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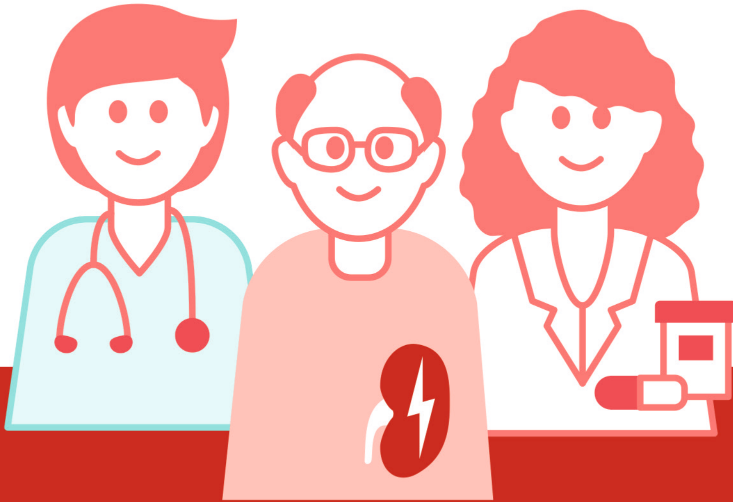
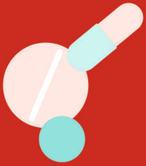

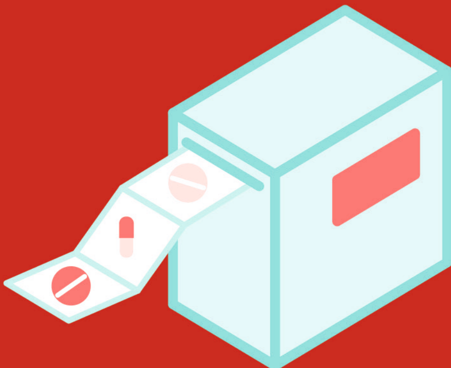

CHAPTER 8

General discussion

Introduction

The progression of chronic kidney disease results in several complications, such as hypertension, high potassium, phosphate, and parathyroid hormone concentrations, and renal anaemia. Treatment of CKD and its complications is complex [1] and requires lifestyle and dietary modifications, as well as pharmacological treatment, resulting in a high disease and treatment burden [2–5]. To help manage their disease, comorbidities, complications, and the detrimental effects of all of these on daily life, patients with progressing chronic kidney disease are treated by a multidisciplinary team, consisting of nephrologists, social workers, nephrology nurses, renal dietitians, and pharmacists, as recommended in the most recent KDIGO guideline [6]. Although medication is an important cornerstone of CKD treatment, the pharmacist's role in CKD is still evolving. In this thesis, we focus on the nephrology pharmacist's views on CKD and haemodialysis treatment. To explore and expand the nephrology pharmacist's role, we investigated several pharmacist interventions in patients with CKD and on haemodialysis in this thesis.

Patients with CKD and patients on haemodialysis generally use 10 to 15 types of medication, with a pill burden of around 15 to 20 a day [7,8]. As such, polypharmacy occurs in more than 80% of patients with CKD and almost 90% of haemodialysis patients. However, polypharmacy in patients with CKD can be inappropriate [7,8], and increases the risk of medication-related problems (MRPs), such as higher medication nonadherence and adverse drug reactions [7,9–12]. Polypharmacy is also associated with a higher risk of all-cause mortality, kidney failure, faster eGFR decline, and lower QoL[7]. Furthermore, patients with CKD and patients on haemodialysis are frequently hospitalised and yearly spend around 11 days in the hospital. Readmission rates are high: around 30% of the patients are readmitted within 30 days [1,13–15].

Medication management can help reduce polypharmacy and its associated medication-related problems. Medication management, also called comprehensive medication management, therapy management, or medication therapy management (MTM), is an umbrella term used to describe pharmaceutical care for patients with chronic diseases. Several definitions of medication management are used[16]. Central to medication management is the role of the pharmacist in optimising medication using a patient-centred approach to improve clinical patient outcomes. Medication management aims to improve the safety and

effectiveness of especially chronically prescribed medications and often includes medication reconciliation and medication review [9,14].

In addition to medication management, the term “drug stewardship” has recently been introduced and described in patients with chronic kidney disease [6,17]. In the KDIGO guideline, drug stewardship is described as maximising medication safety and effectiveness [6,17], while taking into account sustainability for patients, the healthcare system, and the environment. In patients with CKD, drug stewardship is of utmost importance due to the high frequency of polypharmacy and all its associated negative outcomes [1,3,7].

The nephrology pharmacist, as part of the multidisciplinary nephrology treatment team, can contribute to maximising medication safety and effectiveness by organising structured medication reconciliation, periodically as well as after care transitions, performing medication reviews, and providing advice on medication selection during prescribing (see also Figure 1 [6]). Healthcare professionals (HCPs), mostly prescribers and pharmacists, are in the lead for drug stewardship, but the patient is an important, indispensable partner.

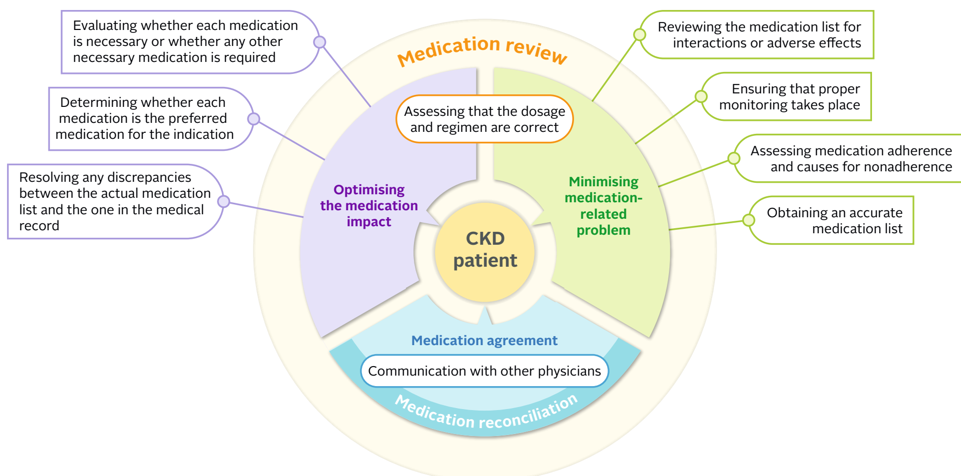

Figure 1. Suggested steps in medication review and medication reconciliation.

Figure extracted from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [6] (http://creativecommons.org/licenses/by-nc-nd/4.0/)

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The pharmacist, as a partner of prescribers and patients in CKD treatment, should provide care as part of the 3P (prescriber, patient, pharmacist) triad. An effective collaboration between the partners within the 3P triad is essential for optimal drug stewardship and medication management. Both prescribers and pharmacists have their specific roles and focus within this triad. Although prescribers have also been trained in pharmacotherapy, their focus is often more on diagnostic considerations and adding new medication for a new problem, than on reviewing and deprescribing medications. The pharmacist, on the other hand, has an overview of all medications, focuses on reviewing them all, checks interactions, and determines whether for some medication an indication no longer exists, or the dose needs to be modified.

In the studies described in this thesis, we investigated how the interventions of a specialised nephrology pharmacist contribute to rational, safe, and effective medication use in patients with CKD and, more specifically, in patients on haemodialysis. Health literacy and implementation fidelity were also investigated as they are important moderators of the effectiveness of (pharmacist) interventions in clinical practice. We have shown that the nephrology pharmacist can positively contribute to medication management and drug stewardship, including medication self-management and adherence. We have also demonstrated that the nephrology pharmacist can improve medication utilisation and patient outcomes in this patient group. In this discussion, we will synthesise the research presented in this thesis, distil themes, and provide a view on the role of the nephrology pharmacist in CKD patient care in the future.

Main findings

In chapters 2 and 3, we present the results of a systematic review and an RCT on pharmacist-managed treatment of renal anaemia with erythropoietin-stimulating agents (ESA). In the systematic review, the high heterogeneity, the wide array of pharmacist interventions, and a high risk of bias precluded a quantitative synthesis of the data on pharmacist-managed renal anaemia in a meta-analysis. However, low-quality evidence suggests that pharmacist-managed renal anaemia may reduce ESA dose and improve haemoglobin outcomes. In the RCT described in chapter 3, we showed that pharmacist-managed renal anaemia improved haemoglobin and

iron outcomes and reduced ESA dose. Notwithstanding these positive results, some questions remain regarding the effectiveness of pharmacist-managed renal anaemia, as this was a single-centre study, and differences in baseline characteristics were observed between patients in the intervention and control groups. For future research, the definition of an outcome set for pharmacist interventions could help to provide focus and facilitate evidence synthesis.

Chapter 4 of this thesis describes the long-term acceptance rate, number of interventions, and clinical relevance of pharmacist interventions in the nephrology ward. During five years, the acceptance rate and percentage of clinically relevant interventions remained stable with a mean value of 67.3% and 57.0%, respectively. The number of interventions per patient increased over time, from 1.41 to 1.93 (p=0.010, test for trend). In this study, we did not find evidence of a long-term learning effect in the multidisciplinary nephrology team.

In chapters 5 and 6 of this thesis, the results of the PIDO-P (Pharmacist Intervention with Dose Optimisation of Phosphate-binding medication) intervention study, in which we assessed medication-related health literacy (HL) and self-reported medication adherence, are presented. In this study, the phosphate-binding medication (PBM) pill burden was reduced, and individual patient barriers to adherence were addressed with the aim of decreasing serum phosphate concentrations by improving adherence. Contrary to our hypothesis, the PIDO-P intervention did not reduce mean serum phosphate concentration. However, we found that this intervention improved adherence to PBM during 12 months. This higher adherence can probably be attributed to the combination of a reduction in pill burden and addressing individual patient barriers to adherence. Focusing the intervention on patients with a serum phosphate concentration above 2.0 mmol/L might improve its effectiveness in clinical practice, as a post-hoc analysis suggested. In the PIDO-P study, we also discovered that more than 80% of the patients perceived difficulties with medication-related HL when using phosphate-binding medication, mostly within the critical domain. Around 65% of the patients perceived difficulties with assessing the applicability and reliability of information. No association could be established between medication-related HL and self-reported medication adherence.

Chapter 7 described the implementation fidelity of the PIDO-P intervention using Carroll's Conceptual Framework for Implementation Fidelity. The adherence to the intervention was generally high, with only minor aspects of the intervention not performed as intended. Therefore, the absence of an effect on phosphate concentration was not caused by an inadequate execution of the PIDO-P intervention. Facilitators for the intervention were the elaborate, detailed intervention materials, adequate communication and collaboration with other healthcare professionals, and the individualised training of participating pharmacists. Barriers were the inefficient screening process and restricted human and financial resources. To improve the effectiveness of the intervention and aid possible implementation in the future, the intervention should be targeted at patients with a higher serum phosphate concentration, patient selection should be improved, and reimbursement for pharmacists performing the intervention should be sought.

Discussion of main findings

Two main themes regarding pharmacist interventions and the role of nephrology pharmacists in CKD patient care can be identified based on the studies described in this thesis:

- The role of the nephrology pharmacist in medication management and drug stewardship: improving medication utilisation
    - Pharmacist prescribing
    - Deprescribing
    - On-ward pharmacist participation in nephrology multidisciplinary patient rounds
- The role of nephrology pharmacist-patient consultations in medication self-management, medication adherence and medication-related health literacy.

The role of the nephrology pharmacist in medication management and drug stewardship: improving medication utilisation

Several pharmacist interventions as described in this thesis can improve medication utilisation and contribute to a better use of prescribed medications in patients with CKD. In the case of pharmacist-managed renal anaemia, suboptimal prescribing

was reduced by focusing on high as well as on low haemoglobin concentrations and providing optimal iron dosing strategies. In patients using PBM, suboptimal adherence is a barrier to effective medical utilisation. By reducing individual patient barriers to adherence, including the high pill burden, adherence was enhanced, and medication utilisation was improved. To optimise effective PBM use, adequate collaboration and communication with all involved HCPs is warranted, including dietitians, as they have a prominent role in the management of hyperphosphataemia. Furthermore, on-ward pharmacist interventions can improve medication utilisation by reducing medication-related problems (MRPS), such as medication without indication, insufficient (laboratory) monitoring, etcetera.

More than 20 years ago, Nesbit and colleagues already stated that a clinical staff pharmacist could yearly provide direct cost savings of around $90,000, and an estimated cost avoidance of around $490,000, leading to an estimated economic benefit of around $390,000 [18]. In 2021, Daifi and colleagues showed that the implementation of a clinical pharmacist in a haemodialysis facility identified 1403 medication-related problems in 157 patients, with an average of almost 9 MRPs per patient. Suboptimal adherence was found to be the most frequently occurring MRP in 31% of the patients. In this study, the deployment of the clinical pharmacist led to an estimated cost avoidance of almost $450,000 in 6 months, based on the avoidance of physician visits, emergency department visits and hospital admissions [19].

Furthermore, English et al showed in 2020 that pharmacist interventions during ward rounds were more timely, more clinically relevant, and took less time than interventions not performed during ward rounds. These on-ward interventions might also lead to significant potential cost savings, as for every dollar spent on a pharmacist in ward rounds, 33.74 Australian dollars were saved [20].

Pharmacist prescribing

Pharmacist prescribing plays an important role in the two interventional studies in this thesis. In the RCT on pharmacist-managed renal anaemia, the pharmacist provided dose recommendations for ESA and iron to the nephrologist, based on predefined treatment algorithms for both medications. These recommendations could consist of maintaining the dose, changing the dose, or withholding ESA or iron. The nephrologist had to approve these recommendations before the

proposed dose was implemented. In almost all cases, the nephrologist approved the recommendations, but this procedure was considered cumbersome by the participating pharmacists and sometimes led to a delay in medication changes. In the PIDO-P study, during three months, the pharmacist was leading in the treatment of a high serum phosphate concentration with phosphate-binding medication (PBM). During this period, the pharmacist reduced the PBM dose, changed the medication regimen, stopped medication, and switched to other dosage forms, such as tablets to powder, or even to an entirely different PBM. The dose reduction was performed according to a predefined treatment algorithm, which was established after consulting the nephrologists. All changes in PBM were made taking patient preferences into account, using shared decision-making. In the PIDO-P study, the pharmacist directly changed the medication in the electronic medical record, thereby improving efficiency and preventing delays.

Based on these two interventional studies, including the study on implementation fidelity, we can conclude that within the Franciscus Gasthuis and Vlietland Hospital, nephrologists and nurse practitioners support pharmacist prescribing based on predefined treatment protocols and clear agreements. This illustrates the trust of nephrologists and other prescribers in the individual nephrology pharmacists and their added value in the treatment of haemodialysis patients. The foundation lies in the intensive collaboration that the nephrologists and pharmacists have shared for more than 30 years in our hospital. However, adequate communication and collaboration remain essential in the preparation as well as in the implementation phase of interventions. Of course, shared patient information and shared medical records are of utmost importance. Furthermore, supportive legislation should be pursued, and may need to be implemented before pharmacist prescribing in long-term therapy for chronic diseases such as CKD can take flight.

Two recent studies performed in the Netherlands and the United Kingdom support the findings from this thesis and might guide us further on the way towards nephrology pharmacist prescribing in the Netherlands [21,22]. In those two studies, several conditions for optimal pharmacist prescribing were mentioned:

- Diagnosis of the condition by a doctor (for the Dutch situation [21])
- Clear definitions of tasks and responsibilities
- Support of relevant stakeholders (especially doctors and patients)

- Collaboration, network, and trust, within the organisation, as well as regional and preferably also national
- Pharmacist workforce capacity
- Pharmacist competencies and skills
    - Consultation skills, such as motivational interviewing techniques, teach-back
    - Social skills
    - Clinical reasoning
    - Clinical decision-making
    - Professional attitude, for example, taking responsibility, dealing with uncertainties, and being aware of one's limitations
    - Interprofessional communication
    - Self-efficacy
- Access to patient information (electronic medical records)
- Supportive legislation and regulations
- Reimbursement of pharmacist activities
- Implementation planning
- Auditing and peer review of prescribing.

Major barriers to pharmacist prescribing were considered to be a lack of reimbursement, time, personnel, appropriate legislation, and regulations.

Based on the abovementioned list, we would like to focus on pharmacist competencies and skills required for optimal prescribing. In the United Kingdom, a Competency Framework for Prescribers has been established [23,24], describing ten competencies within two domains: consultation and prescribing governance. The ten competencies listed are, among others, identifying evidence-based treatment options available for clinical decision-making, presenting options and reaching a shared decision, prescribing professionally, and prescribing as part of a team. Below, we will focus on the competencies of clinical reasoning, clinical decision-making, and shared decision-making.

A recent scoping review conceptualised pharmacist clinical reasoning as a "context-dependent cognitive process in which pharmacists apply and integrate knowledge and clinical experience to interpret available clinical data" [25]. Two different approaches to clinical reasoning can be used: a more analytical or a more

intuitive approach. Analytical reasoning is a slow, conscious process, requiring more effort, whereas intuitive reasoning is rapid and unconscious. Analytical reasoning allows the pharmacist to confirm or reject hypotheses. The two types of reasoning are ideally combined to maximise efficacy and minimise bias [26].

Depending on the expertise of the HCP or the complexity of the clinical case, the relative contributions of the two types will vary [26]. When healthcare professionals gain experience, their approach often shifts from analytical to more intuitive reasoning [25]. The pharmacist's clinical reasoning may be classified as diagnostic or therapeutic, depending on the goal of reasoning. To identify a disease or adverse drug reaction, diagnostic reasoning is used, whereas, for example, during a medication review, mostly therapeutic reasoning is used [25,26].

Clinical reasoning includes clinical decision-making. For optimal clinical reasoning and decision-making, it is important to gather all available clinical information [25]. Besides medical data, such as medical history, laboratory parameters, and medication information, this clinical information should also contain relevant patient information. This could include the patient's health literacy status, views and beliefs about their disease and treatment, sources of patient support, and the role of informal caregivers in patient treatment [27].

An important element of decision-making is shared decision-making (SDM). SDM can be described as "collaborative treatment planning, incorporating the patient's own health goals and context" [28,29]. Approximately 35% of the patients in the PIDO-P study mentioned they did not participate in SDM or found it difficult to do. Therefore, the degree to which patients can participate in SDM differs. However, in all patients, SDM should be pursued, as SDM strengthens the patient-HCP relationship, which in turn stimulates treatment adherence. An example of shared decision-making, feasible for almost all patients, is taking into account patient preferences while prescribing. For example, in the PIDO-P study, most patients expressed a strong preference for one specific form of phosphate-binding medication (PBM), such as chewable or film-coated tablets.

Deprescribing

Polypharmacy occurs in 82% of patients with CKD [7] and is associated with a higher mortality risk and poorer health-related quality of life in patients on haemodialysis [30].

Earlier research has estimated that 50 to 90% of the patients on haemodialysis are treated with at least one potentially inappropriate medication [31,32].

Deprescribing can be seen as the process of deliberately withdrawing or lowering the dose of (inappropriate) medications to reduce pill burden and improve health and quality of life [33,34]. Deprescribing is an important intervention in medication management and drug stewardship in patients with CKD. In this thesis, we reported that almost 30% of the pharmacist interventions in the nephrology ward were stopping medication (Chapter 4). This percentage is comparable to earlier data, reporting percentages of 28.3 to 38.6% [35,36].

For patients, deprescribing is also a relevant topic. One of the major reasons patients were willing to participate in the PIDO-P study was the reduction in the pill burden of phosphate-binding medication. In the PIDO-P study, we were able to reduce PBM pill burden by an average of 34% while maintaining stable serum phosphate concentrations. Furthermore, during the consultations, patients frequently expressed their frustration about the ever-growing number of medications, stating, ”Doctors only prescribe more medications, and they never stop any of them”. This statement underscores the patients' wish to lower their substantial medication and pill burden.

Deprescribing is increasingly studied in patients with chronic kidney disease [31,34,37–43], and can reduce the use of medications that may carry greater risks than benefits [34]. Deprescribing is feasible in this patient group and may have several patient benefits, such as better adherence to the remaining medication and a higher quality of life [34]. However, several barriers exist in deprescribing in patients with CKD. In a qualitative study, four barrier themes were identified: 1) system-level barriers, 2) undefined co-management among clinicians, 3) limited knowledge about potentially inappropriate medications among clinicians and patients, and 4) patients prioritising symptom control over potential harm [31].

Indeed, a substantial part of the patients are worried about stopping medications [44]. Therefore, taking into account the individual patient context is essential [45]. Patient participation and shared decision-making (SDM) both improve deprescribing success rates. For example, the willingness to reduce medication load is an important success factor, as well as trust in the HCP [31,40,44]. Therefore, when

implementing pharmacist deprescribing, a patient-centred deprescribing process should be instigated, providing patient education, support, monitoring, and follow-up, such as has been initiated in Canada by Battistella and colleagues [38,40,42].

On-ward pharmacist participation in nephrology multidisciplinary patient rounds

Several guidelines advocate the importance of integrating pharmacists into the multidisciplinary team, as is also the case for patients with CKD [6]. Part of this integration is on-ward pharmacist participation in nephrology multidisciplinary patient rounds. In this thesis, we have demonstrated the long-term value of the participation of the nephrology pharmacist in multidisciplinary nephrology ward rounds.

Pharmacist participation in on-ward multidisciplinary rounds can enhance patient care [20,46–48]. Furthermore, it improves medication safety by reducing MRPs [49–53], and stimulates interprofessional collaboration [54]. To enhance patient care, effective on-ward collaboration between physicians and pharmacists is warranted, and an adequate integration of pharmacists into the multidisciplinary team is needed.

In their systematic review, Hatton and colleagues described barriers and facilitators for the integration of pharmacists into a ward-based multidisciplinary team. Three key themes emerged: professional knowledge and skills, interpersonal skills and relationships, and working patterns [54]. Regarding professional knowledge and skills, the pharmacist's expertise in medications was highly valued and facilitated interprofessional working within the team. When pharmacists demonstrated their competency and confidence, this enhanced teamwork. Facilitators within the theme of interprofessional skills and relationships were positive interactions with team members and strong interdisciplinary relationships. A hierarchical structure and poor interpersonal skills were barriers to the integration of pharmacists into a ward-based multidisciplinary team. Being physically present on-ward, and continuity of team membership were facilitators within the working patterns and environment theme. Profession-specific goals, in contrast to goals for the team, and an excessive workload for pharmacists, were barriers to successful integration [54].

Interestingly, it has been shown that the time spent on pharmacist interventions is significantly lower for on-ward round interventions versus off-ward round

interventions: 73.6% of the on-ward round interventions took less than 1 minute, versus 33.8% of the off-ward round interventions [20]. This, combined with the finding that on-ward interventions are earlier, have a higher clinical relevance [20] and are more readily accepted [55], implies that the pharmacist's participation in ward rounds has a high value for money. All in all, this evidence suggests that it might be best to focus pharmacist resources on in-ward multidisciplinary patient round participation and reduce the amount of time spent on off-ward interventions.

The role of nephrology pharmacist-patient consultations in medication self-management, medication adherence, and medication-related health literacy

Patients with CKD perceive self-management as difficult, and the perceived level of difficulty increases as their disease progresses. An essential part of self-management in patients with CKD is medication self-management, because of the large number of medications they use and their complex medication regimen [7]. Adequate medication self-management is a prerequisite for medication adherence.

However, limited medication adherence occurs in around 50% of patients with chronic diseases, including chronic kidney disease [56–60]. In patients with CKD, suboptimal adherence is associated with negative treatment outcomes, including disease progression, a higher incidence of adverse events, lower quality of life, and increased healthcare costs [57,61–65].

Notwithstanding all the negative outcomes of limited medication adherence, in clinical practice, HCPs do not seem to regard medication adherence as a high priority. A recent survey on medication adherence management in 2875 European healthcare professionals (pharmacists, physicians, and nurses) from 37 countries showed that "asking the patient" was the most used method for assessing medication adherence (performed by 86.4% of the respondents) [66]. Checking dispensing history and checking prescriptions were performed by around 57% of the respondents, whereas validated questionnaires were used by only 5.9% of the respondents. A substantial part of the HCPs (36.5%) did not consider it their professional task to improve adherence [66].

The results of this survey are concerning. The high prevalence of suboptimal medication adherence and the lack of prioritisation of the assessment of medication adherence by HCPs suggest that, in current clinical practice, there

is a high degree of unnecessary dose and treatment escalations [67]. To improve medication effectiveness and reduce treatment costs, assessing medication adherence and providing patient guidance on adherence should be a more prominent part of medication management and clinical decision-making, for all HCPs involved, including doctors, pharmacists, and nurses, prescribing as well as non-prescribing. Furthermore, more robust methods for “diagnosing” suboptimal medication adherence than simply asking the patient should be used.

To improve adherence, individualised approaches are needed, incorporating patient context and providing support to patients and their informal caregivers [68–70]. One important aspect of patient context is health literacy (HL), including medication-related HL. In this thesis, we have shown that more than 80% of the haemodialysis patients using phosphate-binding medication experience difficulties with medication-related HL skills, most often with critical skills. These data are supported by other recent studies reporting adequate HL skills in only around 20% of haemodialysis patients [71–73]. Limited HL skills hamper effective medication self-management.

Several interventions to improve HL have been studied in CKD [74,75]. Educational interventions, self-management interventions, and combinations of both probably improve knowledge, self-care behaviour, and self-efficacy in patients with CKD. These interventions may reduce the progression of CKD and hospitalisations in patients with limited HL, but given the high variability in the interventions and methodological limitations, no definite conclusions could be drawn in a recent Cochrane Review [75]. Another systematic review reported weak evidence that HL interventions in patients with CKD could improve knowledge, decision-making, and self-care behaviours [74]. The most promising interventions in improving HL are tailored to the needs of patients and address functional, communicative, and critical HL. The use of visual aids, such as videos, may be helpful to increase HL and the comprehension of health information [76–79].

To optimise self-management in patients with CKD and limited HL, three strategies should be used: 1) providing information to optimise the patient’s understanding, 2) applying person-centred strategies to maintain changes, and 3) improving the competencies of HCPs [80].

Although in this thesis we could not find evidence of an association between medication-related HL skills and self-reported medication adherence to phosphate-binding medication, assessing and addressing limited HL skills is necessary to optimally support patients with CKD in adhering to their medication. In clinical practice in CKD care, HCPs should take into account the needs of patients with limited HL and adjust their communication and information strategies. Using the teach-back method can assist with communicating important health information and can improve patients' knowledge, confidence, and self-management skills in patients with CKD [81] . Besides HCPs, organisations also have to change to meet the needs of patients with limited HL skills [82–85].

Many patients with CKD struggle with the demands of navigating nephrology healthcare [1,86]. Healthcare organisations and systems are generally complex and do not suit the needs of patients with limited health literacy [82–84,87]. Organisational health literacy (OHL) describes a healthcare organisation that facilitates patients in engaging in the healthcare process, navigating the healthcare system, understanding health information, and managing their health [83,87]. In 2012, Brach described in a discussion paper the 10 attributes of health-literate healthcare organisations, including, for example, leadership on HL, integrating HL into planning and evaluating and improving quality and patient safety, and addressing HL in high-risk situations, such as care transitions and communication about medication [87]. Until now, in healthcare organisations and systems, too little attention has been paid to OHL to optimally support patients with limited HL. Recently, Smith and colleagues advocated for a shift towards more focus on OHL in patients with chronic kidney disease and prioritising OHL for patients with CKD to improve nephrology healthcare [82].

Pharmacist interventions might improve medication adherence in patients with CKD, although mixed data are reported [70,88–91]. Optimising and simplifying medication regimens and empowering patients with knowledge regarding their condition and medications might contribute to higher medication adherence. Effective interventions include medication reviews, patient counselling and patient education [70]. The use of digital health interventions has been proven effective in improving medication adherence in patients on haemodialysis [92], but may not be suited for patients with limited HL skills, as they often also lack digital skills [93–95]. In this thesis, we have shown that a multi-component intervention (the PIDO-P,

Pharmacist Intervention and Dose Optimisation of Phosphate-binding medication) addressing barriers to adherence and reducing pill burden was effective in improving adherence to phosphate-binding medication (PBM). Part of this intervention was optimising the complex medication regimen of PBM to fit the patient's daily schedule. In all patients, information about a high serum phosphate concentration and PBM was provided. As visual support for patients, we developed information leaflets for each specific phosphate-binding medication, adapted to the needs of patients with limited HL. These leaflets contain little text and several infographics.

The PIDO-P intervention reduced pill burden, improved self-reported adherence to PBM, but did not improve serum phosphate concentrations. If the PIDO-P intervention were targeted at patients with serum phosphate concentrations above 2.0 mmol/L, its effectiveness would improve, as we showed in a post-hoc analysis in Chapter 6. When the screening and selection of patients could also be arranged more effectively, a potentially potent intervention would be available for these patients.

To conclude, pharmacist-patient consultations add value to the treatment of patients with CKD by providing individualised, person-centred advice taking into account patient barriers to adherence, including limited HL. One aspect of this added value is that patients often feel more comfortable discussing problems with and barriers to medication adherence with pharmacists than with physicians [96–98]. Patients might feel less dependent on pharmacists for their haemodialysis treatment than on nephrologists and dialysis nurses. This may lower the barrier to admitting suboptimal medication adherence. We believe discussing medication adherence and barriers to adherence is one of the designated tasks of the nephrology pharmacist. Due to the pharmacist's unique capacities, skills, and knowledge, value is added to the multidisciplinary treatment team.

Implications for daily practice and future research

Implications for daily practice

In this thesis, we have shown that the nephrology pharmacist improves medication utilisation in patients with CKD and on haemodialysis. This role is described and acknowledged in the recent KDIGO (Kidney Disease Initiative on Global Outcomes)

Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [6].

Therefore, in the coming years, we believe it is important to provide specialised nephrology pharmacist care to patients with an eGFR < 30 ml/min/1.73m^2 and incorporate this care in the standard multidisciplinary treatment of patients with CKD. This care should be based on three cornerstones, in accordance with the KDIGO Guideline [6]:

1. Adequate medication reconciliation when patients are hospitalised and discharged, preferably before or otherwise as soon as possible after discharge, by direct consultation with the treating nephrologist, to minimise discrepancies and hospital-induced MRPs
2. Medication review by a nephrology pharmacist in consultation with the patient and the nephrologist, preferably also transferring relevant findings to the general practitioner and community pharmacy
3. Pharmacist-patient consultations, for example, as part of medication reviews, or as part of a specific pharmacist intervention, for example, in the PIDO-P intervention or pharmacist-managed renal anaemia. Pharmacist prescribing should be further explored as part of pharmacist-patient consultations.

Additional training is necessary to prepare the nephrology pharmacist for this role within CKD patient care. In the United Kingdom, a competency framework for nephrology pharmacists has been developed, with three stages of professional development: advanced stage I, advanced stage II, and mastery [24]. In the Netherlands, a generic nephrology differentiation for hospital pharmacists in training is in the last stage of development. This generic differentiation, incorporating Entrustable Professional Activities (EPAs) for nephrology pharmacists, with input from the renal pharmacist competency framework from the UK, may serve as a framework for the training of nephrology pharmacists in the Netherlands.

The nephrology pharmacist should provide care as part of the 3P triad, as described in the introduction of this chapter. The 3P triad of the nephrology pharmacist, patients, and prescribers should be implemented on an individual,

institutional, and national level to fully utilise its potential. Within this 3P triad, based on the levels of collaboration and trust, informal and professional pharmacist prescribing should be explored and, wherever possible, instigated.

Several factors contribute to a fruitful collaboration in the 3P triad. Effective interprofessional collaboration, adequate knowledge and competencies of the nephrology pharmacist, in CKD care, organisational support, and adequate human and financial resources are all required to reap the maximal benefits of this triad. It goes without saying that the role of prescribers within the 3P triad is essential. Without effective interprofessional collaboration with and support from prescribers, the pharmacist cannot be optimally effective in this triad.

Besides the prescriber, the patient also plays an indispensable role as part of the 3P triad. The patient experiences individual-specific barriers to medication adherence and side effects, and has certain beliefs about medication. Therefore, the patient's input is essential to make the appropriate treatment choices. Shared decision-making is one of the core values of the 3P triad and stimulates equality between the three partners of the triad.

Sometimes the 3P triad needs to be expanded to a 4P "triad" (patient, partner, prescriber, pharmacist), as in some cases, the patient is not able to participate in this triad on his own [99]. Especially in chronic diseases, informal caregivers perform a wide variety of medication-related activities and provide support [27]. During haemodialysis treatment, patients are often overburdened and feel overwhelmed [100], as haemodialysis is a very intensive treatment, and the burden of disease is very high [3,4,101]. Therefore, support from informal caregivers may play an essential role in medication self-management. Information on patient support, as well as on other relevant non-medical patient characteristics, such as level of health literacy, should be incorporated into clinical reasoning and decision-making to provide better patient guidance and optimise treatment choices.

The nephrology pharmacist may also improve pharmacological treatment in patients with earlier stages of CKD or after renal transplantation. In earlier stages of CKD, pharmacists may play an important role in optimising medication use, potentially slowing CKD progression. A recent meta-analysis showed that pharmacist interventions improved blood pressure regulation and reduced

medication errors in patients with CKD; however, no clear effects were seen on eGFR and medication adherence, due to substantial heterogeneity in study design, including interventions [88]. To further investigate the potential beneficial effects of pharmacists in earlier stages of CKD, we are preparing a pilot study in the Franciscus Gasthuis and Vlietland Hospital in patients with earlier stages of CKD. With this study, we will investigate whether pharmacist consultations and structured pharmacist participation in the multidisciplinary nephrology team can improve medication adherence and medication-related HL. We will also determine relevant clinical and patient outcomes, such as kidney function, albumin-creatinine ratio, hospitalisations, pill burden and medication-related problems.

In analogy with the contribution of a clinical pharmacist in liver transplant recipients [102,103], the nephrology pharmacist may also improve outcomes in kidney transplant recipients. High intra-patient variability of tacrolimus trough concentrations is associated with adverse transplant outcomes [104–106] and intra-patient variability seems to be higher in non-adherent patients [107,108]. As we have shown in this thesis, the nephrology pharmacist can improve adherence by reducing barriers to adherence. Probably, this will also be the case in patients after kidney transplantation. All in all, the nephrology pharmacist as part of the multidisciplinary team may improve medication therapy management by reducing medication-related problems and improving adherence in patients with earlier stages of CKD as well as after kidney transplantation.

The role of the nephrology pharmacist within the CKD patient care pathway

Below, the proposed roles of the nephrology pharmacist within the CKD patient care pathway are described. In this CKD patient care pathway, the nephrology pharmacist performs these activities within the 3P triad.

The role of the nephrology pharmacist in the CKD patient care pathway on an individual patient level

The nephrology pharmacist contributes to adequate individual medication management by providing patient support and guidance. The nephrology pharmacist helps patients to incorporate the use of medication in daily life, while overcoming individual barriers to medication adherence such as forgetfulness, side effects, negative beliefs, and limited health literacy. The nephrology

pharmacist uses shared decision-making and includes patient preferences while effectively cooperating and communicating with other healthcare professionals.

The role of the nephrology pharmacist in the CKD patient care pathway on an institutional level

The nephrology pharmacist contributes to adequate institutional medication management for CKD patients by optimising medication effectiveness and safety, thereby reducing MRPs. The nephrology pharmacist does this by stimulating effective medication reconciliation (periodically and after care transitions). He participates in multidisciplinary on-ward patient rounds, performing interventions and providing advice. The nephrology pharmacist contributes to improving clinical decision support systems to meet the needs of patients with acute kidney injury and chronic kidney disease, for example, to detect acute or acute-on-chronic kidney injury in an early stage or even prevent it. He also performs medication reviews with patients and prescribers and implements deprescribing protocols. Furthermore, the nephrology pharmacist implements pharmacist prescribing in patients with chronic kidney disease and contributes to improving organisational health literacy.

A powerful way to improve institutional medication management and drug stewardship in patients with CKD may be the formation of an N-team (nephrology team). This N-team can be formed in analogy with the A-team (antibiotic team) and anticoagulation team, and consists of nephrologists, nurse practitioners, and nephrology pharmacists, but may also include other healthcare professionals.

The role of the nephrology pharmacist in the CKD patient care pathway on a national level

Organised on a national level, the nephrology pharmacist provides recommendations regarding incorporating nephrology pharmacists in N-teams and participates in guideline committees. Furthermore, the nephrology pharmacist establishes and further expands regional and national collaborations in clinical practice as well as in research, seeking collaboration with prescribers and patient representatives. Regarding research, the nephrology pharmacist participates in the NEFRO-NL research network, together with nephrologists. The nephrology pharmacist contributes to the development and revision of a generic nephrology differentiation program for hospital pharmacists in training, incorporating relevant EPAs. The generic differentiation program should be based on relevant input, such as the

competency frameworks in the training of renal pharmacists and pharmacist prescribing, for example, as established in the UK.

Implications for future research

To optimise the impact of future research on pharmacist interventions in chronic kidney disease, three important aspects should be taken into account.

- A core outcome set for pharmacist interventions should be developed and used
- All interventions should be adapted to patients with limited health literacy
- An implementation plan should be included in the design of all studies.

The development and use of a core outcome set for pharmacist interventions could help to provide focus and target pharmacist interventions investigating specific, predefined outcomes, enabling interpretation and comparison of study results. The COSP-KD (Core Outcome Set for Pharmacist-led Interventions in CKD) study aimed to define a core outcome set for evaluating the effectiveness of pharmacist-led interventions in CKD [109]. The four outcome domains of interest are adverse events, clinical outcomes, delivery of care, and perceived health status. This study finished in December 2024, but its results have not yet been published [109,110]. Hopefully, this study will lead to the development of a core outcome set for pharmacist interventions in patients with CKD that can be used in future research.

As a substantial part of patients with CKD have limited health literacy, and this percentage increases with CKD progression, it is important to adapt future pharmacist interventions in patients with CKD to fit the needs of patients with limited health literacy. As limited health literacy impairs optimal medication self-management and adherence, all future research involving medications, including studies targeting adherence, should be suited to patients with different levels of health literacy. Patient involvement and participation in the whole study cycle, including its design, may facilitate alignment of study goals and procedures to the needs of patients with different levels of health literacy.

Implementation should be part of the development of the intervention and should be planned well in advance. Implementation plans and toolboxes should be used to optimise the benefit of pharmacist interventions in clinical practice and reduce

the gap between research and clinical practice. Development and use of a toolkit to facilitate implementation of an intervention can improve implementation by the use of several implementation strategies [111]. These strategies include the identification of "champions", individuals who dedicate themselves to supporting, marketing, and driving through an implementation, overcoming indifference or resistance that the intervention may provoke in an organisation. Furthermore, implementation can be improved by the assessment of adoption readiness, identification of barriers, and promotion of the adaptability of the intervention [112]. Implementation science/support practitioners (ISPs) may help to optimise implementation efficacy. Recently, in the Netherlands, 40 ISPs have finished their training and education program and are ready to act as ambassadors and build bridges to spread and implement (cost-)effective interventions in clinical practice.

Conclusion

This thesis aimed to investigate how 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. In this thesis, we showed that the nephrology pharmacist, as part of the 3P triad, can play an important role in optimising medication impact and minimising medication-related problems in patients with CKD, as advocated in the KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [6].

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