient from 80% ammonium formate 10mM in 0.1% formic acid to 80% 0.1% formic acid in acetonitrile. The oven temperature was set at 40°C, the flow at 0.6 ml/min and the injection volume was 3 µl. Amitriptyline-D3-HCl was used as internal standard. Amitriptyline was detected with MRM 278.20 → 233.35 and amitriptyline-D3-HCl with MRM 281.2 → 233.1, measured in positive mode. Linearity was demonstrated from

1-100 µg/l. The between run accuracy ranged from 88.5-107.0%. The variation coefficient of the between run precision ranged from 5.7-7.4%. The method was validated in line with the European Medicines Agency guideline on bioanalytical validation.[29] This assay is routinely used for Therapeutic Drug Monitoring in clinical practice. Data is reported quantitatively for all time points.

Cmax was determined as the highest concentration measured and $AUC_{0\text{-}8h}$ was calculated by using the trapezoidal rule. Difference in Cmax and $AUC_{0\text{-}8h}$ was analysed with a Wilcoxon signed rank test, a p-value <0.05 was considered statistically significant. Participant demographics; age, length, weight, gender and race, were collected at inclusion.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments, and Good Clinical Practice. The trial protocol was approved by an independent ethics committee and institutional review boards.

# Results

Eight of the nine participants enrolled in the study completed both visits to the hospital. Demographic information is presented in table 1.

One participant did not complete the study, because sample withdrawal was experienced as unpleasant.

**Table 1 Demographics of the participants**

| Subject characteristics | N=8 |
|---|---|
| Age, years (median, Q1-Q3) | 27.5 (24.25-28.75) |
| Length, cm (median, Q1-Q3) | 179 (166-188) |
| Weight, kg (median, Q1-Q3) | 72 (66-80) |
| Gender n (%) | |
| Male | 4 (50) |
| Female | 4 (50) |
| Race n (%) | |
| Caucasian | 8 (100) |

Figure 1 shows the serum concentration time curves of amitriptyline of the eight participants, when taken alone and when taken concomitantly with polystyrene sulfonate.

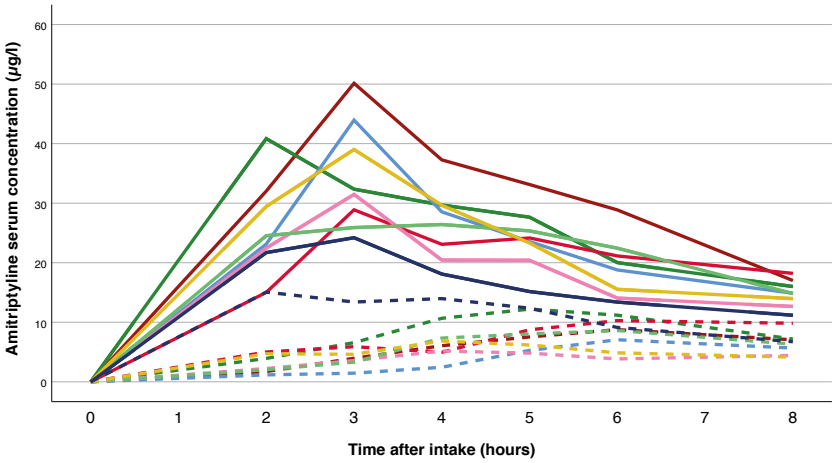


**Figure 1 Amitriptyline serum concentration over time (µg/l) of each participant after intake of amitriptyline alone (continuous line) and concomitantly with polystyrene sulfonate (dotted line)**

The Cmax of amitriptyline when taken alone amounted 35.61 µg/l ± 9.23 µg/l, compared to a Cmax of 9.25 µg/l ± 3.19 µg/l when amitriptyline was taken with polystyrene sulfonate. This difference was statistically significant (p=0.012) and these results are depicted in figure 2. Cmax was reached at a later time point, in all but one participant, when amitriptyline was taken with polystyrene sulfonate, compared to amitriptyline alone, i.e. 4-6 hours versus 2-4 hours (figure 1).

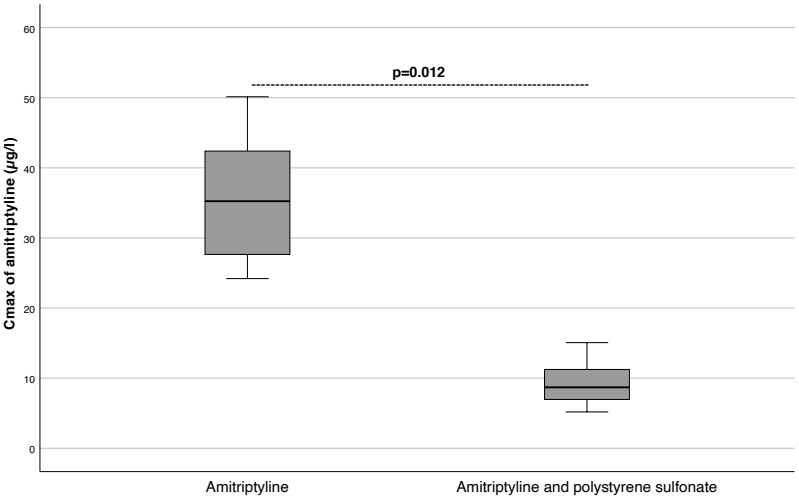


**Figure 2 Comparison of Cmax of amitriptyline after intake of amitriptyline alone and concomitantly with polystyrene sulfonate**

Exposure to amitriptyline in both situations is shown in figure 3. The $AUC_{0\text{-}8h}$ of amitriptyline was 168.20 h*µg/l ± 33.79 h*µg/l when taken alone compared to 45.78 h*µg/l ± 18.64 h*µg/l when taken simultaneously with polystyrene sulfonate (p=0.012).
The Cmax and $AUC_{0\text{-}8h}$ of amitriptyline decreased with 74% and 73%, respectively, when intake was concomitant with polystyrene sulfonate.
Most common adverse effects of amitriptyline taken alone were drowsiness/sleepiness in eight subjects (100%), and nausea and dry mouth, both in one subject (12.5%). When amitriptyline and polystyrene sulfonate were taken concomitantly four subjects reported drowsiness/sleepiness (50%), one subject reported dizziness (12.5%) and one subject had a tingling sensation in the fingers (12.5%).

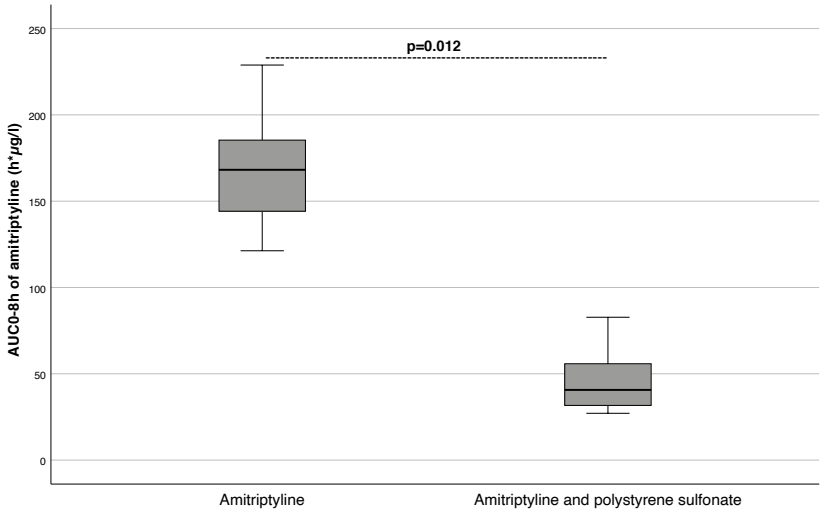


**Figure 3 Comparison of $AUC_{0\text{-}8h}$ of amitriptyline after intake of amitriptyline alone and concomitantly with polystyrene sulfonate**

# Discussion

In this prospective cross-over trial in healthy volunteers we have shown that Cmax and $AUC_{0\text{-}8h}$ of amitriptyline is significantly decreased when it is taken simultaneously with polystyrene sulfonate. This result confirms that the binding interaction between amitriptyline and polystyrene sulfonate that was found *in vitro* is also present *in vivo*.
Some medications have already been identified that bind to polystyrene sulfonate. Hoge et al. described a case where quetiapine blood concentrations were undetectable with simultaneous use of polystyrene sulfonate in a haemodialysis patient. A binding

interaction was detected *in vitro* after which intake of medication was separated by eight hours and therapeutic blood levels of quetiapine were achieved.[4] Another case has been described where therapy with levothyroxine failed after initiation of concomitant polystyrene sulfonate therapy and was restored after staggered intake of the medication. This binding interaction was also confirmed *in vitro*.[6] Moreover, a study in healthy volunteers showed a reduction in AUC and peak concentration of lithium when taken simultaneously with polystyrene sulfonate.[5] The results of our study add to the already known binding interactions with polystyrene sulfonate. Our own previous *in vitro* study indicates that there may be more relevant binding interactions that are still unknown which should be investigated *in vivo* to be able to give tailored advice. This would be preferred to the current general advice by the FDA which is staggered intake of polystyrene sulfonate with all other orally taken medication. This is very difficult to achieve in daily practice considering frequent polypharmacy and associated complex dosing schedules in this population.[3,7] Moreover, currently, medication surveillance on oral co-medication with polystyrene sulfonate in general is not performed in clinical practice. Our study highlights the need for specific drug-drug interaction monitoring for patients taking polystyrene sulfonate, instead of a general advice that is not feasible in clinical practice.

A strength of this study is the cross-over design, which eliminates variation between subjects when comparing Cmax and $AUC_{0\text{-}8h}$ in both situations. In addition, subjects where healthy adults that did not use any other medication that might influence the amount of binding of polystyrene sulfonate to amitriptyline. Because of this, we were able to properly investigate the effect of polystyrene sulfonate on the exposure of amitriptyline. Also, amount and composition of the food consumption before intake of the medication was standardized, in accordance with daily practice, in which polystyrene sulfonate is taken with food. By consuming the same snack at both visits, we minimalised variation in the effect of food on absorption of amitriptyline and on the binding capacity of polystyrene sulfonate. However, in daily practice polystyrene sulfonate is taken with larger meals to increase the degree of binding to potassium, which is obtained with a patient's diet. The snack given to the participants in this study might not have completely simulated the effect of a meal, so the binding capacity of polystyrene sulfonate to amitriptyline may be smaller when taken with a full meal, instead of a snack, with less effect on exposure of amitriptyline than seen in this study.

A limitation of this study concerns the inclusion of healthy volunteers, whereby the effect of CKD itself and associated comorbidities on exposure of amitriptyline is not accounted for. It is known that CKD patients may experience gastroparesis, which may affect the extend and rate of drug absorption.[30,31] The amount of binding by polystyrene sulfonate to amitriptyline seen in this study might, therefore, be different in patients with CKD and haemodialysis.

Based on the results of this study, where we see a decrease in Cmax of amitriptyline of 74% and a decrease in $AUC_{0\text{-}8h}$ of 73% because of simultaneous intake with polystyrene sulfonate, staggered intake of these medications is needed in daily practice. We also advice to include this binding interaction in the electronic medication surveillance system of pharmacists and physicians.

The optimal time interval between intake of polystyrene sulfonate and comedication has not been assessed yet. In clinical practice, a time interval of three hours is recommended between intake of polystyrene sulfonate and other orally taken medications, which is based on time needed for gastric emptying in healthy individuals.[3] However, a substantial part of CKD patients experience gastroparesis in which a high variability in gastric emptying is seen, which can be accompanied by dysmotility-like dyspepsia. This makes it hard to evaluate whether gastroparesis is present in the individual user of polystyrene sulfonate.[30,31] Gastroparesis may prolong the time to reach maximum drug concentrations, but this delay generally does not affect the extent of absorption.[33] This raises the question whether the standard time interval for staggered dosing can be used or that a longer time interval between intake of polystyrene sulfonate and amitriptyline is needed in CKD patients. This has to be further investigated.

The adverse effects, sleepiness, nausea, dry mouth and dizziness, reported by subjects are all known adverse effects of amitriptyline.[28] Nausea is also reported in users of polystyrene sulfonate, but is usually seen when calcium polystyrene sulfonate is used and not the sodium salt that was used in this study.[3,33] Sleepiness/drowsiness seems to be reported less by participants when amitriptyline is combined with polystyrene sulfonate, which is in line with our results of decreased exposure.

Our findings are clinically relevant because reduced bioavailability of amitriptyline due to concomitant intake with polystyrene sulfonate can lead to reduced efficacy and treatment failure of amitriptyline in CKD and haemodialysis patients. This is particularly not wanted in these patients for which polypharmacy is common, the risk of drug-drug interactions is high and appropriate alternative treatment is difficult to find.

## Conclusion

Polystyrene sulfonate significantly decreases exposure to amitriptyline with approximately 75% when taken concomitantly and intake should therefore be staggered. Further research in patients with CKD and haemodialysis is needed to establish the optimal time interval needed between intake for safe and effective use of amitriptyline in combination with polystyrene sulfonate.

## Ethics approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments. The trial protocol was approved by the independent ethics committee of Isala (Zwolle, Netherlands).

# References


1. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management. *JAMA*. 2019;322:1294-1304
2. KDIGO. 2012 Clinical Practice Guidelines for the Evaluation and management of Chronic Kidney Disease. Accessed at www.kdigo.org. Consulted on 1 March 2021
3. Summary of Product Characteristics: Resonium A. Accessed at www.cbg-meb.nl. Consulted on 1 March 2021
4. Hoge RHL, Arbouw MEL, Radstake DWS, van Berlo-van de Laar IRF. Subtherapeutic serum quetiapine concentrations after absorption inhibition by binding resins: a case report. *J Clin Pharm Ther*. 2015;40:355-357
5. Bélanger DR, Tierney MG, Dickinson G. Effect of sodium polystyrene sulfonate on lithium bioavailability. *Ann Emerg Med.* 1992;21:1312-1315
6. McLean M, Kirkwood I, Epstein M, Jones B, Hall C. Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet.* 1993;341:1286
7. FDA Drug Safety Communication: FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs. Accessed at www.fda.gov. Consulted on 25 March 2021
8. Sommer J, Seeling A, Rupprecht H. Adverse Drug Events in patients with Chronic Kidney Disease Associated with Multiple Drug Interactions and Polypharmacy. *Drugs & Aging.* 2020;37:359-372
9. Schmidt IM, Hubner S, Nadal J, Titze S, Schmid M, Barthlein B et al. Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: the German Chronic Kidney Disease study. *Clinical Kidney Journal.* 2019;12: 663-672
10. Laville SM, Metzger M, Stengel B, Jacquelinet C, Combe C, Fouque D et al. Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort. *Br J Clin Pharmacol.* 2018;84:2811-2823
11. Al-Ramahi R, Raddad AR, Rashed AO, Bsharat A, Abu-Ghazaleh D, Yasin E et al. Evaluation of potential drug-drug interactions among Palestinian hemodialysis patients. *BMC Nephrology.* 2016;17:96-101
12. Fasipe OJ, Akhideno PE, Nwaiwu O, Adelosoye AA. Assessment of prescribed medications and pattern of distribution for potential drug-drug interactions among chronic kidney disease patients attending the Nephrology Clinic of Lagos University Teaching Hospital in Sub-Saharan West Africa. *Clinical Pharmacology: Advances and Applications.* 2017;9:125-132
13. Marquito AB, Da Silva Fernandes NM, Colugnati FAB, Baumgratz de Paula R. Identifying potential drug interactions in chronic kidney disease patients. *J Brass Nefrol.* 2014;36(1):26-34
14. Santos-Diaz G, Perez-Pico AM, Suarez-Santisteban MA, Garcia-Bernalt V, Mayordomo R, Dorado P. Prevalence of potential drug-drug interaction risk among chronic kidney disease patients in a Spanish hospital. *Pharmaceutics.* 2020;12:713-724
15. Koncicki HM, Unruh M, Schell JO. Pain Management in CKD: A Guide for Nephrology Providers. *Am J Kidney Dis.* 2016;69:451-460
16. Davison SN. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. *CJASN.* 2019;14:917–391
17. Walker JR, Brown K, Rohatagi S, Bathala MS, Xu C, Wickremasingha PK, Salazar DE, Mager DE. Quantitative Structure-Property Relationships Modeling to Predict in Vitro and in Vivo Binding of Drugs to the Bile Sequestrant, Colesevelam (Welchol). *J Clin*

*Pharmacol.* 2009;49:1185-1195
18. Johansson S, Leonsson-Zachrisson M, Knutson M, Specer AG, Labonte ED, Deshpande D et al. Preclinical and healthy volunteer studies of potential drug-drug interactions between tenapanor and phosphate binders. *Clin Pharmacol Drug Dev.* 2017;6:448-456
19. Nakai A, Nishikata M, Matsuyama K, Ichikawa M. Drug interaction between simvastatine and cholestyramine in vitro and *in vivo*. *Biol Pharm Bull.* 1996;19:1231-1233
20. King CY, Barriere SL. Analysis of the in vitro interaction between vancomycin and cholestyramine. *Antimicrob Agents Chemother.* 1981;19:326-327
21. Muzeeb S, Venkatesh P, Mullangi R, Srinivas NR. Influence of cholestyramine on the pharmacokinetics of rosiglitazone and its metabolite desemthylrosiglitazone, after oral and intravenous dosing of rosiglitazone: impact on oral bioavailability, absorption, and metabolic disposition in rats. *Xenobiotica.* 2006;36:838-856
22. Muck W, Ritter W, Frey R, Wetzelsberger N, Lucker PW, Kuhlmann J. Influence of cholestyramine on the pharmacokinetics of cerivastatin. *Int J Clin Pharmacol Ther.* 1997;35:250-254
23. Johansson C, Adamsson U, Stiemer U, Lindsten T. Interaction by cholestyramine on the uptake of hydrocortisone in the gastrointestinal tract. *Acta Med Scan.* 1978;204:509-512
24. Young MA, Lettis S, Eastmond R. Concomitant administration of cholestyramine influences the absorption of trioglitazone. *Br J Clin Pharmacol.* 1998;45:37-40
25. Geeze DS, Wise MG, Stigelman WH. Doxepin-cholestyramine interaction. *Psychosomatics.* 1988;29:233-236
26. Burke S, Amin N, Incerti C, Plone M, Watson N. Sevelamer Hydrochloride (Renagel), a Nonabsorbed Phosphate-Binding Polymer, Does Not Interfere with Digoxin or Warfarin Pharmacokinetics. *J Clin Pharmacol.* 2001;41:193-198
27. Burke SK, Amin NS, Incerti C, Plone MA, Lee JW. Sevelamer Hydrochloride (Renagel®), a Phosphate-Binding Polymer, Does Not Alter the Pharmacokinetics of Two Commonly Used Antihypertensives in Healthy Volunteers. *J Clin Pharmacol.* 2001;41:199-205
28. Summary of Product Characteristics: Amitriptyline HCl. Accessed at www.cbg-meb.nl. Consulted on 1 March 2021.
29. Committee for medicinal products for human use (CHMP). Guideline on bioanalytical method validation. European medicines agency. 21 Juli 2011
30. Vlem van B, Schoonjans R, Vanholder R, Vos de M, Vandamme W, Laecke van S, et al. Delayed Gastric Emptying in Dyspeptic Chronic Hemodialysis Patients. *American Journal of Kidney Diseases.* 2000;36:962-968
31. Strid H, Simrén M, Stotzer PO, Abrahamsson H, Björnsson ES. Delay in gastric emptying in patients with chronic renal failure. *Scandinavian Journal of Gastroenterology.* 2004;39:516-520
32. Gabardi S, Abramson S. Drug Dosing in Chronic Kidney Disease. *Med Clin N Am.* 2005;89:649–687
33. Summary of Product Characteristics: Sorbisterit. Accessed at www.cbg-meb.nl. Consulted on 4 May 2021

# Chapter 11

General discussion and perspectives

# General discussion and perspectives

## Main findings of this thesis

The aim of this thesis was to describe how the clinical pharmacist can improve pharmacotherapy of hospital patients. We performed studies on three different topics. Firstly, we assessed the clinical value of pharmacist-led medication reviews in two complex patient groups: (pre) dialysis patients and older patients with cancer treated with intravenous chemotherapy. Secondly, we focused on the management of metformin associated lactic acidosis (MALA), a rare but serious adverse effect of a frequently used drug for diabetes mellitus type 2. Finally, we identified several potential new drug binding interactions with sevelamer and polystyrene sulfonate, drugs that are often used by chronic kidney disease (CKD) patients.

Chapter 2 of this thesis describes the evaluation of pharmacist-led medication reviews in pre-dialysis and dialysis patients in clinical practice. A large number of different types of drug related problems (DRPs) were detected. Overall, 80% of the patients had on average three medication discrepancies per patient of which the majority (81%) was acknowledged by the nephrologist. Patient counseling in order to improve adherence and adequate timing of administration was performed in 37% of patients. In addition, medication reviews were conducted resulting in prescription changes in 48% of the patients with nearly two medication changes per patient. Ninety percent of these changes remained implemented on follow-up after at least 1 month. Forty-six percent of the changed prescriptions were identified with the STOPP/START criteria, whereas 54% was based on the clinical pharmacists' expert opinion. The average time investment was 85 minutes per patient for the clinical pharmacist and 15 minutes for the nephrologist. For the latter, the time investment and unclear responsibility for medication management due to multiple prescribers were the main reasons to reject pharmacist interventions.

In chapter 3, pharmacist-led comprehensive medication reviews in older cancer patients using both STOPP/START criteria and pharmacists' expert opinion are described. A prevalence of 78% of potentially inappropriate medications (PIMs) and potentially omitted medications (POMs) was found. Pharmacists' expert opinion in addition to only STOPP/START criteria contributed to 49% of the PIMs and 23% of the POMs. A follow-up action was required in 73% of the PIMs and POMs. The number of medicines and Charlson Comorbidity Index (CCI) score were both associated with at least one PIM and/or POM per patient.

The incidence of metformin associated lactic acidosis (MALA) reported in literature varies widely. In our clinical study (Chapter 4), the incidence was estimated at 47 per 100,000 patient-years, which is 5 to 16 times higher than previously reported. This may

be explained by the use of metformin in the presence of risk factors for lactic acidosis. Remarkably, we found that survivors of MALA had a higher metformin serum concentration than non-survivors, probably because of fewer comorbidities in the survivor group.
Several studies suggest that early recognition of MALA and timely starting the right treatment may reduce morbidity and mortality. However, MALA is difficult to differentiate from sepsis, since clinical symptoms are similar. Therefore, in **chapter 5**, a study is presented to establish clinical parameters for identification of MALA in patients with suspected sepsis induced lactic acidosis in the emergency department. The combined parameters lactate ≥ 8.4 mmol/l and creatinine ≥ 256 umol/l showed a sensitivity of 85% and a specificity of 95% for identifying MALA in suspected sepsis induced lactic acidosis patients in the emergency department. When combined with metformin use the specificity increased to 99%. The multidisciplinary, international EXTRIP Consensus Work Group formulated specific recommendations for starting extracorporeal treatment (ECTR) in metformin poisoning. However, the evidence levels of these criteria were low and their validity in clinical practice was not assessed. **Chapter 6** of this thesis describes the study in which we assessed whether ECTR improved outcome of patients with MALA and the clinical applicability of the EXTRIP-criteria for starting ECTR in metformin poisoning. We found that lactate, creatinine, metformin serum concentrations and vasopressor requirement were significantly higher in the patient group that received ECTR. Blood pH and bicarbonate were significantly lower. Mortality, length of hospital stay and mechanical ventilation requirement were not statistically significantly different between the two groups. Despite these findings, ECTR might be lifesaving in MALA, considering that patients in the ECTR-group were significantly sicker than patients in the non-ECTR-group. In 83% of patients, treatment of MALA was in accordance with the EXTRIP criteria and severity of lactic acidosis and renal impairment were the main indications for initiating ECTR.

Drug binding interactions with sevelamer and polystyrene sulfonate were studied using a combined *in silico, in vitro* and *in vivo* approach.
In **chapter 7**, we present a patient with unexplainable low serum quetiapine concentrations. Our hypothesis, that this was the result of a drug-drug interaction between quetiapine and the binding resins polystyrene sulfonate and sevelamer, was confirmed *in vitro* as well as *in vivo*. The *in vitro* binding assay showed pH-independent absorbance inhibition of quetiapine by polystyrene sulfonate and pH-dependent absorbance inhibition by sevelamer. In the *in vivo* experiment, the time of ingestion of quetiapine, polystyrene sulfonate and sevelamer were separated, whereafter serum quetiapine concentrations rose from a not detectable level to a level well in the therapeutic range.
In an *in silico* study, we identified several candidates for potential binding interactions with sevelamer and polystyrene sulfonate. In a large database we determined frequently

co-dispensed drugs and assessed their potential for binding based on pKa value and charge at gastro-intestinal pH levels (**chapter 8**). Hereby, twenty-eight drugs were selected for further *in vitro* experiments. These subsequent *in vitro* experiments revealed 14 and 23 potentially new binding interactions with sevelamer and polystyrene sulfonate, respectively (**chapter 9**). From these findings, the binding interaction between amitriptyline and polystyrene sulfonate was selected for further investigation *in vivo* in healthy volunteers. This study is described in **chapter 10**. The Cmax and $AUC_{0\text{-}8h}$ of amitriptyline decreased by 75% and 73% respectively when amitriptyline was simultaneously ingested with polystyrene sulfonate compared to intake of amitriptyline alone. As a consequence, we recommend staggered intake of these drugs in daily practice. Further research in CKD patients is needed to establish the optimal time interval between intake for safe and effective use of amitriptyline in combination with polystyrene sulfonate.

## Discussion and perspectives

In this last chapter, the results of this thesis will be put into a broader perspective with a specific focus on the role of the clinical pharmacist in relation to the three different topics studied in this thesis (figure 1). The goal of clinical pharmacists is to provide appropriate, effective and safe pharmacotherapy for patients to ensure that the drugs prescribed contribute to the best possible health outcomes. To achieve this goal, clinical pharmacists collaborate with health professionals and patients contributing with their in-depth knowledge of drugs including drug action, dosing, adverse effects and drug interactions.[1,2] In this thesis, we have shown that the clinical pharmacist can improve pharmacotherapy in hospital patients by performing generic, patient oriented activities such as pharmacist-led medication reviews and by performing more specific drug oriented activities as the management of MALA and the management of drug binding interactions with sevelamer and polystyrene sulfonate.

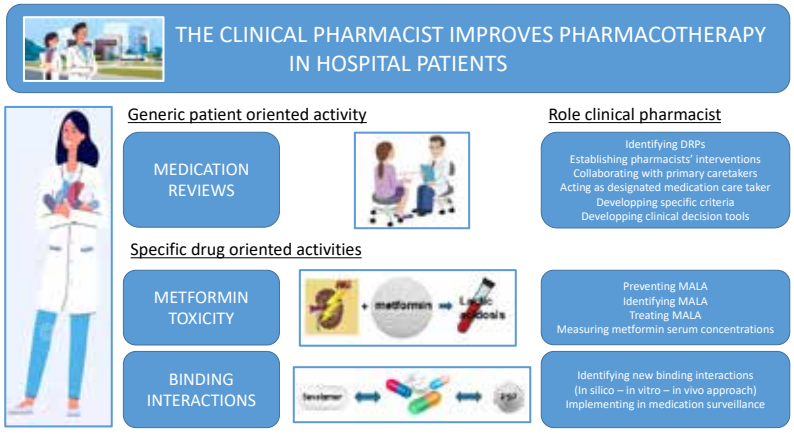


**Figure 1 The role of the clinical pharmacist in improving pharmacotherapy of hospital patients; focusing on pharmacist-led medications reviews, management of metformin toxicity and drug binding interactions with sevelamer and polystyrene sulfonate**

## Medication reviews

We showed that pharmacist-led clinical medication reviews in predialysis/dialysis and older oncology patients with intravenous chemotherapy are good instruments for identifying DRPs and inappropriate prescribing, establishing pharmacists' interventions and improving medication treatment in these patient groups. This is in line with literature.[3-6] There is, however, high heterogeneity in the methods (levels) of performing medication reviews and the reported outcomes.[7] In some studies, patient interviews are not included in performing medication reviews and or only standardized criteria for identifying inappropriate prescribing are used.[8-12] We performed comprehensive pharmacist-led medication reviews including patient interviews and we used the standardized START-STOPP criteria as well as the pharmacists' expert opinion. We showed that half of the PIMs and a quarter of the POMs in older cancer patients were identified by the pharmacists' expert opinion. In addition, in (pre)dialysis patients 46% of the accepted pharmacist interventions was based on the START-STOPP criteria and 54% was identified by pharmacist expert opinion. Strengths of our studies were the combination of pharmacist-led comprehensive medication review and medication reconciliation (described in detail), the incorporation of pharmacists' expert opinion, identifying DRPs, PIMs and POMs and measuring time investment and the follow-up of the recommendations. Both studies were, however, single-center uncontrolled studies and the effects on patient outcomes were not assessed.

Effects on patient outcomes have been studied and published in literature and different systematic reviews and meta-analyses have shown beneficial effects on both medication errors and patient outcomes of conducting medication reviews in hospital patients. Khalil et al. showed consistent evidence of significant reducing both medication errors and medication adverse effects by performing medication reviews in hospital patients but not in preventing death.[7] The systematic review and meta-analysis of Renaudin et al. showed no difference in readmission rates but medication review did significantly lower drug-related readmissions and all cause emergency visits.[13] Another systematic review investigating the effect of medication review in hospital patients on reducing morbidity and mortality showed no significant reduction of mortality or readmission rates.[14] However, there was evidence that medication reviews may reduce emergency department visits. Moreover, Vestergaard et al. showed a significant reduction in the number of readmitted patients within 30 days and within 180 days after discharge by performing extended medication reviews in hospital patients.[15]

Despite these beneficial effects, implementing structural pharmacist-led medication review in hospitals may be too expensive or too difficult to organize.[7] This was also one of

the barriers we encountered in our studies. The time investment in predialysis/dialysis patients was 118 minutes for one accepted pharmacist intervention. Another barrier was unclear responsibility in medication management between different prescribers. This was an important reason for nephrologists to not implement a pharmacists' intervention. In the PIMPOM study we showed that 73% of the PIMs and POMs identified by the pharmacist needed follow up according to the oncologists/hematologists. They delegated 44% of this follow-up to the general practitioner but this was not further evaluated with the general practitioners.

In what way may the clinical pharmacist stimulate medication reviews in hospital patients in clinical practice?

It is essential that primary and secondary caretakers work together in this process. Walraven et al. concluded that medication reviews in hospitals have to be complementary to medication reviews in primary care.[16] Therefore, a medication review in a hospital has to focus on complex patients (chronic polypharmacy patients treated by specialists in the hospital) and on high-risk patients (patients with high risk of medication errors for example at the emergency department). There have to be clear agreements on patient selection, responsibilities and communication between secondary and primary caretakers to improve the process of medication review.[16]

## Complex patients

We think the clinical pharmacist can play an important role in improving pharmacotherapy of complex patients, i.e chronic polypharmacy patients treated by specialists in the hospital, acting as designated medication management care taker, making agreements and communicating with secondary as well as primary caretakers. In this thesis, we focused on two groups of complex patients, i.e. (pre)dialysis patients and older patients with cancer treated with intravenous chemotherapy. Other complex patients, which may be interesting for pharmacist-led medication reviews in hospitals are chronic heart failure patients or patients treated by clinical geriatrics. To further improve the efficiency of the process and reducing time investment of medication review, it is important to focus on specific problems in these complex patient groups. We showed that the START-STOPP criteria were not fully suitable in (pre)dialysis patients and therefore the clinical pharmacist may develop specific criteria for performing medication reviews in specific patient groups and implement these into clinical rules in the electronic medication surveillance system of the hospital. Attempts for such a selection algorithm have been done in the primary care setting.[17] This has to be further studied and validated. Additionally, a large part of time spent during the medication reviews consisted of medication reconciliation

activities because electronic medication systems in hospital and in primary care are not identically. Time investment would be drastically reduced if there were a national electronic system with up to date patient medication overviews available used in both primary and secondary care. Hopefully, the current efforts of personal health areas (PGOs) will improve this. Finally, expanding prescribing responsibilities for clinical pharmacists will improve efficiency and reduce time investment of pharmacists-led medication reviews. This is already current practice in other countries as the United Kingdom, the United States of America and New Zealand.[18] In the Netherlands, this has already been regulated by law for specialized nurses and physician assistants, but not for clinical pharmacists. Further evaluation of these suggestions is necessary.

## High risk patients

The other group of interest concerns high-risk patients, i.e. patients with a high risk to experience preventable harm from medication. Several studies have been performed to identify high-risk patients in the emergency department for conducting pharmacist-led medication reviews.[19-23] Hohl et al. developed a clinical decision tool to identify patients in the ER with high risk of adverse effects. This clinical decision tool was based on age, the use of opiates/antihypertensives/antibiotics, recent medication changes (last 28 days), number of drugs used (≥ 4 drugs), recent hospital admission (last month) and renal function (creatinine > 150 ug/l). The sensitivity was > 90% and the specificity was 40% when used by clinical pharmacists.[19] Conducting a medication review based on this tool resulted in a reduction of hospital length of stay of 0.48 days in patients < 80 years of age and 0.6 days in patients ≥ 80 years of age.[20] Bonnerup et al. studied the use of MERIS (Medication Risk Score), developed by Saedder et al., in the emergency department clinical practice to identify patients at risk for medication errors.[21,24] MERIS is a score based on renal function, number of drugs and the toxicity and drug-drug interaction potential of drugs involved. Conducting medication reviews in the ER by pharmacists based on MERIS did however not result in reduction of prescribing errors during admission, mortality and health care consumption 90 days after discharge or an improved quality of life.[22]

In a recent systematic review different tools varying in complexity, outcome measures and validation were identified for screening older patients at risk for drug related problems on hospital admission.[25] The BADRI score showed the best results, which is based on number of drugs used (≥ 8 drugs), hyperlipaedimia, increased white blood cell count, use of antidiabetics and length of stay ≥ 12 days).[23,25] However, at present no tool is suitable for clinical implementation yet and more studies on clinically suitable tools to identify high-risk patients in the emergency department are necessary.[25]

In this thesis, we have not studied the effects of medication reviews by a clinical pharmacist in patients at risk for medication errors in the ER. We agree however with Brady et al., that clinical decision tools may be beneficial for identifying patients at risk for medication errors in the ER.[25] For the identified high-risk patients, the clinical pharmacist may conduct medication reviews to assess drug related problems and propose suggestions for optimizing pharmacotherapy during hospital admission. In this way, for example, the rare but serious adverse effect of metformin, MALA, could be identified and managed by a clinical pharmacist at the ER, which is discussed in the next topic.

# Metformin toxicity

## Management of MALA

The incidence of MALA may increase in the coming years by the release of the contraindication for metformin in patients with more severe renal failure (eGFR < 45 ml/min).[26] Different studies showed the advantages of metformin in CKD patients with a decreased risk of all-cause mortality and ESDR progression without increasing the risk of lactic acidosis.[27,28] When dosages are adjusted to renal function there is no increased risk of lactic acidosis.[29]

Although not withholding metformine from CKD patients seems justified, our studies and literature show that more awareness and attention for the management of lactic acidosis in metformin use is warranted and that the clinical pharmacist may play an important role in this.

## Preventing MALA

Metformin is the most inappropriate prescribed drug in CKD patients.[30] Patients using metformin are often not counselled about the risk of lactic acidosis and how to prevent lactic acidosis.[31] Also, MALA is frequently not recognized by professionals in the ER.[32] Community pharmacists and clinical pharmacists in the hospital can play an important role in preventing MALA by performing electronic medication surveillance with clinical rules to identify metformin patients with an eGFR < 60ml/min and adjusting the dose accordingly.[33] Secondly, pharmacists can counsel patients using metformin who are at risk for lactic acidosis, i.e elderly patients using RAAS inhibitors or NSAIDs and CKD patients, in order to stop metformin use in case of dehydration i.e vomiting, diarrhoea and decreased fluid intake, which helps to prevent MALA.[34] Additionally, creating awareness by physicians for this serious adverse effect by education and discussing this topic in pharmacotherapeutic meetings, may contribute in preventing MALA. Finally, conducting medication reviews by pharmacists in primary care can help to prevent evolving MALA.[35]

## Identifying MALA

Acute deterioration of kidney function is very difficult to predict and may develop very fast.[36] In the ER, several patients with MALA are admitted every year.[32] It is important to recognize and identify MALA in the ER to start the right treatment. We investigated several criteria to distinguish MALA from sepsis in the ER. A lactate concentration ≥ 8.4 mmol/l and creatinine ≥ 256 umol/l in combination with metformin use appeared to be suitable criteria to identify MALA from sepsis. This was in line with the study results of Schadle et al. who also used renal function, lactate concentration and metformin use to identify MALA which they confirmed by measuring metformin serum concentrations.[37] These criteria are important to add to the clinical decision tools to be developed to identify patients with high risk of medication errors in the ER.[37,38]

Additionally to the above-mentioned criteria, metformin serum concentrations may be an important diagnostic criterium for identifying MALA in the ER. Several studies showed a clear relationship between metformin accumulation and lactic acidosis.[39-41] Bennis et al. showed that metformin concentrations > 9.9 mg/l were associated with lactic acidosis (sensitivity 67% and specificity 93%).[42] In order to use metformine serum concentrations for MALA identification, a 24/7 availability of laboratory facilities is needed. The clinical pharmacist is responsible for these facilities in relation to therapeutic drug monitoring and clinical toxicology of metformine, amongst other drugs and xenobiotics.

## Treating MALA

The clinical pharmacist can advise the ER physicians in starting the right treatment in MALA patients. Medication reviews based on clinical decision tools may improve this process. For MALA, ECTR is the treatment of choice.[43] Although we did not measure a significant difference in mortality comparing treatment of MALA with ECTR to treatment with no ECTR, we found that ECTR might be lifesaving considering that patients in the ECTR group were much sicker. Severity of lactic acidosis and renal impairment appeared to be the main criteria for starting ECTR in clinical practice. The EXTRIP-criteria for starting ECTR in metformin toxicity are applicable in MALA and are in line with clinical practice. Bennis et al. suggested to add a metformin concentration > 9.9 mg/l as a threshold for starting ECTR, which makes measuring metformin concentrations even more important.[42] The prognostic value of metformin serum concentrations is however not clear yet. In the study of Bennis et al, metformin concentrations > 9.9 mg/l were not associated with mortality.[42] In addition, in our study, we found no association of metformin concentrations and mortality. Survivors had even higher metformin serum concentration (18.9 mg/l) than non-survivors (2.9 mg/l, p=0.006) which could be explained by less severe underlying disease in patients who survived MALA, rather than an effect of metformin itself. This is in line with literature showing that mortality in lactic

acidosis induced by metformin was lower than lactic acidosis from other causes.[44,45] Metformin may have tissue protective effects but in MALA these effects are probably decreased.[45]

Large prospective randomized trials for management of MALA are difficult to perform because MALA is rare and comorbidities may contribute to lactic acidosis. We think future clinical pharmacist activities should focus on preventing MALA, by performing adequate medication surveillance, counselling patients and creating awareness with physicians as well as developing clinical decision tools to identify MALA in the ER.

# Binding interactions

## Management of drug binding interactions with sevelamer and polystyrene sulfonate

### In silico-, in vitro and in vivo approach

In this thesis, it was unique that we studied drug binding interactions with sevelamer and polystyrene sulfonate by an *in silico-, in vitro- and in vivo* approach. This model offers many opportunities for clinical pharmacists in identifying new drug binding interactions. Clinical pharmacists have access to dispensing data of their patients and have knowledge on chemical properties of drugs. In this way, we identified clinically relevant candidates for potential binding interactions with sevelamer and polystyrene sulfonate for further *in vitro* studies. We have shown that *in vitro* experiments are a relative quick and simple tool to identify many potential novel drug binding interactions. We identified 37 potential new binding interactions with sevelamer and polystyrene sulfonate. The well-described design of the study, mimicking gastro-intestinal environment, makes it easy to reproduce in clinical pharmacy laboratories performing routine Therapeutic Drug Monitoring and Clinical Toxicology assays. This design did not reflect all physiological factors influencing absorbance of drugs. Therefore, confirmatory *in vivo* studies remain necessary to assess the clinical relevance. In literature, there are more sophisticated *in vitro* and computational designs described to study drug binding and drug absorbance that are worthwhile to investigate, because they may reduce necessary confirmatory *in vivo* studies.[46,47] However, these are not available in routine daily practice of clinical pharmacists.

We have shown that *in vitro* binding to sevelamer and to polystyrene sulfonate is well predicted based on pKa values. Clinical pharmacists can use their knowledge of chemical properties as pKa values and analytical assays for quantifying drugs for further executing relevant *in vitro* studies for binding interactions with these resins. Relevant

candidates from our *in silico* study which we have not studied *in vitro* yet are several antihypertensives and antibiotics. This *in silico – in vitro* approach can also be expanded to other resins such as colestyramine and the newer potassiumbinders patiromer and sodiumzirkoniumcyclosilicate. Another chemical property we took into account was the log P value for predicting binding to sevelamer. Log P, however, appears to be less suitable for predicting binding to sevelamer *in vitro*. Walker et al. showed that pKa in combination with log P (= log D) showed the best prediction for binding interactions with colesevalam.[48] Further investigation into the application of these combined parameters is warranted.

When selecting candidates for confirmatory *in vivo* studies it is important to take into account the extent of relative binding *in vitro*, the incidence of concomitant use, the availability of a clinical parameter to evaluate clinical effectiveness, the consequences of therapeutic failure and the needed number of dosages of the drug per day. Based on these factors we suggest further *in vivo* studies for sevelamer with flucloxacillin, acetylic salicylic acid, cotrimoxazole and amiodarone. For polystyrene sulfonate there are many drugs, which probably will bind *in vivo*, but based on above mentioned criteria we suggest to start with amitriptyline, amiodarone, metfomin and cotrimoxazole.
In this thesis, we studied the possible binding between amitriptyline and polystyrene sulfonate *in vivo* in healthy volunteers instead of CKD patients. We assume that binding of drugs in the gastrointestinal tract will be at least as high as in healthy volunteers, since several studies have shown that many CKD patients experience gastroparesis which may lead to even longer contact time of polystyrene sulfonate with amitriptyline.[49,50] The cross-over design with the standardisation of food consumption during intake of medication is a strength of our *in vivo* study because of reduction of variation between subjects and variation of food effects on Cmax and $AUC_{0\text{-}8h}$. Performing *in vivo* studies in patients is far more difficult and has more risks compared to healthy volunteers because of the necessity of introducing wash out periods and changes in clinical dosing regimens. In addition, patients use many more drugs, which can influence the specific binding and take medication with different meals.

## Implications for clinical practice

The results of our binding interaction studies are highly relevant for clinical practice. *In vivo* binding interactions that are identified and confirmed have to be implemented in the electronic medication surveillance systems used by pharmacists and physicians with the advice to stagger dosing. The duration of time needed between intake is, however, not clear yet. In practice, a time interval of three hours is recommended, which is based on the time needed for gastric emptying in healthy individuals.[51] Because of the

higher incidence of gastroparesis in CKD patients a longer time interval between intake may be needed for which further research is needed. This also counts for the impact of decreased bioavailability on clinical effectiveness.

In addition to monitoring binding interactions in electronic medication surveillance, it is important to assess binding interactions in medication reviews. When performing medication reviews in patients using sevelamer or polystyrene sulfonate in primary and secondary care it is important for clinical pharmacists to evaluate the ingestion times of the concurrently used drugs and the clinical effectiveness of these drugs. When the effect of a drug taken together with sevelamer or polystyrene sulfonate is low, the clinical pharmacist should analyse if this may be due to a binding interaction. Changing therapy or introducing staggered dosing may be an option to improve treatment of these patients. On the other hand, when patients are well treated with drugs that are ingested simultaneously with sevelamer or polystyrene sulfonate it is important to inform patients to maintain this dosing scheme, because changing ingestion times may result in introducing adverse effects.
Finally, it is important for clinical pharmacists to create awareness with prescribers for these binding interactions and their clinical implications.

# Conclusions

This thesis describes different studies of how the clinical pharmacist can improve pharmacotherapy in hospital patients focusing on three different topics: pharmacist-led medication reviews, management of metformin toxicity and management of drug binding interactions with sevelamer and polystyrene sulfonate.

## The main conclusions

Pharmacist-led medication reviews are a suitable instrument to identify drug related problems and inappropriate prescribing in (pre)dialysis and older patients with cancer treated with intravenous chemotherapy to improve medication management in these complex hospital patients.

The incidence of MALA is 5 to 16 times higher than reported in literature. When managing lactic acidosis in the emergency department the diagnosis MALA should be considered in patients with a creatinine concentration ≥ 256 umol/l and lactate concentration ≥ 8.4 mmol/l. Severity of lactic acidosis and renal impairment are the main indications for initiating ECTR, that may be lifesaving in treating MALA.

Fourteen potentially new binding interactions with sevelamer and 23 potentially new binding interactions with polystyrene sulfonate were established based on an *in silico* – *in vitro* approach, which have to be confirmed *in vivo* to assess the clinical relevance. One of these binding interactions, amitriptyline with polystyrene sulfonate, is confirmed in healthy volunteers. The exposure of amitriptyline was decreased with 75% when amitriptyline was simultaneously ingested with polystyrene sulfonate compared to intake of amitriptyline alone, necessitating staggered dosing between drugs.

# References


1. Jacobi J. Clinical pharmacists: practitioners who are essential members of your clinical care team. *Rev med Clin Condes* 2016;27(5):571-577
2. American College Clinical Pharmacy. Accessed at www.accp.com. Consulted on 23 april 2021
3. Pai AB, Boyd A, Depczynski J, Chavez IM, Khan N, Manley H. Reduced drug use and hospitalization rates in patients undergoing hemodialysis who received pharmaceutical care: a 2-year, randomized, controlled study. *Pharmacotherapy* 2009;29:1433-1440
4. Chia BY, Cheen MHH, Gwee XY et al. Outcomes of pharmacist-provided medication review in collaborative care for adult singaporeans recieving hemodialysis. *Int J Clin Pharm*. 2017;39:1031-1038
5. Patricia NJ, Foote EF. A pharmacy-based medication reconciliation and review program in hemodialysis patients: a prospective study. *Pharmacy Practice* 2016;14:785. Doi: 10.18549/PharmPract.2016.03.785
6. Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *J Clin Oncol* 2015;33:1453-1459
7. Khalil H, Kynoch K, Hines S. Interventions to ensure medication safety in acute care: an umbrella review. *Int J Evid Based Healthc* 2020;18:188-211
8. Paksoy C, Özkan Ö, Ustaalioğlu BB, Sancar M, Demirtunç R, Izzettin FV, et al. Evaluation of potentially inappropriate medication utilization in elderly patients with cancer at outpatient oncology unit. *J Oncol Pharm Pract* 2019;25:1321-1327
9. Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. *J Geriatr Oncol* 2012;3:228-237
10. Feng X, Higa GM, Safarudin F, Sambamoorthi U, Tan X. Potentially inappropriate medication use and associated healthcare utilization and costs among older adults with colorectal, breast, and prostate cancers. *J Geriatr Oncol* 2019;10:698-704
11. Karuturi MS, Holmes HM, Lei X, Johnson M, Barcenas CH, Cantor SB, et al. Potentially inappropriate medications defined by STOPP criteria in older patients with breast and colorectal cancer. *J Geriatr Oncol* 2019;10:705-708
12. Saarelainen LK, Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, et al. Potentially inappropriate medication use in older people with cancer: prevalence and correlates. *J Geriatr Oncol* 2014;5:439-446
13. Renaudin P, Boyer L, Esteve MA, Bertault-Peres P, Auquier P, Honore S. Do pharmacist-led medication reviews in hospitals help reduce hospital re-admissions? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2016;82:1660-1673
14. Christensen M, Lundh A. Medication review in hospital patients to reduce morbidity and mortality. *Cochrane Database of Systematic Reviews* 2016;2:CD008986
15. Vestergaard Ravn-Nielsen L, Duckert ML, Lolk Lund M, Pilegaard Hendriksen J, Lyndgaard Nielsen M, Skovsende Eriksen C et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission. A randomized clinical trial. *JAMA Intern Med* 2018;178(3):375-382
16. Walraven B, Ponjee G, Heideman W, Karapinar carkit F. Medications reviews in hospitalized patients: a qualitative study on perceptions of primary and secondary

care providers on interprofessional collaboration. *BMC Health Services Research* 2020;20:902
17. Crutzen S, Schuling J, Hugtenburg JJ, Verduijn M, Teichert M, Taxis K et al. Development and piloting of an algorithm to select older patients for different types of medication reviews. *Front Pharmacol* 2019;10:217
18. Salgado TM, Moles R, Benrimoj SI, Fernadez-Llimos F. Pharmacists interventions in the management of patients with chronic kidney disease: a systematic review. *Nephrol Dial Transplant* 2012;27:276-292
19. Hohl CM, Badke K, Zhao A, Wickham ME, Woo SA, Sivilotti MLA et al. Prospective validation of clinical criteria to identify emergency department patients at high risk for adverse drug events. *Acad Emerg Med* 2018;25(9):1015-1026
20. Hohl CM, Partovi N, Ghement I, Wickham ME, Mcgrail K, Reddekopp LN et al. Impact of early in-hospital medication reviews by clinical pharmacists on health services utilization. *PLoS One* 2017;12(2):e0170495
21. Krogsgaard Bonnerup D, Lisby M, Aggerholm Saedder E, Arp Sorensen C, Brock B, Andersen L et al. Risk of prescribing errors in acutely admitted patiens: a pilot study. *Int J Clin Pham* 2016;38:1157-1163
22. Krogsgaard Bonnerup D, Lisby M, Aggerholm Saedder E, Brock B, Truelshoj T, Arp Sorensen C et al. Effects of stratified medication review in high-risk patients at admission to hospital: a randomized controlled trail. *Ther Adv Drug Saf* 2020;11:1-10
23. Tangiisuran B, Scutt G, Stevenson J, Wright J, Onder G, Petrovic M, Cammen van der TJ et al. Develpoment and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton Adverse Drug Reacions Risk (BADRI) model. *PLoS One* 2014;9(10):e111254
24. Aggerholm Saedder E, Lisby M, Nielsen LP, Rungby J, Vukelic Andersen L, Krogsgaard Bonnerup D et al. Detection of patients at high risk of medication errors: development and validation of an algorithm. *Basic Clin Pharmacol Toxicol* 2016;118:143-149
25. Brady A, Curtis CE, Jalal Z. Screening tools used by clinical pharmacists to identify elderly patients at risk of drug-related problems on hospital admission: a systematic review. *Pharmacy* 2020;8:64
26. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* 2015;30: ii1–142
27. Kwon S, Kim YC, Park JY, Lee J, An YN, Kim CT et al. The log-term effects of metformin on patients with diabetic kidney disease. *Diabetes Care* 2020;43:948-955
28. Ekstrom N, Schioler L, Svensson AM, Olofsson KE, Jonasson JM, Zethelius B et al. Effectiveness and safety of metformin in 51675 patients with type 2 diabetes mellitus and different levels of renal failure: a cohort study from the Swedish national diabetes register. *BMJ Open* 2012;2(4):e001076
29. Lalau JD, Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B or 4. *Diabetes Care* 2018;41(3):547-553
30. Tesfaye WH, Castelino RL, Wimmer BC, Zaidi STR. Inappropriate prescribing in chronic kidney disease: a systematic review of prevalence, associated clinical outcomes and impact of interventions. *Int J Clin Pract* 2017;71:e12960
31. Eugenio KR, Eugenio Clark LM. Community pharmacists' counseling about metformin associated lactic acidosis. *J Am Pharm Assoc* 2004;44:629-630
32. Manders M, Luin van M, Kramers C, Bosch FH. Metformine geassocieerde lactaatacidose; een onvoldoende onderkend problem. *Ned Tijdschr Geneeskd*

2017;161:D1823
33. Niedrig D, Krattinger R, Jodicke A, Gott C, Bucklar G, Russman S. Development and implementation and outcome analysis of semi-automated alerts for metformin dose adjustments in hospitalized patients with renal impairment. *Pharmacoepidemiol Drug Saf* 2016;25:1204-1209
34. Angioi A, Cabiddu G, Conti M, Pili G, Atzeni A, Matta V, et al. Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long term follow up. *BMC Nephrol* 2018;19(1):77
35. Naunton M, Kyle G, Owoka F, Naunton-Boom K. Pharmacist review prevents evolving metformin associated lactic acidosis. *J Clin Pharm Ther* 2014;39:567-570
36. Lim CC, Wong MWY, Koh HL, Mok LYJ, Chin YM, Choo JCJ. Metformin-Associated Lactic Acidosis: Are we looking in the right direction? *Diabet Metab* 2020;46:72-73
37. Schadle P, Tschritter O, Kellerer M. Metformin Associated Lactic Acidosis in clinical practice – a case series. *Exp Clin Endocrinol Diabetes* 2020;May 13:doi:10.1055/a-1149-9030
38. Krowl L, Al-Khalisy H. Pratibha K. Metformin-Induced lactic Acidosis (MILA): review of current diagnostic paradigm. *Am J Emerg Med* 2018;36(5):908.e3-908.e5
39. Corchia A, Wynckel A, Journet J, Frances JM, Skandrani N, Lautrette A. et al. Metformin-related lactic acidosis with acute kidney injury: results of a French observational multicentre study. *Clin Toxicol* 2019;aug 6:1-8
40. Vecchio S, Giampretti A, Petrolini M, Lonati D, Protti A, Papa P et al. Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. *Clin Toxicol* 2014;52:129-135
41. Duong JK, Furlong TJ, Roberts DM, Graham GG, Greenfield JR, Williams KM, Day RO. The role of metformin in metformin-associated lactic acidosis (MALA): case series and formulation of a model of pathogenesis. *Drug Saf* 2013;36:733-746
42. Bennis Y, Bodeau S, Batteux B, Gras-Champel V, Masmoudi K, Maizel J et al. A study of associations between plasma metformin concentration, lactic acidosis and mortality in an emergency hospitalization context. *Crit Care Med* 2020;48(12):e1194-e1202
43. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med* 2015;43(8):1716-1730
44. Kajbaf F, Lalau JD. The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. *BMC Pharmacol Toxicol* 2013;14:22
45. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Safety* 1999;20:377-384
46. Usansky HH, Sinko PJ. Estimating Human Drug Oral Absorption Kinetics From Caco-2 Permeability Using an Absorption-Disposition Model: Model Development and Evaluation and Derivation of Analytical Solutions for K(a) and F(a). *J Pharmacol Exp Ther* 2005;314(1):391-399
47. Ferdousi R, Safdari R, Omidi Y. Computational prediction of drug-drug interactions based on drugs functional similarities. *J Biomed Inform* 2017;70:54-64
48. Walker JR, Brown K, Rohatagi S, Bathala MS, Xu C, Wickremasingha PK, Salazar DE, Mager DE. Quantitative Structure-Property Relationships Modeling to Predict in Vitro and in Vivo Binding of Drugs to the Bile Sequestrant, Colesevelam (Welchol). *J Clin Pharmacol* 2009;49(10):1185-1195

49. Vlem van B, Schoonjans R, Vanholder R, Vos de M, Vandamme W, Laecke van S, et al. Delayed Gastric Emptying in Dyspeptic Chronic Hemodialysis Patients. *Am J Kidney Dis*. 2000;36:962-8
50. Strid H, Simrén M, Stotzer PO, Abrahamsson H, Björnsson ES. Delay in gastric emptying in patients with chronic renal failure. *Scandinavian Journal of Gastroenterology*. 2004;39:516-20
51. FDA Drug Safety Communication: FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs. Accessed at www.fda.gov. Consulted on 25 March 2021

# Appendices

# Summary

## Background and aim

Clinical pharmacists are specialized pharmacists working in different health care settings, directly with physicians, other health professionals and patients to ensure that the drugs prescribed contribute to the best possible health outcomes. Clinical pharmacists possess in-depth knowledge of drugs and use this knowledge to optimize drug use, to avoid adverse effects and to improve health and quality of life. This thesis describes, in three different parts, how the clinical pharmacist can contribute in improving pharmacotherapy of hospital patients.

Firstly, the clinical value of pharmacist-led medication reviews was assessed in two complex patient groups: (pre)dialysis patients and older patients with cancer treated with intravenous chemotherapy. Secondly, the management of metformin associated lactic acidosis (MALA), a rare but serious adverse effect of a frequently used drug for diabetes mellitus type 2, was studied. Finally, several potential new drug binding interactions were identified with sevelamer and polystyrene sulfonate, drugs that are often used by chronic kidney disease (CKD) patients.

## Medication reviews

Pharmacist-led medication reviews aim to improve patient outcomes by preventing adverse drug events and decreasing healthcare utilization. A medication review is a judgement of the pharmacotherapy by the patient, pharmacist and physician by means of a structured critical evaluation of the medical, pharmaceutical and utilization information. In agreement with the patient and his physician, the pharmacist identifies areas of improvement and suggests a follow-up treatment plan. We investigated the benefits of pharmacist-led medication reviews in clinical practice for two complex patient groups in hospital. In our case, we use the concept of a complex patient group for patients with chronic polypharmacy having a high risk to experience drug related problems and being under treatment of one or more specialists in the hospital.

Chapter 2 of this thesis describes the evaluation of pharmacist-led medication reviews in pre-dialysis and dialysis patients in clinical practice. A large number of different types of drug related problems (DRPs) were detected. Overall, 80% of the patients had on average three medication discrepancies per patient of which the majority (81%) was acknowledged by the nephrologist. Patient counseling in order to improve adherence and adequate timing of administration was performed in 37% of patients. In addition, medication reviews were conducted resulting in prescription changes in 48% of the patients with nearly two medication changes per patient. Ninety percent of these changes

remained implemented on follow-up after at least 1 month. Forty-six percent of the changed prescriptions were identified with the STOPP/START criteria, whereas 54% was based on the clinical pharmacists' expert opinion. The average time investment was 85 minutes per patient for the clinical pharmacist and 15 minutes for the nephrologist. For the latter, the time investment and unclear responsibility for medication management due to multiple prescribers were the main reasons to reject pharmacist interventions. In **chapter 3**, pharmacist-led comprehensive medication reviews in older cancer patients using both STOPP/START criteria and pharmacists' expert opinion are described. A prevalence of 78% of potentially inappropriate medications (PIMs) and potentially omitted medications (POMs) was found. Pharmacists' expert opinion in addition to only STOPP/START criteria contributed to 49% of the PIMs and 23% of the POMs. A follow-up action was required in 73% of the PIMs and POMs. The number of medicines and Charlson Comorbidity Index (CCI) score were both associated with at least one PIM and/or POM per patient.

## Metformin toxicity

Metformin is the most commonly prescribed oral antidiabetic drug in non-insulin dependent type 2 diabetes mellitus. Although metformin is considered to be a safe and well-tolerated drug, its use may rarely be complicated by lactic acidosis. There appears to be a clear relationship between metformin accumulation and lactic acidosis, although some authors have pointed out that several such patients had other confounding risk factors for lactic acidosis. The incidence of metformin associated lactic acidosis (MALA) reported in literature varies widely.

In our clinical study (**Chapter 4**), the incidence was estimated at 47 per 100,000 patient-years, which is 5 to 16 times higher than previously reported. This may be explained by the use of metformin in the presence of risk factors for lactic acidosis.

Remarkably, we found that survivors of MALA had a higher metformin serum concentration than non-survivors, probably because of fewer comorbidities in the survivor group. Several studies suggest that early recognition of MALA and timely starting the right treatment may reduce morbidity and mortality. However, MALA is difficult to differentiate from sepsis, since clinical symptoms are similar. Therefore, in **chapter 5**, a study is presented to establish clinical parameters for identification of MALA in patients with suspected sepsis induced lactic acidosis in the emergency department. The combined parameters lactate ≥ 8.4 mmol/l and creatinine ≥ 256 umol/l showed a sensitivity of 85% and a specificity of 95% for identifying MALA in suspected sepsis induced lactic acidosis patients in the emergency department. When combined with metformin use the specificity increased to 99%. The multidisciplinary, international EXTRIP Consensus Work Group formulated specific recommendations for starting extracorporeal treatment

(ECTR) in metformin poisoning. However, the evidence levels of these criteria were low and their validity in clinical practice was not assessed. Chapter 6 of this thesis describes the study in which we assessed whether ECTR improved outcome of patients with MALA and the clinical applicability of the EXTRIP-criteria for starting ECTR in metformin poisoning. We found that lactate, creatinine, metformin serum concentrations and vasopressor requirement were significantly higher in the patient group that received ECTR. Blood pH and bicarbonate were significantly lower. Mortality, length of hospital stay and mechanical ventilation requirement were not statistically significantly different between the two groups. Despite these findings, ECTR might be lifesaving in MALA, considering that patients in the ECTR-group were significantly sicker than patients in the non-ECTR-group. In 83% of patients, treatment of MALA was in accordance with the EXTRIP criteria and severity of lactic acidosis and renal impairment were the main indications for initiating ECTR.

## Binding interactions

Resins such as, sevelamer and polystyrene sulfonate, are used for binding phosphate and potassium to treat hyperphosphatemia and hyperkaliemia which can cause serious complications in patients with Chronic Kidney Disease. Because of their binding properties, these resins can also bind other drugs in the gastrointestinal tract, thereby decreasing their bioavailability and clinical effectiveness. In the Netherlands, these known binding interactions are included in the electronic medication surveillance systems with the advice for staggered dosing between drugs. This is, however, difficult to accomplish in a patient group using on average 8 different drugs a day. In addition, nephrologists may not be aware of binding interactions of these resins with co-medication and their clinical implications. There are potentially many more drugs binding to sevelamer or polystyrene sulfonate that are not accounted for in the current medication surveillance systems, leading to ineffective treatment in clinical practice.

We therefore studied drug binding interactions with sevelamer and polystyrene sulfonate using a combined in silico, in vitro and in vivo approach.

In chapter 7, we present a patient with unexplainable low serum quetiapine concentrations. Our hypothesis, that this was the result of a drug-drug interaction between quetiapine and the binding resins polystyrene sulfonate and sevelamer, was confirmed in vitro as well as in vivo. The in vitro binding assay showed pH-independent absorbance inhibition of quetiapine by polystyrene sulfonate and pH-dependent absorbance inhibition by sevelamer. In the in vivo experiment, the time of ingestion of quetiapine, polystyrene sulfonate and sevelamer were separated, whereafter serum quetiapine concentrations rose from a not detectable level to a level well in the therapeutic range. In an in silico study, we identified several candidates for potential binding interactions with

sevelamer and polystyrene sulfonate. In a large database we determined frequently co-dispensed drugs and assessed their potential for binding based on pKa value, charge at gastro-intestinal pH levels and Log P values (**chapter 8**). Hereby, twenty-eight drugs were selected for further in vitro experiments. These subsequent in vitro experiments revealed 14 and 23 potentially new binding interactions with sevelamer and polystyrene sulfonate, respectively (**chapter 9**). From these findings, the binding interaction between amitriptyline and polystyrene sulfonate was selected for further investigation in vivo in healthy volunteers. This study is described in **chapter 10**. The Cmax and $AUC_{0\text{-}8h}$ of amitriptyline decreased by 75% and 73% respectively when amitriptyline was simultaneously ingested with polystyrene sulfonate compared to intake of amitriptyline alone. As a consequence, we recommend staggered intake of these drugs in daily practice. Further research in CKD patients is needed to establish the optimal time interval between intake for safe and effective use of amitriptyline in combination with polystyrene sulfonate.

## Discussion and conclusions

In **chapter 11** General discussion and perspectives, the results of this thesis have been put into a broader perspective with a specific focus on the role of the clinical pharmacist in relation to the three different topics studied in this thesis. In this thesis, we have shown that the clinical pharmacist can improve pharmacotherapy in hospital patients by performing generic, patient oriented activities such as pharmacist-led medication reviews and by performing more specific drug oriented activities as the management of MALA and the management of drug binding interactions with sevelamer and polystyrene sulfonate.

To implement pharmacist-led medication reviews in hospital patients it is essential that primary and secondary care takers work together and make agreements on patient selection, responsibilities and communication. Clinical pharmacist may focus on complex patients and high risk patients. For complex patients the clinical pharmacist may acts as a designated medication management caretaker and develop specific criteria for performing medication reviews. For high risk patients it is firstly important to develop suitable tools for identifying these patients.

In the management of MALA, future clinical pharmacist activities should focus on preventing MALA, by performing adequate medication surveillance, counselling patients and creating awareness with physicians as well as developing clinical decision tools to identify MALA in the ER. In the latter, measuring metformin serum concentrations may be an important diagnostic tool.

With the *in silico – in vitro – in vivo* approach we used to study new binding interactions with sevelamer and polystyrene sulfonate it is possible to identify in a relatively simple and fast way potential new binding interactions. This approach can be used for further identifying and confirming new binding interactions with sevelamer and polystyrene sulfonate but also for other resins as colestyramine and patiromer. The confirmed binding interactions have to be implemented in the electronic medication surveillance systems so the pharmacist can counsel patients in taking these drugs not concommitantly.

## The main conclusions

Pharmacist-led medication reviews are a suitable instrument to identify drug related problems and inappropriate prescribing in (pre)dialysis and older patients with cancer to improve medication management in these complex hospital patients.

The incidence of MALA is 5 to 16 times higher than reported in literature. When managing lactic acidosis in the emergency department the diagnosis MALA should be considered in patients with a creatinine concentration ≥ 256 umol/l and lactate concentration ≥ 8.4 mmol/l. Severity of lactic acidosis and renal impairment are the main indications for initiating ECTR, that may be lifesaving in treating MALA.

Fourteen potentially new binding interactions with sevelamer and 23 potentially new binding interactions with polystyrene sulfonate were established based on an *in silico – in vitro* approach, which have to be confirmed *in vivo* to assess the clinical relevance. One of these binding interactions, amitriptyline with polystyrene sulfonate, is confirmed in healthy volunteers. The exposure of amitriptyline was decreased with 75% when amitriptyline was simultaneously ingested with polystyrene sulfonate compared to intake of amitriptyline alone, necessitating staggered dosing between drugs.

# Samenvatting

## Achtergrond en doel van het onderzoek

Ziekenhuisapothekers zijn gespecialiseerde apothekers die in samenwerking met artsen, andere zorgverleners en patiënten ervoor zorgdragen dat de voorgeschreven geneesmiddelen bij patiënten in het ziekenhuis tot de best mogelijke behandeling leiden. Ziekenhuisapothekers hebben hiervoor uitgebreide kennis van geneesmiddelen en gebruiken deze kennis om het gebruik van geneesmiddelen te verbeteren, bijwerkingen te voorkomen en gezondheid en kwaliteit van leven van patiënten te verbeteren. Dit proefschrift beschrijft, in drie verschillende delen, hoe de ziekenhuisapotheker kan bijdragen aan verbetering van de behandeling met geneesmiddelen van patiënten in het ziekenhuis. In het eerste deel is de klinische meerwaarde van medicatiebeoordelingen door ziekenhuisapothekers bij 2 verschillende patiëntgroepen onderzocht: predialyse en dialyse patiënten en oudere patiënten met kanker. In het tweede deel is een zeldzame maar zeer ernstige bijwerking van het geneesmiddel metformine bestudeerd: metformine geassocieerde lactaat acidose (MALA). Metformine is het meest gebruikte geneesmiddel bij de behandeling van diabetes mellitus type 2. Tenslotte zijn er in het derde deel verschillende potentiële nieuwe geneesmiddelinteracties geïdentificeerd met de geneesmiddelen sevelameer en polystyreensulfonzuur. Dit zijn geneesmiddelen die vaak gebruikt worden door mensen met chronische nierfunctiestoornissen.

## Medicatie beoordelingen

Medicatiebeoordelingen hebben als doel om de behandeling van patiënten met geneesmiddelen te verbeteren. Bij een medicatiebeoordeling evalueren de apotheker, arts en patiënt samen op een gestructureerde manier de behandeling met geneesmiddelen. Hierbij wordt gebruik gemaakt van de beschikbare medische en farmaceutische informatie en van de gebruiksinformatie van de patiënt zelf. De apotheker doet aan de hand van deze evaluatie specifieke verbetervoorstellen en overlegt dit met de arts en patiënt. Wij onderzochten de meerwaarde van deze medicatiebeoordelingen door een ziekenhuisapotheker bij 2 complexe patiëntgroepen in het ziekenhuis: predialyse en dialyse patiënten en oudere patiënten met kanker die behandeld werden met intraveneuze chemotherapie. We hebben complexe patiënten gedefinieerd als patiënten die langdurig meer dan 5 verschillende geneesmiddelen gebruiken en behandeld worden in het ziekenhuis door 1 of meerdere specialisten.

**Hoofdstuk 2** van dit proefschrift beschrijft de evaluatie van medicatiebeoordelingen door de ziekenhuisapotheker bij predialyse en dialyse patiënten in het ziekenhuis. Bij het uitvoeren van deze medicatiebeoordelingen zijn een groot aantal verschillende

geneesmiddel gerelateerde problemen geïdentificeerd. Bij 80% van de patiënten werden gemiddeld 3 verschillen gesignaleerd in het actuele medicatiegebruik en de geregistreerde medicatie in het patiëntendossier. Eenentachtig procent van deze verschillen werd door de nefroloog naar aanleiding van deze medicatiebeoordelingen gecorrigeerd in het patiëntendossier. Bij 37% van de patiënten heeft de ziekenhuisapotheker de patient extra voorlichting/advies gegeven over het juiste gebruik van geneesmiddelen. Bij 48% van de patiënten werd het gebruik van gemiddeld 2 geneesmiddelen gewijzigd door de arts. Dit betrof stoppen, starten of het wijzigen van de dosering van geneesmiddelen. Een maand later was 90% van deze wijzigingen nog steeds doorgevoerd. Deze wijzigingen zijn gesignaleerd met behulp van de START/STOPP-criteria (46%) en op basis van de kennis van de ziekenhuisapotheker (54%). De START-criteria zijn op evidence gebaseerde voorschrijfadviezen bij ouderen bij regelmatig voorkomende aandoeningen. De STOPP-criteria zijn klinisch significante criteria om potentieel ongeschikte geneesmiddelen bij oudere patiënten te signaleren. Een medicatiebeoordeling kostte de ziekenhuisapotheker gemiddeld 85 minuten per patient en de nefroloog 15 minuten. De belangrijkste redenen voor de nefroloog om bepaalde verbetervoorstellen van de ziekenhuisapotheker niet te accepteren waren tijdsinvestering en het niet verantwoordelijk zijn voor geneesmiddelen voorgeschreven door andere behandelaren van de patiënt. In hoofdstuk 3 worden medicatiebeoordelingen bij oudere patiënten met kanker beschreven waarbij gebruik werd gemaakt van de START/STOPP-criteria en de kennis van de ziekenhuisapotheker. Er werd een prevalentie van 78% van potentieel ongeschikte medicatie (PIMs) en potentieel vergeten medicatie (POMs) gevonden. De kennis van de ziekenhuisapotheker droeg voor 49% bij aan de identificatie van de PIMs en voor 23% aan identificatie van de POMs als aanvulling op de START/STOPP-criteria. In 73% van de PIMs en POMs beoordeelde de oncoloog dat een vervolgactie nodig was. Het aantal geneesmiddelen van de patiënt en de mate van co-morbiditeit waren geassocieerd met het vinden van minstens 1 PIM en of POM per patiënt.

## Metformine toxiciteit

Metformine is het meest voorgeschreven geneesmiddel in de behandeling van diabetes mellitus type 2. Alhoewel metformine een veilig en goed verdragen geneesmiddel is kan tijdens gebruik de zeldzame maar zeer ernstige bijwerking lactaat acidose optreden. Lactaatacidose is verzuring van het bloed door ophoping van lactaat (melkzuur) in het lichaam. Lactaat wordt in het lichaam gemaakt uit glucose wanneer er te weinig zuurstof is. Bij lactaatacidose kunnen maagdarmklachten, spierpijn, benauwdheid of kortademigheid, lage bloeddruk of coma optreden. De mortaliteit van MALA kan oplopen tot 50%. Er lijkt een relatie te bestaan tussen metformine stapeling in het lichaam en lactaat acidose maar verschillende auteurs geven aan dat patiënten waarbij MALA

gerapporteerd is ook andere risico factoren hadden voor het optreden van lactaat acidose waaronder bijvoorbeeld acute nierfunctiestoornissen. De gerapporteerde incidentie van MALA in de literatuur varieert heel erg. In onze klinische studie (**hoofdstuk 4**), werd de incidentie van MALA geschat op 47 per 100.000 patiëntjaren en dat is 5-16 keer hoger dan hiervoor gerapporteerd was. Dit zou mogelijk verklaard kunnen worden door het gebruik van metformine door patiënten met ook andere risicofactoren voor lactaatacidose. Verrassend vonden we in onze studie dat patiënten die MALA overleefden hogere concentraties metformine in hun bloed hadden dan patiënten die overleden. Dit kan mogelijk verklaard worden door minder co-morbiditeit in de overlevende groep. Diverse studies geven aan dat het belangrijk is om MALA zo snel mogelijk te herkennen om de juiste behandeling te kunnen starten en daarmee morbiditeit en mortaliteit te verminderen. Het is echter moeilijk om MALA te onderscheiden van lactaat acidose door sepsis omdat de klinische symptomen vergelijkbaar zijn. Sepsis is een ontstekingsreactie van het lichaam op een infectie die zo ernstig verloopt dat weefsels beschadigd raken en orgaanfuncties uitvallen. Hierbij neemt ook de concentratie lactaat in bloed toe. De behandeling van MALA en sepsis zijn echter verschillend. Bij sepsis moet gestart worden met antibiotica en bij MALA moet nierfunctie vervangende therapie overwogen worden. Daarom hebben we een studie uitgevoerd om klinische parameters vast te stellen waarmee MALA-patiënten onderscheiden kunnen worden van patiënten met lactaat acidose door sepsis op de spoedeisende hulp van het ziekenhuis (**hoofdstuk 5**). De gecombineerde parameters lactaat ≥ 8.4 mmol/l en creatinine ≥ 256 umol/l hadden een sensitiviteit van 85% en een specificiteit van 95% voor het onderscheiden van MALA-patiënten in patiënten met het vermoeden op lactaat acidose door sepsis. Wanneer de parameter metformine gebruik werd toegevoegd nam de specifiteit toe tot 99%. Dit betekent dat 85% van de patiënten met deze gecombineerde parameters terecht geïdentificeerd worden als MALA en dat 1% van de patiënten met deze gecombineerde parameters ten onrechte geïdentificeerd wordt als MALA.

Bij de behandeling van MALA moet nierfunctie vervangende therapie (ECTR) overwogen worden.

De multidisciplinaire internationale EXTRIP-consensus werkgroep heeft specifieke aanbevelingen gedaan voor het starten van ECTR bij metformine intoxicaties. Echter de onderbouwing voor deze aanbevelingen is laag en de aanbevelingen zijn niet gevalideerd in de klinische praktijk. **Hoofdstuk 6** van dit proefschrift beschrijft een studie waarin we onderzocht hebben of ECTR de klinische uitkomst van MALA-patiënten verbetert en of de EXTRIP-criteria toepasbaar zijn in de klinische praktijk. We vonden dat lactaat, creatinine, metformine concentraties en de benodigde hoeveelheid vasopressoren (stoffen die de samentrekking van spieweefsel bevorderen) significant hoger waren in de ECTR-groep vergeleken met de groep niet behandeld met ECTR. Bloed pH

en bicarbonaat concentratie waren significant lager. Mortaliteit, duur van ziekenhuisopname en benodigde mechanische ventilatie waren niet significant verschillend tussen de beide groepen. Ondanks deze bevindingen denken we dat ECTR mogelijk levensreddend is bij MALA-patiënten omdat de ECTR-groep significant zieker was dan de patiënten niet behandeld met ECTR. Bij 83% van de patiënten was de behandeling van MALA in overeenstemming met de EXTRIP-criteria. De ernst van de lactaat acidose en nierfalen waren de belangrijkste indicaties voor het starten van ECTR.

## Binding interacties

Patiënten met nierfunctiestoornissen hebben vaak te hoge fosfaat en kalium concentraties in hun bloed waardoor ze fosfaatbinders en of kaliumbinders moeten gebruiken om hun fosfaat en kaliumconcentraties in het bloed te verlagen. Dit is nodig omdat te hoge fosfaat en kalium concentraties in het bloed kunnen leiden tot botziekten en cardiovasculaire complicaties. Sevelameer bindt fosfaat en polystyreensulfonzuur bindt kalium in het maagdarmkanaal en verlaagt op deze manier de fosfaat en kaliumconcentraties in het bloed. Vanwege hun bindingseigenschappen kunnen sevelameer / polystyreensulfonzuur ook andere geneesmiddelen binden in het maagdarmkanaal waardoor de opname van deze geneesmiddelen in het bloed en dus ook de klinische effectiviteit kan afnemen. In Nederland zijn reeds bekende bindingsinteracties met sevelameer en polystyreensulfonzuur opgenomen in het elektronisch medicatiebewakingssysteem van apotheken. Apothekers adviseren in deze situaties om deze geneesmiddelen niet gelijktijdig in te nemen met sevelameer / polystyreensulfonzuur. Patiënten met nierfunctiestoornissen gebruiken echter gemiddeld 8 verschillende geneesmiddelen per dag waardoor het in de praktijk moeilijk is om doseerschema's te maken waarbij geneesmiddelen minimaal 3 uur voor of na sevelameer / polystyreensulfonzuur ingenomen moeten worden. Daarbij komt dat nefrologen vaak niet op de hoogte zijn van deze bindingsinteracties en de klinische gevolgen hiervan. Waarschijnlijk zijn er veel meer bindingsinteracties met sevelameer / polystyreensulfonzuur dan waarop nu bewaakt wordt door apotheken welke kunnen leiden tot ineffectieve therapie. Daarom hebben wij nieuwe bindingsinteracties met sevelameer / polystyreensulfonzuur onderzocht met behulp van een in silico – in vitro en in vivo benadering. Bij in silico onderzoek wordt gebruik gemaakt van computerberekeningen, in vitro onderzoek wordt uitgevoerd op het laboratorium en in vivo onderzoek vindt plaats in mensen. In **hoofdstuk 7** is een patiënt beschreven met onverklaarbare lage quetiapine concentraties in het bloed. Onze veronderstelling, dat dit veroorzaakt werd door een bindingsinteractie met sevelameer en polysytreensulfonzuur werd zowel in vitro als in vivo bevestigd. De in vitro studie liet pH onafhankelijke binding van quetiapine aan polystyreensulfonzuur zien en pH afhankelijke binding aan sevelameer. In het in vivo experiment werden bij de patiënt de

inname tijden van quetiapine, sevelameer en polysytreensulfonzuur gescheiden waarna de quetiapine concentratie in het bloed steeg naar een normale therapeutische waarde. Met behulp van een database met aflevergegevens van apotheken in Noord-Nederland werden verschillende potentiële nieuwe kandidaten geïdentificeerd voor binding aan sevelameer en polystyreensulfonzuur (in silico studie). Deze potentiële nieuwe kandidaten werden geïdentificeerd uit geneesmiddelen die het meest samen met sevelameer en polystyreensulfonzuur afgeleverd zijn en waarbij potentiële binding werd bepaald op basis van de chemische eigenschappen (pKa waarde, lading in het maagdarmkanaal en log P waarde) van deze geneesmiddelen (**hoofdstuk 8**). Vervolgens werden 28 geneesmiddelen geselecteerd waarvan binding aan sevelameer en polystyreensulfonzuur in een in vitro studie werd onderzocht. Van deze 28 geneesmiddelen toonden 14 geneesmiddelen relevante binding aan sevelameer en 23 geneesmiddelen aan polystyreensulfonzuur. Dit is beschreven in **hoofdstuk 9**. In **hoofdstuk 10** hebben we de binding van amitriptyline, een geneesmiddel dat gebruikt wordt als antidepressivum en voor de behandeling van neuropathische pijn, aan polystyreensulfonzuur in vivo onderzocht in gezonde proefpersonen. De Cmax en de $AUC_{0\text{-}8u}$ (Cmax is de maximale concentratie in het bloed en de $AUC_{0\text{-}8u}$ is een maat voor de blootstelling) van amitriptyline nam respectievelijk met 75% en 73% af wanneer amitriptyline gelijktijdig werd ingenomen met polysytreensulfonzuur ten opzichte van inname van amitriptyline alleen. Om onvoldoende effect van amitriptyline te voorkomen adviseren wij op basis van deze resultaten dan ook om amitriptyline en polysytreensulfonzuur niet gelijktijdig in te nemen. Er is verder onderzoek nodig in patiënten met nierfunctiestoornissen om het optimale tijdsinterval tussen inname van amitriptyline en polystyreensulfonzuur vast te stellen.

## Discussie en conclusies

In **hoofdstuk 11** zijn de resultaten van dit proefschrift in een breder perspectief geplaatst waarbij specifiek de nadruk is gelegd is op de rol van de ziekenhuisapotheker in relatie tot de drie verschillende onderwerpen van dit proefschrift. We hebben laten zien dat de ziekenhuisapotheker de behandeling met geneesmiddelen van patiënten in het ziekenhuis kan verbeteren door het uitvoeren van algemene patiëntgerichte activiteiten zoals medicatiebeoordelingen en door meer geneesmiddel gerichte activiteiten als behandeling van MALA en het onderzoeken van nieuwe bindingsinteracties met sevelameer en polystyreensulfonzuur.

Voor de implementatie van medicatiebeoordelingen in het ziekenhuis is het belangrijk dat zorgverleners uit de eerste en tweede lijn met elkaar samenwerken en afspraken maken over patiënt selectie, verantwoordelijkheden en communicatie. Ziekenhuisapothekers moeten zich richten op complexe patiënten en patiënten met een hoog risico op medicatie gerelateerde problemen. Voor complexe patiënten kan de ziekenhuisapotheker optreden als aangewezen medicatie zorgverlener en kan hij specifieke criteria ontwikkelen voor het uitvoeren van medicatiebeoordelingen per complexe patiëntgroep. Bij hoog risico patiënten is het eerst belangrijk om geschikte tools te ontwikkelen waarmee deze patiënten geïdentificeerd kunnen worden.

In de behandeling van MALA moet de apotheker zich richten op het voorkomen van MALA door goede medicatiebewaking uit te voeren, voorlichting te geven aan patiënten en bewustwording te creëren bij artsen. Daarnaast is het ontwikkelen van klinische beslissingstools om MALA te kunnen herkennen en te kunnen behandelen belangrijk. De rol van het meten van metformine concentraties in bloed hierin is een belangrijk aandachtsgebied.

We hebben laten zien dat met de *in silico – in vitro – in vivo* benadering op een relatief eenvoudige en snelle manier het mogelijk is om diverse potentiële nieuwe bindingsinteracties met sevelameer en polysytyreensulfonzuur te identificeren en te bevestigen. Deze benadering kan ook gebruikt worden voor het onderzoeken van nieuwe interacties met andere bindende geneesmiddelen zoals bijvoorbeeld colestyramine (cholesterolverlager) en patiromeer (kaliumbinder). Wanneer de bindingsinteracties bevestigd zijn *in vivo* dienen deze opgenomen te worden in het elektronisch medicatiebewakingssysteem van de apotheken zodat patiënten geïnformeerd gaan worden om deze geneesmiddelen niet gelijktijdig in te nemen.

## De belangrijkste conclusies van dit proefschrift

Het uitvoeren van medicatiebeoordelingen door een ziekenhuisapotheker is een geschikt instrument om geneesmiddel gerelateerde problemen en om inadequaat voorschrijven van geneesmiddelen bij (pre)dialyse patiënten en oudere patiënten met kanker te identificeren. Hierdoor kan het medicatie management van deze complexe patiëntgroepen verbeterd worden.

De incidentie van MALA in de klinische praktijk is 5 tot 16 keer hoger dan beschreven in de literatuur. Bij patiënten met lactaat acidose op de SEH moet gedacht worden aan MALA wanneer de lactaat concentratie ≥ 8.4 mmol/l en de creatinine concentratie ≥ 256 umol/l. De ernst van de lactaatacidose en de aanwezigheid van nierfalen zijn de

belangrijkste indicaties voor het starten van ECTR wat mogelijk levensreddend is in de behandeling van MALA.

Veertien potentieel nieuwe bindingsinteracties voor sevelameer en 23 potentieel nieuwe bindingsinteracties voor polystyreensulfonzuur zijn geïdentificeerd op basis van een *in silico – in vitro* benadering. Om de klinische relevantie vast te stellen moeten deze nog bevestigd worden *in vivo*. De interactie amitriptyline – polystyreensulfonzuur is bevestigd in gezonde proefpersonen. De blootstelling van amitriptyline nam met 75% af wanneer amitriptyline gelijktijdig werd ingenomen met polysytreensulfonzuur ten opzichte van inname van amitriptyline alleen waardoor gescheiden inname noodzakelijk is.

# Dankwoord

Mijn proefschrift is af. Na het afronden van mijn studie Farmacie wilde ik graag gaan werken en datgene wat ik tijdens mijn studie geleerd had gaan toepassen in de praktijk. Ik had het geluk direct na mijn studie te mogen beginnen aan de opleiding tot ziekenhuisapotheker, wat een prachtig vak is. Al tijdens deze opleiding maar ook in de jaren daarna tijdens mijn werk als ziekenhuisapotheker was ik geinteresseerd in het doen van onderzoek in de klinische praktijk. Ik heb vaak gezegd dat ik wel zou willen promoveren maar deze stap zetten met een fulltime baan en een gezin was lastig. Ik ben erg blij en ook wel een beetje trots dat het mede met jullie hulp gelukt is om dit proefschrift tot stand te brengen. Dank dus aan iedereen die op een of andere manier een bijdrage heeft geleverd aan de tot stand koming van dit proefschrift.

Uiteraard zijn er een aantal personen die ik in het bijzonder wil bedanken.

Allereerst dank aan de patiënten en proefpersonen die geheel belangenloos hebben deelgenomen aan de verschillende onderzoeken.

Vervolgens een bijzonder woord van dank aan mijn promotoren.

Beste Frank, we hadden al vaker gesproken over een promotietraject maar met de kennismaking met Katja bij de RUG werd het ineens serieus. In augustus 2018 is dit promotietraject officieel gestart. Ik ben je erg dankbaar dat je mij gemotiveerd hebt om hier daadwerkelijk mee te beginnen. Je hebt me veel vrijheid gegeven en je had altijd tijd om oplossingen te bedenken. Wanneer een manuscript afgewezen werd bleef jij altijd optimistisch en wist je mij weer te motiveren om verder te gaan. Ik wens je veel succes met het invullen van het buitengewoon hoogleraarschap aan de RUG.

Beste Katja, al bij onze eerste ontmoeting op je kamer bij de RUG dacht ik dat voelt goed. We zijn begonnen met regelmatige overleggen in Groningen maar vanwege de COVID pandemie hebben we dit vervangen door maandelijks contact via Google Meet. Het was jammer dat we elkaar niet fysiek spraken maar het videobellen werkte heel erg goed. Hartelijk dank voor je wetenschappelijke bijdrage aan de onderzoeken. Ik vond het fijn dat je altijd naar mogelijkheden keek om de onderzoeken in een breder perspectief te plaatsen dan het Deventer Ziekenhuis. Ook zijn er via jou diverse studenten naar Deventer gekomen die hebben bijgedragen aan de verschillende onderzoeken. Het was erg leuk om de begeleiding van deze studenten samen met jou te doen.

Geachte leden van de beoordelingscommissie, prof. Patricia van den Bemt, prof. Teun van Gelder en prof. Daan Touw, en leden van de oppositie, ik stel het zeer op prijs dat u tijd heeft vrijgemaakt om mijn proefschrift te beoordelen en deel te nemen aan mijn oppositie. Heel hartelijk dank hiervoor.

Alle co-auteurs, Henk, Esther, Alex, Kees, Asiye, Arthur, Esther, Marjo, Rien, Maurits, Steven, Nyncke, Aliesa en Marieke heel hartelijk dank voor jullie kritische bijdragen aan de verschillende onderzoeken. Zonder jullie was dit niet gelukt.

Beste Kees Vermeij, je hebt me veel geleerd over MALA en je enthousiasme over dit onderwerp was erg aanstekelijk. Je hebt niet alleen een belangrijke bijdrage geleverd aan het MALA onderzoek maar ook aan de medicatiebeoordelingen bij dialyse patienten en het mogelijk maken van het interactie onderzoek. Ik ben erg blij dat je ook nog een bijdrage wilt leveren aan het minisymposium op mijn promotiedag. Heel hartelijk dank.

Beste Fianne en Ilona, jullie registratie-onderzoeken voor jullie opleiding tot ziekenhuisapotheker zijn belangrijke hoofdstukken geworden in dit proefschrift. Ik ben trots dat ik heb mogen bijdragen aan jullie opleiding tot ziekenhuisapotheker en jullie heb mogen begeleiden in jullie registratie onderzoeken. Heel hartelijk dank voor jullie bijdrage aan dit proefschrift.

Ik wil ook graag alle apothekers, apothekerassistenten, medewerkers en KFTL analisten van de Deventer Ziekenhuis Apotheek bedanken voor de fijne samenwerking al deze jaren. Collega apothekers, dank voor jullie belangsteling, het meedenken en mij de ruimte geven om dit onderzoek te doen. Apothekersassistenten dialyse, dank voor het uitvoeren van de vele medicatie verificaties op de dialyse afdeling. Tenslotte, beste KFTL analisten, dank voor alle analyses die jullie hebben uitgevoerd in het kader van deze onderzoeken.

Dan kom ik bij mijn paranimfen. Lieve Thijs, jij ging mij voor en ik vond het een eer om jouw paranimf te zijn. Ik vind het fijn dat jij dit nu ook voor mij doet. Ik had mij geen betere broer kunnen wensen. Je bent er altijd voor mij en voor mama en we kunnen voor alles bij je terecht. Ik hoop dat we snel een keertje bij jou en Tatchatrin op bezoek kunnen komen in Thailand. Dank je wel.

Lieve Marieke, we zijn al vriendinnen sinds de tweede klas VWO. We zijn elkaar nooit uit het oog verloren ondanks dat we ons eigen pad hebben bewandeld en niet meer bij elkaar in de buurt wonen. Dank je wel dat je mijn vriendin bent en voor de nodige ontspanning hebt gezorgd tijdens dit traject. Ik vind het bijzonder dat je mijn paranimf wilt zijn.

Het ontwerp en de opmaak van dit proefschrift is gemaakt door mijn vriendin Antje. Antje, dank voor het prachtige ontwerp, het is helemaal geworden wat ik wilde.

Lieve buurvrouw Aylien, tijdens onze regelmatige koffie en wandel uurtjes op vrijdag toonde je heel veel belangstelling voor mijn onderzoek. Ook wist je mij te motiveren als het weer even tegenzat. Dank je wel hiervoor.

Dank aan alle vrienden die niet direct hebben bijgedragen aan dit proefschrift maar indirect wel een belangrijke bijdrage hebben geleverd door voor ontspanning te zorgen. Jullie zijn erg belangrijk voor mij.

Gerard en Maria, lieve schoonouders, ook al staat dit alles misschien wat verder van jullie af, toch hebben jullie een hele belangrijke bijdrage geleverd. Jullie zijn er altijd voor ons en we kunnen altijd een beroep op jullie doen. Hierdoor was het mogelijk dit proefschrift te schrijven tijdens een full time baan en met een gezin. Dank jullie wel.

Lieve mama, dank voor jouw liefde en steun. Ik heb lang getwijfeld of ik aan dit traject zou beginnen maar jij zei “probeer het gewoon, als je het niet probeert krijg je daar later spijt van en als het niet lukt is dat geen ramp. Dan heb je het in ieder geval geprobeerd”. Ik zeg het niet vaak genoeg maar ik hou van je.

Tim, Jelle en Koen, jullie begrijpen dit alles misschien nog niet zo goed. Al helemaal niet waarom ik op mijn vrije vrijdagen toch aan het werk was. Ik hoop dat jullie later net zo veel plezier hebben in jullie toekomstige baan als ik en het dan een beetje begrijpen. Ik ben heel erg trots op jullie.

Tot slot, allerliefste Jeroen, ook voor jou is dit onderzoek misschien een ‘ver van je bed show’ maar zonder jou was dit nooit gelukt. Je bent mijn rots in de branding. Je stimuleert me om te doen wat ik graag wil maar houdt me ook in balans. Dank je wel voor je liefde en je vertrouwen. Op naar nog vele mooie jaren samen.

# About the author

Inge van de Laar werd op 10 November 1974 geboren in Gemert. Zij groeide hier ook op en behaalde in 1993 haar VWO diploma aan het Macropedius College te Gemert. Aansluitend begon Inge met de studie Farmacie aan de Universiteit in Utrecht waar ze in 1994 haar propedeuse, in 1997 haar doctoraal (cum laude) en in 1999 haar apothekersdiploma behaalde. Aansluitend na haar afstuderen is Inge begonnen aan de opleiding tot ziekenhuisapotheker bij Stichting Apotheek Deventer Ziekenhuizen. Na afronding van deze opleiding is Inge blijven werken als ziekenhuisapotheker bij deze ziekenhuisapotheek. Zij heeft een divers takenpakket en is onder andere professioneel verantwoordelijk voor het Klinisch Farmaceutisch en Toxicologisch Laboratorium, Farmaceutische patiëntenzorg voor GGZ instelling Dimence en medicatie overdracht bij opname en ontslag. In 2008 is de Stichting Apotheek Deventer Ziekenhuizen opgeheven en is de ziekenhuisapotheek een afdeling geworden van het Deventer Ziekenhuis; de afdeling Klinische Farmacie. In 2018 is Inge officieel gestart met haar promotietraject in het Deventer Ziekenhuis in samenwerking met de Rijksuniversiteit Groningen onder begeleiding van prof. dr. Frank Jansman en prof. dr. Katja Taxis. Het onderzoek richtte zich op verschillende manieren waarop de ziekenhuisapotheker kan bijdragen aan verbetering van de farmacotherapie van patiënten in het ziekenhuis waarbij specifiek gekeken is naar het uitvoeren van medicatiebeoordelingen, het identificeren en behandelen van een zeldzame bijwerking van metformine en het identificeren van nieuwe bindingsinteracties met sevelameer en polystyreensulfonzuur. Dit onderzoek is beschreven in dit proefschrift. Naast haar promotiewerkzaamheden was en is Inge nog altijd met veel plezier werkzaam in het Deventer Ziekenhuis. Inge is getrouwd met Jeroen en heeft 3 zonen Tim, Jelle en Koen.

# List of publications

Berlo van IRF, Tromp YH, Sluiter HE, Ploeger B.
Klinisch verloop na een fatale inname van diquat: Suicide met onkruidbestrijdingsmiddel.
Pharm Weekbl. 2003; 138(20): 720-724

Berlo van IRF.
Evaluatie van de transmurale informatie-overdracht na interventie door Steunpunt Apotheken. Pharm Weekbl. 2004; 29/30: 974-977

Berlo van IRF, Teijeiro R, Westerkamp D, Ploeger B.
De rol van het CYP2D6 genotype in de onderhoudsbehandeling met zuclopenthixoldecanoaat. Pharm Weekbl. 2004; 21: 740-743

Berlo van IRF.
Opnamegesprekken verbeteren medicatieveiligheid.
Medisch Contact. Mei 2005

Berlo van IRF.
Opnamegesprekken verminderen fouten.
Pharm Weekbl. 2008; 15: 28-29

Engel-Dettmers EM, Knijff de RC, Ploeger B, Zwet van der WC, Berlo van IRF.
Interventie door de ziekenhuisapotheek als hulpmiddel bij reductie benzodiazepinegebruik in tweedelijnspsychiatrie.
Pharm Weekbl. 2008; 2(5): WP102-105

Berlo van IRF, Goet ER, Hellden A, Sluiter HE.
Bijwerkingen valaciclovir bij gestoorde nierfunctie.
Ned Tijdschr Geneeskd. 2009; 11 april; 153(15): 706-709

Berlo van – Laar van de IRF, Vermeij CG, Doorenbos CJ.
Metformin Associated Lactic Acidosis: Incidence and Clinical Correlation with Metformin Serum Concentration Measurements.
J Clin Pharm Ther. 2011; 36(3): 376-382

Berlo van -Laar van de IRF, Driessen E, Merkx MM, Jansman FGA.
Analysis of medication information exchange at discharge from a Dutch hospital.
Int J Clin Pharm. 2012; 34(4): 524-528

Tak LM, Berlo van – Laar van de IRF, Doornbos B.
Geen quetiapine bij slaapstoornissen.
Ned Tijdschr Geneeskd. 2013; 157(5): A5740

Berlo van-Laar van de IRF, Arbouw MEL, Bles CAM.
Strychnine intoxicatie: zeldzaam maar niet vergeten.
Ned Tijdschr Geneeskd. 2015; 159: A8877

Hoge RHL, Arbouw MEL, Radstake SDWS, Berlo van - Laar van de IRF.
Subtherapeutic serum quetiapine concentrations after absorption inhibition by binding resins: a case report.
J Clin Pharm Ther. 2015; 40(3): 355-7

Berlo van - Laar van de IRF, Brummelhuis W, Imholz ALT. Schellens JH, Huitema ADR, Jansman FGA
Dosing oxaliplatin in a haemodialysis patient with metastatic rectum cancer monitored by free platinum concentrations.
J Clin Pharm Ther. 2018; 43(4): 574-577

Wilkes S, Berlo van – Laar van de IRF, Oever ten J, Jansman FGA, Heine ter R.
Population pharmacokinetic modelling of total and unbound flucloxacillin in non-critically ill patients to devise a rational continuous dosing regimen.
Int J Antimicrob Agents. 2019; 52(3): 310-317

Berlo van - Laar van de IRF, Vermeij CG, Elsen van den-Hutten M, Meijer de A, Taxis K, Jansman FGA.
Extracorporeal treatment of metformin associated lactic acidosis in clinical practice: a restrospective cohort study.
Eur J Clin Pharmacol. 2020; 76(6): 815-820

Berlo van – Laar van de IRF, Sluiter HE, Riet van ‘t E, Taxis K, Jansman FGA.
Pharmacist-led medication reviews in predialysis and dialysis patients.
Res Soc Adm Pharm. 2020; 16(12): 1718-1723

Berlo van – Laar van de IRF, Gedik A, Meijer de A, Riet van 't E, Taxis K, Jansman FGA.
Identifying patients with metformin associated lactic acidosis in the emergency department.
Int J Clin Pham. 2020; 42(5): 1286-1292

Loveren van FMAM, Berlo van – Laar van de IRF, Imholz ALT, Riet van 't E, Taxis K, Jansman FGA.
Prevalence and follow-up of Potentially Inappropriate Medication and Potentially Omitted Medication in older patients with cancer – the PIM POM study.
J. Geriatr Oncol. 2021; 12(1): 80-84

Berlo – van Laar van de IRF, Prins – Can I, Lange de AA, Taxis K, Jansman FGA.
Binding interactions with sevelamer and polystyrene sulfonate in vitro.
Pharmacol Res Perspect. 2021; Aug 9(4): e00834