Quality of prescribing in chronic kidney disease and type 2 diabetes
Smits, Kirsten Petronella Juliana

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Prescribing quality in secondary care patients with different stages of chronic kidney disease: a retrospective study in the Netherlands

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G.J. Navis
P. Denig

Submitted
ABSTRACT

Background: Insight in the prescribing quality for patients with chronic kidney disease (CKD) in secondary care is limited. The aim of this study is to assess the prescribing quality in secondary care patients with CKD stage 3-5, and assess possible differences in quality between CKD stages.

Methods: Between March 2015 and August 2016, data were collected from patients with stage 3-5 CKD seen at two university (n=569 and n=845) and one non-university nephrology outpatient clinic (n=1,718) in the Netherlands. Physical examinations, laboratory measurements and prescription data were extracted from medical records. Potentially appropriate prescribing of antihypertensives, renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, phosphate binders, and potentially inappropriate prescribing according to prevailing guidelines was assessed using prescribing quality indicators. Chi-square or Fisher’s Exact tests were used to test for differences in prescribing quality.

Results: RAAS inhibitors alone or with diuretics (57% respectively 52%) and statins (42%) were prescribed less often than phosphate binders (72%) or antihypertensives (94%) when indicated. Active vitamin D was relatively often prescribed when potentially not indicated (19%). Patients with high CKD stages were less likely to receive RAAS inhibitors but more likely to receive statins when indicated than stage 3 CKD patients. They also received more active vitamin D and erythropoietin stimulating agents when potentially not indicated.

Conclusions: Priority areas for improvement of prescribing in CKD outpatients include potential underprescribing of RAAS inhibitors and statins, and overprescribing of active vitamin D. CKD stage should be taken into account when assessing prescribing quality.
INTRODUCTION

Assessing quality of care in chronic kidney disease patients (CKD) is important for identifying areas for improvement. Several recent studies have shown that detection of CKD, monitoring of disease progression and metabolic parameters, and achievement of risk factor target levels are suboptimal in CKD care. Three of these studies showed that prescribing of selected medication treatment may also be suboptimal, for example, showing potential underprescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors and statins, and overprescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in primary care patients with CKD. In addition, one study showed an increasing trend in prescribing of RAAS inhibitors and statins in secondary CKD patients. Not much is known about differences in prescribing quality in CKD patients between healthcare organizations. Recently, our research group has developed and validated a set of prescribing quality indicators (PQIs) for assessing the prescribing quality in patients with CKD according to clinical guideline recommendations, which has been validated in a primary care population. The set is intended also for secondary care, and includes several indicators which are specifically relevant for patients with higher CKD stages. Previously it was found that with increasing CKD stages prescribing of RAAS inhibitors and NSAIDs decreased, while prescribing of phosphate binders, vitamin D and erythropoiesis-stimulating-agents (ESA) increased. However, this was based on the number of prescriptions regardless of whether the medication was indicated for the included patients. The aim of this study is to assess prescribing quality in secondary care patients with CKD stage 3a-5 and differences in prescribing quality between patients with these CKD stages. In addition, we explored differences in prescribing quality between different outpatient clinics in the Netherlands.

METHODS

This was a retrospective cross-sectional study assessing the prescribing quality between March 2015 and August 2016 in the Netherlands in two university nephrology outpatient clinics A and B, and one non-university nephrology outpatient clinic C. Included were patients with CKD stage 3a-5 based on estimated glomerular filtration rate (eGFR), i.e. stage 3a was defined as an eGFR ≥45 and <60 ml/min/1.73m², stage 3b as an eGFR ≥30 and <45 ml/min/1.73m², stage 4 as an eGFR ≥15 and <30 ml/min/1.73m², and stage 5 as an eGFR <15 ml/min/1.73m².
Patients who received dialysis or renal transplantation were excluded from the study.

The medical ethical committee of the University Medical Center Groningen ascertained that this study using anonymized medical record data does not fall under the Medical Research Involving Human Subjects Act.

**Clinics**

Clinic A and clinic B are academic hospitals, which provided data from their general nephrology outpatient clinic and their predialysis outpatient clinic. Clinic C is a nonacademic hospital, which provided data from the general nephrology outpatient clinic. In all three clinics, the included CKD patients commonly visit the outpatient clinics 2-4 times per year depending on the progression of their disease. At these visits, the medication can be reviewed and changed. In all clinics, the medication included in this study is usually prescribed by the nephrologist or nephrologist in training, although other specialists or the general practitioner may also prescribe medication during the year.

**Prescribing quality**

A previously developed set of PQI was used for the assessment of prescribing quality. This set of twelve PQIs was based on clinical guideline recommendations, and intends to provide insight in prescribing of antihypertensives, RAAS inhibitors, statins and phosphate binders when recommended (potentially appropriate prescribing) as well as prescribing of dual RAAS blockade, active vitamin D, ESA, NSAIDs, metformin, and digoxin when considered not needed or unsafe (potentially inappropriate prescribing) (Table 4.1). To specify the indicators to specific needs of patients, most indicators focus on a subgroup of the population selected based on kidney function, risk factor levels and/or age. Since there will always be individual cases for whom this is not the case, we speak of ‘potentially’ appropriate (or inappropriate) prescribing. Antihypertensives include diuretics, beta blocking agents, calcium channel blockers, agents acting on the RAAS system and other antihypertensives such as centrally acting agents. RAAS inhibitors include angiotensin-converting-enzyme inhibitors and angiotensin-II-receptor-blockers.

**Data collection**

Data were collected over twelve consecutive months at each clinic. For each patient with at least one visit to a nephrologist within the study period, the physical examination, laboratory measurement and prescription data of the most recent visit were extracted from the medical records, either by computerized or manual extraction routines. Age was determined on the visit day. For some patients, the
visit date was unknown, in which case the most recent date of an eGFR assessment was used as a proxy for the visit date. The eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) formula. If serum creatinine was not available, the reported eGFR calculated with the MDRD formula was used. Proteinuria was defined as more than 0.5 g of protein in 24 hour or per litre urine, depending on availability.

Table 4.1: Indicator definitions as previously defined

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Indicator definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appropriate prescribing</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>The percentage of patients with CKD stages 4-5 between 18 and 80 years with hypertension†, that is prescribed antihypertensives unless undesirable because of low diastolic blood pressure (&lt;70 mmHg)</td>
</tr>
<tr>
<td>2</td>
<td>The percentage of patients with CKD stages 3-5 between 18 and 80 years with proteinuria‡, that is prescribed an ACE-i or ARB</td>
</tr>
<tr>
<td>3</td>
<td>The percentage of patients with CKD stages 3-5 between 18 and 80 years with proteinuria‡ treated with multiple antihypertensives, that is prescribed with a combinations of an ACE-i or ARB and a diuretic</td>
</tr>
<tr>
<td>4</td>
<td>The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin</td>
</tr>
<tr>
<td>5</td>
<td>The percentage of patients with CKD stages 3-5 between 8 and 80 years with an elevated phosphate level (&gt;1.49 mmol/l), that is prescribed a phosphate binder</td>
</tr>
<tr>
<td><strong>Inappropriate prescribing</strong></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>The percentage of patients with CKD stages 3-5 18 years or older treated with RAAS inhibitors, that is prescribed at least two RAAS inhibitors simultaneously (dual RAAS blockade)</td>
</tr>
<tr>
<td>7</td>
<td>The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (&gt;2.54 mmol/l), that is prescribed active vitamin D</td>
</tr>
<tr>
<td>8</td>
<td>The percentage of patients with CKD stages 3-5 18 years or older and an haemoglobin level above target (≥7.5 mmol/l), that is prescribed an ESA</td>
</tr>
<tr>
<td>9</td>
<td>The percentage of patients with eGFR &lt; 30 ml/min/1.73m² 18 years or older, that is prescribed an NSAID</td>
</tr>
<tr>
<td>10</td>
<td>The percentage of patients with eGFR &lt; 30 ml/min/1.73m² 18 years or older with diabetes§, that is prescribed metformin</td>
</tr>
<tr>
<td>11</td>
<td>The percentage of patients with eGFR &lt; 50 ml/min/1.73m² 18 years or older treated with digoxin, that is prescribed high dose digoxin (&gt;0.125 mg/day)</td>
</tr>
<tr>
<td>12</td>
<td>The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed a combination of NSAIDs, RAAS inhibitors and diuretics</td>
</tr>
</tbody>
</table>


† Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives. ‡ Proteinuria is defined as > 0.5 g protein per 24h or l urine. § Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs.
Statistical analysis

Means with standard deviations (SD) are reported for normally distributed continuous variables, medians with interquartile ranges for non-normally distributed variables, and percentages for categorical variables. The PQI scores are presented as percentages with 95% confidence intervals. Chi-square tests or Fisher’s Exact tests, in case of cell frequencies below 5, were used to test for differences in prescribing quality across different CKD stages and different clinics. P-values <0.05 were considered statistically significant. When comparing individual PQIs between CKD stages or clinics, Bonferroni correction for multiple testing was applied. Analyses were conducted using Stata version 14.2 Special Edition (Stata Corp., College Station, TX).

Results

In total, 3,132 patients with CKD stage 3a-5 were included in this study. Included patients were on average 68 years (SD: 14) old, 56% were males, the median eGFR was 35 ml/min/1.73m$^2$ (interquartile range: 24-46) and 16% had diabetes (Table 4.2).

Overall prescribing quality

Potentially appropriate prescribing rates varied from 94% of patients receiving antihypertensives, 57% and 52% receiving RAAS inhibitors alone or in combination with a diuretic, 42% receiving statins, and 72% receiving phosphate binders when indicated according to the guideline (Figure 4.1). Potentially inappropriate prescribing rates varied from 19% of patients receiving active vitamin D, 3% receiving ESA, 1% receiving NSAIDs, 3% receiving metformin and 4% receiving high-dose digoxin when this was possibly not needed or unsafe.

Prescribing quality across chronic kidney disease stages

Potential appropriate prescribing of RAAS inhibitors alone occurred significantly less in patients with CKD stage 5 compared to all other stages, which was also true for the combination of RAAS inhibitors and diuretics (Figure 4.2). Patients with stage 3a were less likely to receive recommended treatment with statins than patients with stage 4 or 5. Similarly, patients with stage 3b were less likely to receive statins compared to patients with stage 4. Potential inappropriate prescribing of active vitamin D in patients with elevated calcium occurred significantly less in patients with stages 3a and 3b compared to patients with stages 4 and 5. This was also the case for potentially inappropriate prescribing of ESA.
Prescribing quality in secondary care CKD patients

Partially inappropriate prescribing of metformin in patients with an eGFR <30 ml/min/1.73m² was significantly lower for stage 5 as compared to stage 4.

**Prescribing quality across nephrology outpatient clinics**

Patients visiting the university outpatient clinics A and B were on average younger (63 years (SD: 15) and 65 years (SD: 15)) compared to those visiting the non-university outpatient clinic C (71 years (SD: 13)). Furthermore, patients visiting clinic A more often had CKD stage 4 or 5 compared to patients from clinics B and C (Table 4.2). The diabetes prevalence was higher at clinic A (26%) compared to clinic B (19%) and clinic C (10%) (Appendix 3, Table S4.1).

Significant differences were seen between clinic A and clinic C in potentially appropriate prescribing of antihypertensives, RAAS inhibitors alone, statins, and in potentially inappropriate prescribing of metformin as well as the combination of NSAIDs, RAAS inhibitors and diuretics (Figure 4.3). Furthermore, significantly more potentially appropriate prescribing of phosphate binders was seen in clinic A as compared to clinic B.

---

**Table 4.2: Patient characteristics for the whole population and separate per CKD stage**

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=3,132)</th>
<th>CKD 3a (n=843)</th>
<th>CKD 3b (n=1,125)</th>
<th>CKD 4 (n=862)</th>
<th>CKD 5 (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (males)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>1,738 (55.5)</td>
<td>456 (54.1)</td>
<td>614 (54.6)</td>
<td>488 (56.6)</td>
<td>180 (59.6)</td>
</tr>
<tr>
<td><strong>Diabetes (yes)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>485 (15.5)</td>
<td>96 (11.4)</td>
<td>166 (14.8)</td>
<td>165 (19.1)</td>
<td>58 (19.2)</td>
</tr>
<tr>
<td><strong>Clinic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>569 (18.2)</td>
<td>92 (10.9)</td>
<td>166 (14.8)</td>
<td>183 (21.2)</td>
<td>128 (42.4)</td>
</tr>
<tr>
<td>B</td>
<td>845 (27.0)</td>
<td>255 (30.3)</td>
<td>295 (26.2)</td>
<td>219 (25.4)</td>
<td>76 (25.2)</td>
</tr>
<tr>
<td>C</td>
<td>1,718 (54.9)</td>
<td>496 (58.8)</td>
<td>664 (59.0)</td>
<td>460 (53.4)</td>
<td>98 (32.5)</td>
</tr>
<tr>
<td><strong>Mean (±SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.7 (±14.1)</td>
<td>63.1 (±14.2)</td>
<td>68.9 (±13.2)</td>
<td>70.2 (±13.8)</td>
<td>69.2 (±14.8)</td>
</tr>
<tr>
<td>eGFR (MDRD) (ml/min/1.73m²)</td>
<td>35 [24-46]</td>
<td>52.2 (±4.3)</td>
<td>37.3 (±4.2)</td>
<td>23.1 (±4.3)</td>
<td>11.1 (±2.6)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>132.0 (±18.8)</td>
<td>129.4 (±17.3)</td>
<td>130.7 (±18.6)</td>
<td>133.3 (±19.4)</td>
<td>139.1 (±19.2)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75.1 (±11.2)</td>
<td>76.7 (±10.6)</td>
<td>74.9 (±11.3)</td>
<td>74.6 (±11.2)</td>
<td>74.0 (±12.1)</td>
</tr>
<tr>
<td>Total protein (g/24h urine)</td>
<td>0.4 [0.1-1.3]</td>
<td>0.3 [0.1-0.8]</td>
<td>0.2 [0.1-0.8]</td>
<td>0.4 [0.2-1.3]</td>
<td>1.3 [0.5-2.8]</td>
</tr>
<tr>
<td>Total protein (g/L urine)</td>
<td>0.2 [0.1-0.6]</td>
<td>0.1 [0.1-0.3]</td>
<td>0.2 [0.1-0.4]</td>
<td>0.3 [0.1-0.6]</td>
<td>0.8 [0.3-1.7]</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.08 (±0.29)</td>
<td>0.96 (±0.20)</td>
<td>1.00 (±0.20)</td>
<td>1.10 (±0.25)</td>
<td>1.48 (±0.39)</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.36 (±0.14)</td>
<td>2.38 (±0.11)</td>
<td>2.37 (±0.13)</td>
<td>2.35 (±0.15)</td>
<td>2.30 (±0.16)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)</td>
<td>8.0 (±1.1)</td>
<td>8.5 (±1.1)</td>
<td>8.2 (±1.0)</td>
<td>7.7 (±1.1)</td>
<td>7.0 (±0.9)</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic. * Median with interquartile range.
In the analyses per CKD stage (Appendix 3, Table S4.2 and S4.3), similar differences were found between the clinics. In patients with stage 3a CKD, potentially appropriate prescribing of RAAS inhibitors combined with diuretics occurred the least in clinic B. In patients with stage 3b CKD, potential appropriate prescribing of RAAS inhibitors alone or combined with diuretics occurred the most in clinic A. Patients with stage 4 CKD were significantly more likely in clinic A as compared to clinic C to receive antihypertensives and RAAS inhibitors alone. Also, patients with CKD stage 5 were more likely in clinic A as compared to clinic C to receive phosphate binders when indicated.

**DISCUSSION**

This is a first study to assess the prescribing quality in secondary care CKD patients using a broad set of PQIs and comparing different outpatient clinics. The results show that the prescribing quality varied for different therapeutic areas. RAAS inhibitors and statins were prescribed in less than 60% of the patients for whom this is potentially indicated, whereas potentially appropriate prescribing rates for antihypertensives and phosphate binders were much higher. Potentially inappropriate prescribing occurred most regarding active vitamin D. The prescribing quality also varied across different CKD stages, with decreasing potentially inappropriate prescribing of RAAS inhibitors, increasing potentially appropriate prescribing of statins, and increasing potential inappropriate prescribing of active vitamin D and ESA with higher CKD stages. Finally, significant differences were observed in prescribing between the different outpatient clinics, also after stratification for CKD stage.

Previous studies looking at the overall volume of prescribing suggested that there was underprescribing of RAAS inhibitors and statins and overprescribing of NSAIDs in patients with CKD. Our study using validated PQIs, which assess prescribing in patients for whom this is indicated, confirmed that underprescribing of RAAS inhibitors and statins are areas for possible improvement in CKD care. This was also found in a recent study among patients with stage 3-4 CKD in Canada. In contrast, one older study among elderly primary care patients in Canada found relatively high prescribing rates of 75% for RAAS inhibitors and 65% for statins when recommended. Regarding potentially inappropriate prescribing, that study observed a relatively high prescribing rate of NSAIDs (16%) and low prescribing rate of dual RAAS blockade (3%). Our study showed that potentially unsafe prescribing of both NSAIDs and dual RAAS blockade was uncommon in secondary care patients managed in The Netherlands. Differences in the setting are likely
to influence the rates of potentially appropriate and inappropriate prescribing. This implies that the first step in quality improvement initiatives should include assessing the current prescribing quality, preferably with validated PQIs.

It was shown before that patients with higher CKD stages receive more treatment with antihypertensives, phosphate binders, vitamin D and ESA.\textsuperscript{1,10} This can be expected because these drugs are more likely to be indicated in patients with more severe CKD. In addition, RAAS inhibitors and NSAIDs were less prescribed with increasing CKD stages.\textsuperscript{1} These studies, however, did not take the specific indicators for treatment into account. As said before, the present study used PQIs, that identify and include patients in whom the drug treatment is either recommended or considered not needed or unsafe. We found that RAAS inhibitors were less prescribed and statins were more prescribed with increasing CKD stages. In some patients with CKD stage 5 who are in preparation of dialysis or transplantation, RAAS inhibitors may be deliberately stopped to retain the residual kidney function.\textsuperscript{11} Lower statin prescribing rates in patients with lower CKD stages suggests that prescribers may be less aware or convinced of the need to prescribe statins in these patients. A similar pattern of less statin prescribing in patients with a higher eGFR compared to lower eGFR was observed for the elderly primary care patients in Canada.\textsuperscript{9} In addition, we observed higher rates of potentially inappropriate prescribing of active vitamin D and ESA with increasing CKD stages. Possibly, these patients had an indication for these drugs in the past, and the decision to discontinue treatment was not yet made. Active deprescribing may be uncommon and an area for improvement in CKD care and care in general. Recently, it has been shown that there are several potential benefits of deprescribing, including better health outcomes, quality of life and cost benefits.\textsuperscript{12} However, barriers for deprescribing have been identified, such as lack of awareness of and skills for deprescribing, devolving the responsibility to other health care providers and the complexity of polypharmacy, multimorbidity and poor communication between multiple healthcare providers.

The applied PQIs reflect general guideline recommendations and therefore a perfect score is never pursued. There can be valid reasons to refrain from prescribing according to guideline recommendations in certain patients. Valid reasons include lack of response to certain drugs, drug intolerances or patient preferences for or against certain treatment. However, guideline recommendations should guide clinical practice and are therefore useful to provide insight and monitor the quality of care. It has been argued that patient case-mix including difference in aspects, such as age or comorbidities, may explain differences in quality scores.\textsuperscript{13} However, these may not necessarily be valid reasons for not complying with guideline recommendations. When developing the PQIs, such differences are to
some extent included in the indicator definitions (e.g. age limits), thereby ensuring that the treatments are in general either recommended or inappropriate in the patients included in the indicator. Furthermore, a recent review showed that unjustified case-mix corrections can mask actual differences in quality of care. Therefore, no case-mix adjustment has been made when applying the PQIs.

The results showed several differences regarding potentially appropriate as well as less potentially inappropriate prescribing between the clinics. This may in part be due to differences in the underlying patient population. The patient population from clinic A included more patients with CKD stage 5 and partly
Pre-dialysis patients, who may be treated differently in preparation of dialysis. One would expect that this would lead to less appropriate prescribing when applying general guideline-based PQIs, but the opposite seemed to occur. Diabetes prevalence was also higher in clinic A, which may have affected prescribing. Other

Figure 4.2: Prescribing quality across different CKD stages (3A-5) assessed with 5 PQIs for appropriate prescribing (Ind 1-5) and 7 PQIs for potential inappropriate prescribing (Ind 6-12)

<table>
<thead>
<tr>
<th>Stage 3A</th>
<th>62.7</th>
<th>61.7</th>
<th>32.9</th>
<th>83.3</th>
<th>0.8</th>
<th>0.0</th>
<th>0.6</th>
<th>16.7</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3B</td>
<td>63.8</td>
<td>63.0</td>
<td>39.7</td>
<td>64.5</td>
<td>0.0</td>
<td>6.6</td>
<td>1.0</td>
<td>4.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Stage 4</td>
<td>93.6</td>
<td>57.7</td>
<td>52.3</td>
<td>72.0</td>
<td>0.2</td>
<td>43.5</td>
<td>6.8</td>
<td>0.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Stage 5</td>
<td>94.8</td>
<td>39.7</td>
<td>32.3</td>
<td>72.7</td>
<td>0.0</td>
<td>43.8</td>
<td>22.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Ind 1: Patients with hypertension prescribed antihypertensives; Ind 2: Patients with albuminuria prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors; Ind 3: Patients on multiple antihypertensives prescribed a combination of RAAS inhibitors and diuretics; Ind 4: Patients aged 50 to 65 years prescribed statins; Ind 5: Patients with high phosphate levels prescribed phosphate binders; Ind 6: Patients prescribed dual RAAS blockade; Ind 7: Patients with high calcium levels prescribed active vitamin D; Ind 8: Patients with normal haemoglobin levels prescribed erythropoiesis-stimulating agents; Ind 9: Patients with an estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73m² prescribed high dose non-steroidal anti-inflammatory drugs (NSAIDs); Ind 10: Patients with an eGFR lower than 30 ml/min/1.73m² prescribed metformin; Ind 11: Patients with an eGFR lower than 50 ml/min/1.73m² prescribed high dose digoxin; Ind 12: Patients prescribed a combination of NSAIDs, RAAS inhibitors and diuretics. 95% Confidence Intervals were calculated based on included number of patients in the denominator of each indicator.

* Significant difference between 2 or more CKD stages using Chi-square or Fisher’s exact test with Bonferroni-correction for multiple testing.
studies indicate that CKD patients with diabetes receive better quality of care in general, and have higher prescription rates of RAAS inhibitors and statins. This suggests that prescribing of treatment to reduce cardiovascular and renal compli-

Figure 4.3: Prescribing quality across different outpatient clinics assessed with 5 PQIs for appropriate prescribing (Ind 1-5) and 7 PQIs for potential inappropriate prescribing (Ind 6-12)

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Ind 1</th>
<th>Ind 2</th>
<th>Ind 3</th>
<th>Ind 4</th>
<th>Ind 5</th>
<th>Ind 6</th>
<th>Ind 7</th>
<th>Ind 8</th>
<th>Ind 9</th>
<th>Ind 10</th>
<th>Ind 11</th>
<th>Ind 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>97.6</td>
<td>64.0</td>
<td>56.5</td>
<td>48.7</td>
<td>78.9</td>
<td>0.6</td>
<td>28.6</td>
<td>5.0</td>
<td>1.9</td>
<td>0.3</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>B</td>
<td>96.1</td>
<td>53.1</td>
<td>48.2</td>
<td>42.4</td>
<td>64.6</td>
<td>0.0</td>
<td>17.9</td>
<td>2.3</td>
<td>0.7</td>
<td>2.0</td>
<td>12.5</td>
<td>0.2</td>
</tr>
<tr>
<td>C</td>
<td>90.0</td>
<td>54.0</td>
<td>50.4</td>
<td>37.9</td>
<td>64.7</td>
<td>0.3</td>
<td>16.0</td>
<td>3.1</td>
<td>0.4</td>
<td>2.7</td>
<td>2.4</td>
<td>0.1</td>
</tr>
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Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic. Ind 1: Patients with hypertension prescribed antihypertensives; Ind 2: Patients with albuminuria prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors; Ind 3: Patients on multiple antihypertensives prescribed a combination of RAAS inhibitors and diuretics; Ind 4: Patients aged 50 to 65 years prescribed statins; Ind 5: Patients with high phosphate levels prescribed phosphate binders; Ind 6: Patients prescribed dual RAAS blockade; Ind 7: Patients with high calcium levels prescribed active vitamin D; Ind 8: Patients with normal haemoglobin levels prescribed erythropoiesis-stimulating agents; Ind 9: Patients with an estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73m² prescribed high dose non-steroidal anti-inflammatory drugs (NSAIDs); Ind 10: Patients with an eGFR lower than 30 ml/min/1.73m² prescribed metformin; Ind 11: Patients with an eGFR lower than 50 ml/min/1.73m² prescribed high dose digoxin; Ind 12: Patients prescribed a combination of NSAIDs, RAAS inhibitors and diuretics. 95% Confidence Intervals were calculated based on included number of patients in the denominator of each indicator.

* Significant difference between 2 or all outpatient clinics using Chi-square or Fisher’s exact test with Bonferroni-correction for multiple testing.
cations gets more attention in this high risk population. Another explanation for differences in prescribing may be related to the patients’ age. Patients from the non-university clinic C were on average older, which could be a reason to treat them less aggressively. In older and frail patients, life expectancy and quality of life can play an important role in decision making regarding treatment. However, all PQIs focusing on the recommended treatment with antihypertensives, RAAS inhibitors, statins and phosphate binders have an age limit which excludes a large part of these older, more frail patients.

This study assessed the prescribing quality in a cross-sectional manner, since the PQIs were defined as cross-sectional measures. This may lead to including patients who reached abnormal risk factor levels for the first time. In some cases, the healthcare provider may decide to postpone the start of treatment until a next measurement to make sure that the abnormal risk factor level persists. This also holds for discontinuation of active vitamin D in patients with elevated calcium levels and ESA in patients with normal haemoglobin levels. Furthermore, it is possible that the laboratory results became available after the visit. Therefore, the healthcare provider may not have been aware at the time of the visit that they should start or discontinue medication. In the diabetes field, it has been proposed that indicators using multiple time points may give a more accurate assessment of the prescribing quality. Such indicators assess whether the healthcare providers start or intensify treatment when patients do not return to normal risk factor levels.

Some limitations need to be addressed. First of all, data collection methods differed for the three outpatient clinics. Data from clinic A were collected manually from electronic medical records, while data from clinic B and C were collected by computerized extraction from electronic medical records. In addition, all three clinics use different medical records systems. Although we were able to extract and combine the data in order to make comparisons possible, there were some differences in availability of measurement values. The creatinine values from clinic C were not present in the anonymized database provided for this study, making eGFR calculation impossible. However, reported eGFR calculated with the MDRD formula was available and therefore used. Furthermore, data from the physical examinations and laboratory measurements were sometimes missing, with the highest rate of missingness for clinic B (Appendix 3, Table S4.2). This could have influenced the outcome of the PQIs, since patients with unknown values were not included in the PQIs. We can only speculate why these values were missing, and how this may have influenced the assessments. It could be that the physical examinations and laboratory measurements were not performed, not recorded or lost during data extraction. Furthermore, besides diabetes, no other
(cardiovascular) comorbidities have been explored to see whether the prevalence differed across patient groups.

In conclusion, using a novel set of PQIs in the present study we successfully identified several areas for improvement, including potential underprescribing of RAAS inhibitors and statins, and overprescribing of active vitamin D in secondary care patients with CKD stage 3-5. We observed differences in prescribing quality between these CKD stages and between outpatient clinics. We conclude that monitoring of the prescribing quality with PQIs is needed in secondary care to identify priority areas for improvement, and that stratification on CKD stage can be useful in quality improvement initiatives.

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REFERENCES

Part II
QUALITY OF PRESCRIBING IN TYPE 2 DIABETES