Pharmacist-driven interventions in patients with chronic kidney disease and end-stage renal failure

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APPENDICES

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Summary

More than 10% of the general population worldwide suffers from chronic kidney disease (CKD), corresponding with around 800 million individuals, involving more people than many other common chronic conditions, such as diabetes, cardiovascular disease, and chronic respiratory disease [1,2]. CKD leads to renal and cardiovascular complications, and increased morbidity and mortality [1,3,4]. To prevent disease progression and reduce the devastating effects of renal and cardiovascular complications, patients with CKD are prescribed an average of around 10 different medications [5], and polypharmacy occurs in around 80% of the patients [5]. Hyperpolypharmacy is defined as the use of at least ten different medications and occurs in 40-55% of patients [5,6] . The high medication and pill burden contributes to the substantial disease and treatment burden in patients with CKD [7,8].

In the studies presented in this thesis, we aimed to investigate how the interventions of a specialised nephrology pharmacist can contribute to rational, safe, and effective medication use in patients with CKD and, more specifically, in patients on haemodialysis.

The general introduction in Chapter 1 describes the current role of the nephrology pharmacist in patients with CKD in relation to polypharmacy. The general introduction is divided into two sections. Section one describes the role of the nephrology pharmacist in drug stewardship for patients with CKD. This section focuses on the role of the nephrology pharmacist in polypharmacy, medication-related problems, and medication management. In the second section, we describe the role of the nephrology pharmacist in improving medication adherence and the impact of health literacy on medication adherence and self-management in general in patients with CKD. The general introduction concludes with the aim and outline of this thesis.

In Chapter 2, we report a systematic review in which we identified and summarised algorithm- and pharmacist-managed dosing of erythropoietin-stimulating agents (ESA) in patients with renal anaemia and determined the effects of this intervention on several outcome parameters. Observational and interventional studies available as full-text articles with a control group and follow-up ≥6 months, investigating

algorithm-managed and pharmacist-managed dosing of ESA in adult patients with renal anaemia, were eligible for inclusion. Relevant databases were searched from their inception through August 2024. Two independent reviewers evaluated all studies. The risk of bias was assessed by the ROBINS-I and RoB1 tools. After screening 140 articles, 17 articles and 4313 patients could be included. Available evidence was of low to moderate quality with a high risk of bias. Meta-analysis was not possible due to the substantial heterogeneity in participants, study design, interventions, comparisons, and outcome parameters. However, standardised metrics could be identified and calculated for haemoglobin and ESA dose. The percentage in target range for haemoglobin varied between 3.5% lower (95%CI -18.67% to + 11.67%) to 32.0% higher (95%CI 14.07 to 49.93%) in the pharmacist-managed group versus the control group (n=1401). The range for reduction in ESA dose was 5.45% (95%CI -7.97% to + 18.87%) to 49.97% (95%CI 20.32% to 79.61%) in the pharmacist-managed group versus the control group (n=2115). No definite conclusions could be drawn on the effectiveness of pharmacist-managed dosing of ESA in renal anaemia. However, low-quality data with high risk of bias suggest that pharmacist-management of renal anaemia may improve the percentage of haemoglobin within target range and reduce the ESA dose.

In Chapter 3, the results of a randomised, controlled trial on pharmacist-managed renal anaemia are described. In clinical practice, the attainment of target haemoglobin levels in haemodialysis patients is low. Several factors play a role, such as hyporesponsiveness to erythropoiesis-stimulating agents (ESA), but also suboptimal prescribing of ESA and iron. The goal of this study was to investigate if a pharmacist-managed dosing algorithm for darbepoetin alfa (DA) and iron sucrose could improve the attainment of target haemoglobin levels. In this randomised controlled trial, 200 haemodialysis patients were included. In the intervention group (n=100), a pharmacist provided dose recommendations for DA and iron sucrose monthly, based on dosing algorithms. The control group (n=100) received usual care. In the intervention group, the percentage of patients within the target range (PTR) for haemoglobin (target range 6.8-7.4 mmol/l) and iron status was higher than in the control group (for haemoglobin median 38.5% versus 23.1%, p=0.001; for iron status median 21.1% versus 8.3%, p=0.003). The percentage of high haemoglobin levels (defined as >8.1 mmol/l) was lower in the intervention group (median 0.0% versus 7.7%, p=0.034). The weekly dose of DA was lower in the intervention group (median 34.0 vs 46.9 mcg, p=0.020), whereas

iron dose was higher (median 75 versus 0 mg). No difference was found for the percentage of haemoglobin levels below target range. In conclusion, pharmacist-managed dosing for DA and iron sucrose increased the attainment of target levels for haemoglobin and iron status, reduced the percentage of high haemoglobin levels, and was associated with a lower DA and a higher iron sucrose dose.

In Chapter 4, the results of a retrospective, observational study on trends in acceptance rate, number, and clinical relevance of on-ward pharmacist interventions in the nephrology ward are presented. Clinical pharmacist interventions in the patient ward reduce medication-related problems in hospitalised patients in the short term, but long-term data are lacking. This study aimed to assess time trends in the acceptance rate, number, and clinical relevance of on-ward pharmacist interventions on the nephrology ward over five years. Nephrology pharmacists proposed interventions during weekly multidisciplinary ward rounds, based on medication appropriateness. Primary and secondary outcomes were, respectively, the acceptance rate of pharmacist interventions and the number and clinical relevance of pharmacist interventions over five years. Clinical relevance was assessed independently by two nephrologists, who were not involved in patient care. Data over five years were analysed using the Cochrane-Armitage test for trend using SPSS. A total of 896 pharmacist interventions in 567 patients were included. Over the 5 year study period no significant trends in acceptance rates (p=0.659, mean 67.3%) or clinical relevance (p=0.370, mean 57.0%) were observed. The mean number of interventions per patient increased from 1.41 to 1.93 (p=0.010). The most frequent interventions involved stopping (29.6%) and starting medication (23.2%). To conclude, we found no trend in acceptance rates and clinical relevance over five years, indicating a stable long-term value of nephrology pharmacists in multidisciplinary rounds. The number of interventions per patient increased over time, probably due to increased patient complexity and the expanding role of the nephrology pharmacist within the multidisciplinary team.

In Chapter 5 of this thesis, we describe medication-related health literacy (HL) in patients on haemodialysis with a high serum phosphate concentration and a high pill burden of phosphate-binding medication (PBM). The objectives of this study were to investigate medication-related health literacy among patients on haemodialysis using PBM and explore its association with medication adherence.

Functional, communicative, and critical medication-related HL were assessed using the Recognizing and Addressing Limited Pharmaceutical Literacy interview guide, and self-reported PBM adherence was evaluated using the MARS-5 (Medication Adherence Report Scale-5) questionnaire. Primary outcome was the proportion of patients who perceived difficulties in ≥1 HL domain, secondary outcome was the prevalence of perceived difficulties within the HL domains. Exploratory outcome was the association between medication-related HL and self-reported adherence to PBM. Data analysis was performed using descriptive statistics and univariable and multivariable logistic regression. Covariates for logistic regression were age, gender, number of medications, and PBM and total pill burden. Of the 75 haemodialysis patients, 81% perceived difficulties, mainly in the critical HL domain. Around 65% of the patients experienced difficulties assessing the applicability and reliability of information. 26.7% of the patients had a MARS-5 score ≤ 22 and were classified as non-adherent. No association was found between medication-related HL in general and medication adherence (OR 1.13, 95%CI 0.31-4.10). However, age was significantly associated with adherence (OR 1.05, 95%CI 1.02-1.09). In conclusion, over 80% of patients on haemodialysis using PBM experience difficulties in using and applying medication and treatment information. These results suggest that patients need more support to effectively use this information. Healthcare professionals should guide patients in the adequate use and application of treatment information to improve the effective use of PBM. Universal use of HL-sensitive communication strategies in patients on dialysis, including the teach-back method, could enhance patient understanding and engagement, potentially improving self-management and medication adherence.

The results of the PIDO-P (Pharmacist Intervention and Dose Optimisation of Phosphate-binding medication) intervention on serum phosphate concentration (SPC), self-reported adherence to PBM, and PBM pill burden are reported in Chapter 6. Suboptimal adherence to PBM is common in patients on haemodialysis with a high SPC. Important barriers to PBM adherence are forgetfulness, complex treatment regimens, and a high pill burden. We hypothesised that a reduction in PBM pill burden in combination with addressing barriers to adherence would reduce SPC by improving adherence. The PIDO-P study was a prospective, pre-post, single-centre intervention study in 75 haemodialysis patients with SPC >1.50 mmol/l and a PBM pill burden of ≥6 sevelamer tablet equivalents. The PIDO-P

intervention consisted of three pharmacist-patient consultations within three months on the haemodialysis ward in which barriers to adherence were addressed, and PBM pill burden was reduced. After three months, the patient returned to usual care. The primary outcome, average SPC, was 1.99±0.34 mmol/L in the three months before versus 2.03±0.37 mmol/L in the three months after start of the intervention (p=0.268). Regarding the secondary outcomes, phosphate remained stable for the first four months, whereafter it decreased gradually (from 2.04±0.45 mmol/L at BL to 1.86±0.57 mmol/L at 12 months, p=0.025). The percentage of patients with SPC within target range increased from 0.0% at baseline to 16.4, 24.2, and 27.8% at 3, 6, and 12 months, respectively (p<0.001 for all timepoints). PBM pill burden decreased the first three months (from 8.8±3.1 at BL to 5.8±2.7, p<0.001), whereafter it increased gradually to approach baseline levels at 12 months (8.4±3.8 at 12M, p=0.261 vs BL). Self-reported adherence increased in the first three months and remained higher during total follow-up (median 24, IQR 22-25 at BL vs median 25, IQR 23-25 after 12 months, p=0.048). To conclude, the PIDO-P intervention did not reduce SPC in the first three months after start of the intervention. However, the percentage of patients with SPC within target range increased, PBM pill burden was reduced by 34%, and self-reported adherence improved. To enhance the effectiveness of the intervention, patient selection and screening should be revised in future.

Chapter 7 describes the implementation fidelity of the PIDO-P intervention and its feasibility in clinical practice. Although the PIDO-P intervention improved PBM adherence, SPC remained high. To determine if the intervention was delivered as intended, this mixed-methods study aimed to evaluate its implementation fidelity. The implementation fidelity of the PIDO-P intervention was studied with Carroll's Framework for Implementation Fidelity. Six key components were identified. Qualitative data from evaluations and semi-structured interviews with both healthcare professionals and patients involved in the study were thematically analysed according to Braun with Atlas.ti, quantitative data were analysed using descriptive statistics in SPSS. The adherence to the intervention was high. Coverage was high, and five out of six key components were delivered to a high degree. Implementation fidelity was also high for frequency and duration. Moderating factors were investigated: the facilitation strategies were helpful, and pharmacists considered the intervention not complex. The quality of delivery and participant responsiveness were generally good. Patients thought

the intervention improved their knowledge and correct use of PBM. Regarding feasibility in clinical practice, pharmacists and prescribers recommended that the intervention should target patients with higher phosphate levels. In conclusion, the lack of effect of the PIDO-P intervention on the SPC could not be explained by low implementation fidelity. Healthcare professionals recommended targeting the intervention to patients with higher phosphate levels, as this may increase the effectiveness of the intervention.

Chapter 8, the general discussion, concludes the thesis. The discussion first refers back to the introduction and the aims of this thesis: to investigate how the interventions of a specialised nephrology pharmacist can contribute to rational, safe, and effective medication use in patients with CKD and, more specifically, in patients on haemodialysis. Subsequently, the main results of this thesis are described and discussed, focusing on two themes: 1) the role of the nephrology pharmacist in medication management and drug stewardship (improving medication utilisation); and 2) the role of the nephrology pharmacist-patient consultations in medication self-management, medication adherence, and medication-related health literacy. The first theme is divided into three subthemes: pharmacist prescribing, deprescribing, and on-ward pharmacist participation in nephrology multidisciplinary patient rounds. After the discussion of the main findings, the implications for daily practice are outlined, in which we advise providing specialised nephrology pharmacist care to all patients with an eGFR of < 30 ml/min/1.73 m^2 (CKD stage 4 and 5). The nephrology pharmacist should provide care as part of the 3P triad (prescriber, patient, and pharmacist), on three levels: the individual patient, organisational, and national. Furthermore, a CKD care pathway is outlined. Three important considerations for future research on pharmacist interventions in this patient population are the development and use of a core outcome set for pharmacist interventions in patients with CKD, the adaptation of health literacy aspects in interventions, and the inclusion of an implementation plan in all research. The discussion ends with the conclusion that a specialised nephrology pharmacist as part of the 3P triad can optimise medication impact and reduce medication-related problems in patients with CKD.