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Quality of prescribing in chronic kidney disease and type 2 diabetes

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DEVELOPMENT AND INITIAL VALIDATION OF PRESCRIBING QUALITY INDICATORS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Quality assessment is a key element for improving the quality of care. Currently, a comprehensive indicator set for measuring the quality of medication treatment in patients with chronic kidney disease (CKD) is lacking. Our aim was to develop and validate a set of prescribing quality indicators (PQIs) for CKD care, and to test the feasibility of applying this set in practice.

Methods: Potential indicators were based on clinical practice guidelines and evaluated using the RAND/UCLA Appropriateness Method. This is a structured process in which an expert panel assesses the validity of the indicators. Feasibility was tested in a Dutch primary care database including more than 4,500 diabetes patients with CKD.

Results: An initial list of 22 PQIs was assessed by twelve experts. After changing ten PQIs, adding two and rejecting eight, a final list of sixteen indicators was accepted by the expert panel as valid. These PQIs focused on the treatment of hypertension, albuminuria, mineral and bone disorder, statin prescribing and possible unsafe medication. The indicators were successfully applied to measure treatment quality in the primary care database, but for some indicators the number of eligible patients was too small for reliable calculation. Results showed that there was room for improvement in the treatment quality of this population.

Conclusions: We developed a set of sixteen PQIs for measuring the quality of treatment in CKD patients, which had sufficient content and face validity as well as operational feasibility. These PQIs can be used to point out priority areas for improvement.

INTRODUCTION

People with chronic kidney disease (CKD) have an increased risk of end-stage renal disease¹ as well as cardiovascular morbidity and mortality.^{2,3} These risks can be reduced by appropriate pharmacotherapy, which is stipulated in clinical practice guidelines. These guidelines emphasize adequate treatment of hypertension, albuminuria, anaemia, mineral and bone disorder (MBD) and treatment with statins.⁴⁻⁷ However, several studies have shown that the provided care is not always in line with these guidelines⁸⁻¹⁰ and that the quality of medication treatment in patients with CKD is not optimal.^{8,11,12}

Prescribing quality indicators (PQIs) are used to measure appropriate pharmacotherapy, which includes aspects of medication need, medication choice, safety, adequate dosing, optimal prescribing and adherence.^{13,14} PQIs reflect the proportion of patients that received appropriate (or inappropriate) pharmacotherapy. Quality indicators can be used to monitor, compare or reward providers and provided care and can be part of a quality improvement strategy in audit and feedback programs.¹⁵ Such audit and feedback programs can lead to an increase of the quality of medication treatment by 13%.¹⁶

Internationally, several quality indicator sets regarding CKD care have been developed. The American Renal Physicians Association developed a list of indicators intended to assess appropriate patient preparation for renal replacement therapy.¹⁷ This set includes nine PQIs focusing on treatment of MBD, hypertension, anaemia and statin prescribing. Litvin and Ornstein¹⁸ developed a set of twelve quality indicators for CKD management in primary care, three of which focused on medication treatment. A Canadian group published a list of 50 criteria that was developed for community pharmacists to assess medication safety issues and adequate medication use by patients with CKD.¹⁹ However, none of these lists covered appropriateness of pharmacotherapy in patients with CKD. Therefore, the goal of this study was to develop a comprehensive set of PQIs for patients with CKD managed in primary or secondary care.

To develop a set of quality indicators, several steps are recommended.^{20,21} First, an initial list of indicators should be generated based on literature, clinical guidelines and expert consultation. Second, the content and face validity of the indicators should be assessed. Content validity represents whether these indicators correctly reflect the recommendations from clinical guidelines, whereas face validity represents whether a group of experts in the field accept the indicators as measuring quality of care. Next, the operational validity of the indicators should be tested. Operational validity represents the feasibility to calculate the indicators in a reliable way, preferably using routinely collected data.¹⁵ Following these

recommendations, our specific aims were to develop a set of PQIs for monitoring CKD care that is both content and face valid and to test the operational validity of the indicators.

METHODS

Selection of indicators

An initial list of PQIs was developed based on existing national^{4,22-24} and international guidelines^{5-7,25-31} and literature.³²⁻³⁴ Recommendations with level A or B evidence according to the national guidelines for medication treatment were extracted and converted in potential PQIs by three members of the research team. This first list of potential indicators was discussed with an experienced clinician to refine the indicator definitions. Next, the list was discussed with three patient representatives to ascertain that all relevant topics from the patient perspective were included.

Content and face validation

To assess the content and face validity of the indicators, the RAND/UCLA Appropriateness Method (RAM) was used.³⁵ This is a three-round modified Delphi method that combines evidence with expert opinion and consensus and is considered an appropriate method for assessing the validity of indicators.³⁶ Since we intended to assess the face validity of the PQIs for primary and secondary care, an expert panel was formed with four experts from each of three relevant specialties in the Netherlands, namely nephrology, general practice and pharmacy. These were all people with a special interest or expertise with regard to the treatment of CKD patients. Financial compensation was offered to the experts for their time.

During the first round, the experts scored the indicators on three criteria using a 9-point Likert scale. Two of these criteria represent content validity, namely whether the indicator reflected the guidelines adequately ('correct reflection of guidelines') and whether the definitions were correctly formulated ('definitions'). The third criterion, whether following the indicators would result in a health gain for the patient ('health gain'), was included as a general reflection of both content and face validity. The experts received background information, including the guideline recommendations and level of evidence provided in the national guidelines. Levels of evidence were 'A' for evidence from randomized controlled trials and meta-analyses; 'B' for evidence from observational studies, case-control studies and case reports; and 'C' for expert opinion. The experts could give comments and propose changes or new indicators during the first round. The second

round was a consensus meeting where the experts discussed the discrepancies and were able to change, add and remove indicators. This discussion was chaired by a moderator (PD). During the third round, the experts received the adjusted list of indicators, including explanations for the changes, deletions and additions made. This third round was similar to the first round, assessing the criteria 'correct reflection of guidelines' and 'health gain', and one new criterion, i.e. whether the indicator measured a necessary aspect of quality of care ('necessary aspect'), reflecting face validity.

Operational validity

We tested whether it was feasible to measure the selected PQIs using routinely collected primary care data. Data from the Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT)³⁷ were used. The GIANTT database includes data extracted from medical records of >50,000 patients with type 2 diabetes managed in Dutch primary care. From these, we selected patients with CKD in the year 2012. CKD was defined as having an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m² calculated with the chronic kidney disease epidemiology collaboration formula.³⁸ This corresponds to CKD stages 3-5 according to the Dutch guidelines.⁴ Patients receiving renal replacement therapy were excluded from analysis. The data included information on age, gender, diabetes duration, physical examination, laboratory measurements, comorbidity and prescribed medication. Indicators were considered feasible if all indicator elements could be measured in more than 2% of patients using the available data. In addition, we calculated the minimum required number of patients for reliable comparison of indicator scores.

The Medical Ethical Committee of University Medical Center Groningen ascertained that the study does not fall under the Medical Research Involving Human Subjects Act, since it used existing anonymized data.

Statistical analysis

A PQI was considered content and face valid when (I) all criteria in the third round were rated with a median score of 7 or higher and (II) the criteria were rated without disagreement. As described in the RAM, disagreement among the experts was calculated using the ratio of the Interpercentile Range Adjusted for Symmetry over the Interpercentile Range, where a score of <1 indicates poor agreement.³⁵

To assess to what extent a PQI can provide reliable scores for performance comparison, we calculated the minimum required number of patients with a moderate precision of 10 percentage points for medication need and medication choice indicators and 5 percentage points for medication safety indicators.³⁹ These

predefined limits were arbitrary, and after observing some indicator scores below 5% we decided to conduct the calculations for such indicators using a precision level of 1 percentage point. Based on the absolute numbers, the percentages of eligible patients in our study population and the observed indicator scores, estimates for the total number of patients with CKD needed for reliable indicator scores were calculated (See Appendix 2, File S3.1).

A sensitivity analysis was conducted to test whether the indicators would yield different results when patients were selected based on two consecutive eGFR measurements. Chi-square test and where appropriate Fisher's exact test were used to compare indicator outcome scores.

All analyses were conducted using Stata version 13.1 Special Edition (StataCorp, College Station, TX, USA).

RESULTS

Face and content validation

Indicator selection

An initial list of 22 indicators was selected and defined. Fourteen indicators focused on measuring medication need or medication choice, including three for treatment of hypertension, two for albuminuria, five for MBD, three for anaemia and one for statin prescribing. In addition, eight indicators focused on measuring medication safety and optimal prescribing and one indicator focused on measuring treatment adherence (Table 3.1). Consultation with the patient representatives did not yield any uncovered topics in our list.

First round

An expert panel was formed of four general practitioners, four nephrologists and four pharmacists working in different regions in the Netherlands. In the first round, nine indicators had one criterion, and one indicator had two criteria that were scored with uncertainty or disagreement by the experts (Figure 3.1).

Second round

Two pharmacists and one nephrologist were unable to attend the consensus meeting. The moderator voiced their comments during the meeting. Several general changes to the whole list of indicators were agreed upon. It was decided that the indicators should be restricted to patients with CKD stages 3-5 and to patients 80 years or younger except for medication safety indicators.

Table 3.1: Prescribing quality indicators with changes made during evaluation process by experts

Final indicator description; (<i>x</i>) indicators in italic are not included in final set of sixteen prescribing quality indicators	Changes made during evaluation process
<i>Treatment of hypertension</i>	
1. The percentage of patients with CKD stages 4-5 between 18 and 80 years with hypertension [†] , that is prescribed antihypertensives (evidence level: A) unless undesirable because of low diastolic blood pressure (<70 mmHg) (added by expert panel)	<ul style="list-style-type: none"> • Age restricted between 18 and 80 years • CKD stage restricted to stage 4 and 5 • Restriction of low diastolic blood pressure added
<i>(I) The percentage of patients with CKD stages 3-5 treated with antihypertensives that is prescribed an ACE-i or ARB (evidence level: B)</i>	Removed
2a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria [‡] treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic (evidence level: B)	<ul style="list-style-type: none"> • Age restricted between 18 and 80 years • No gender-specific albuminuria cut-off level • Restricted to macro-albuminuria
2b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria [‡] and diabetes [§] treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic (evidence level: B)	Added <ul style="list-style-type: none"> • Age restricted between 18 and 80 years • No gender-specific albuminuria cut-off level • Restricted to micro-albuminuria and diabetes
<i>Treatment of albuminuria</i>	
3a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria [‡] , that is prescribed an ACE-i or ARB (evidence level: A)	<ul style="list-style-type: none"> • Age restricted between 18 and 80 years • No gender-specific albuminuria cut-off level • Restricted to macro-albuminuria
3b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria [‡] and diabetes [§] , that is prescribed an ACE-i or ARB (evidence level: A)	Added <ul style="list-style-type: none"> • Age restricted between 18 and 80 years • No gender-specific albuminuria cut-off level • Restricted to micro-albuminuria and diabetes
<i>Prescription of statins</i>	
4. The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin (evidence level B for patients with high cardiovascular risk)	No changes
<i>Treatment of MBD</i>	

Table 3.1: Prescribing quality indicators with changes made during evaluation process by experts (continued)

Final indicator description; (x) indicators in italic are not included in final set of sixteen prescribing quality indicators	Changes made during evaluation process
5. The percentage of patients with CKD stages 3-5 between 18 and 80 years with an elevated phosphate level (>1.49 mmol/l), that is prescribed a phosphate binder (evidence level: B for control of phosphate level)	<ul style="list-style-type: none"> - Age restricted between 18 and 80 years - Aluminium hydroxide added as phosphate binders - For calcium-containing phosphate binders a minimal dose of >1x daily is required
<i>(II) The percentage of patients with CKD stages 3-5 without increased phosphate that start with a phosphate binder (evidence level: B)</i>	Removed
6. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with an elevated calcium level (>2.54 mmol/l), that is prescribed a non-calcium-containing phosphate binder (evidence level: B for control of calcium level)	<ul style="list-style-type: none"> - Age restricted between 18 and 80 years - Aluminium hydroxide added as phosphate binders - A correction of calcium levels for albumin is required
7. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with a low calcium level (<2.10 mmol/l), that is prescribed a calcium-containing phosphate binder (evidence level: B for control of calcium level)	<ul style="list-style-type: none"> - Age restricted between 18 and 80 years - Aluminium hydroxide added as phosphate binders - A correction of calcium levels for albumin is required
<i>(III) The percentage of patients with CKD stages 3-5 with elevated PTH levels that is prescribed vitamin D (evidence level: B)</i>	Removed
<i>Treatment of anaemia</i>	
<i>(IV) The percentage of patients with CKD stages 3-5 with iron deficiency anaemia that is prescribed iron supplements (evidence level: A for control of serum haemoglobin level)</i>	Removed
<i>(V) The percentage of patients with CKD stages 3-5, anaemia and adequate iron supplementation that is prescribed ESA (evidence level: A for control of serum haemoglobin level)</i>	Removed
<i>(VI) The percentage of patients with CKD stages 3-5 without low haemoglobin or haematocrit level that is prescribed iron supplements (evidence level: B)</i>	Removed
<i>Medication safety</i>	
8. 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) (evidence level: A)	No changes
9. The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (>2.54 mmol/l), that is prescribed active vitamin D (evidence level: B for control of calcium level)	<ul style="list-style-type: none"> - Vitamin D restricted to active vitamin D

Table 3.1: Prescribing quality indicators with changes made during evaluation process by experts (continued)

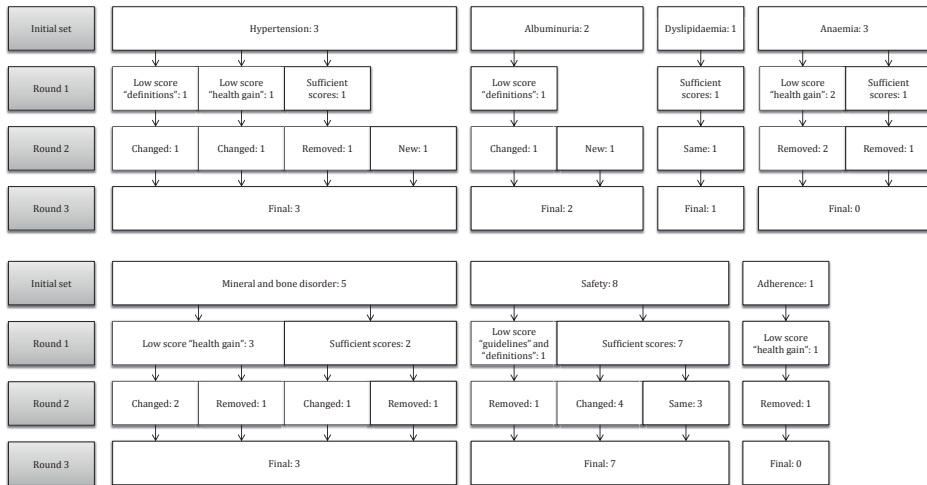
Final indicator description; (<i>x</i>) indicators in italic are not included in final set of sixteen prescribing quality indicators	Changes made during evaluation process
10. The percentage of patients with CKD stages 3-5 18 years or older with an haemoglobin level above target (≥ 7.5 mmol/l), that is prescribed an ESA (evidence level: B)	No changes
11. The percentage of patients with eGFR < 30 ml/min/1.73m ² 18 years or older, that is prescribed an NSAID (evidence level: B)	- NSAIDs including also salicylic acid derivatives (carbasalate calcium) when used for analgesic, antiphlostatic and/or antipyretic effect (> 160 mg/day)
12. The percentage of patients with eGFR < 30 ml/min/1.73m ² 18 years or older with diabetes [§] , that is prescribed metformin (evidence level: B)	- Restricted to diabetes
13. The percentage of patients with eGFR < 50 ml/min/1.73m ² 18 years or older treated with digoxin, that is prescribed high dose digoxin (> 0.125 mg/day) (evidence level: B)	No changes
14. The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed with a combination of NSAIDs, RAAS inhibitors and diuretics (evidence level: B)	- Restricted to stages 3 and 5 - NSAIDs including also salicylic acid derivatives (carbasalate calcium) when used for analgesic, antiphlostatic and/or antipyretic effect (> 160 mg/day)
<i>(VII) The percentage of patients with CKD stages 3-5 and treated with a RAAS inhibitor and a potassium-sparing diuretic simultaneously which potassium levels are measured (evidence level: B)</i>	Removed
<i>Treatment adherence</i>	
<i>(VIII) The percentage of patients with CKD stages 3-5 and treated with a ACE-i/ARB and a diuretic that is prescribed a combination pill (no evidence level)</i>	Removed

CKD: chronic kidney disease; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; MBD: mineral and bone disorder; PTH: parathyroid hormone; ESA: erythropoiesis-stimulating agent; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivatives.

Evidence levels: A: randomized controlled trials and/or meta-analyses; B: observational studies, case-control studies and/or case reports; C: expert opinion.

† Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives. ‡ Micro-albuminuria is defined as albumin/creatinine ratio ≥ 3.0 mg/mmol and < 30 mg/mmol. Macro-albuminuria is defined as albumin/creatinine ratio ≥ 30 mg/mmol. § Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs.

Figure 3.1: Evaluation process of the prescribing quality indicators during the RAND/UCLA rounds



The indicator measuring medication need for statin prescribing and three of the indicators measuring medication safety scored sufficiently during the first round and remained unchanged. The lower limit of 50 years for the indicator on statin prescribing (Table 3.1, PQI 4) was debated but accepted since the overall cardiovascular risk in patients younger than 50 years without any additional cardiovascular risk factors is often too low to warrant prescribing of statins. Two of the indicators measuring medication need for hypertension, one for albuminuria, three for MDB and four safety indicators scored insufficiently in the first round and were changed during the consensus meeting (see Table 3.1). In addition, the selection of patients was adjusted for the indicator on medication need in patients with hypertension. For this indicator, all patients with an indication for treatment, meaning a diagnosis code for hypertension, an elevated level of blood pressure or a prescription for antihypertensives, were considered eligible (Table 3.1, PQI 1). Furthermore, the experts decided to differentiate two indicators for patients based on their diabetes and albuminuria status (Table 3.1, PQIs 2A/2B and 3A/3B). For the safety indicators on non-steroidal anti-inflammatory drugs (NSAIDs) prescribing (Table 3.1 PQIs 11 and 14), the experts decided to include also salicylic acid derivatives when they were prescribed in an oral dose for analgesic, antiphlostatic and/or antipyretic effect (>160 mg/day). Eight indicators were discarded, including one indicator measuring medication need for hypertension, two for MBD treatment, three indicators for anaemia, one measuring medication safety and one measuring treatment adherence (Appendix 2, file S3.2).

Third round

After the consensus meeting, sixteen indicators remained; nine focusing on medication need or medication choice for hypertension, albuminuria, MBD and statin prescribing and seven focusing on medication safety (Figure 3.1). These were rated in the third round by all experts. All criteria for these indicators received a median score of 7 or higher with sufficient agreement and were therefore included for operational validity testing.

Operational validity

The indicators were validated in a cohort of 4,706 diabetes patients with CKD stages 3-5 in 2012 (Table 3.2). Operational definitions could be made for all PQIs using the available data (Appendix 2, Table S3.1). Of the sixteen indicators, ten indicators had sufficient number of eligible patients for reliable calculation in this large primary care cohort and four indicators included less than 2% of the total population (Table 3.3). Given the observed proportions and indicator outcomes, the total number of patients with CKD needed for reliable calculation would lie between 490 and 3,237 patients for the indicators focusing on medication need and medication choice for hypertension, albuminuria, and statin prescribing. For the medication safety indicators, a source population of 327 to 3,241 patients with CKD would be sufficient for reliable calculation. Reliable calculation of the scores of the MBD indicators and the safety indicators on vitamin D, digoxin and NSAID prescribing was not possible due to limited availability of phosphate and calcium levels, the low prevalence of phosphate binders, vitamin D and digoxin prescriptions and the low prevalence of patients CKD stages 4 and 5 in our population.

Indicator outcome scores for medication need and medication choice ranged from 59% for prescribing the recommended combination of an angiotensin-converting enzyme inhibitor (ACE-i)/angiotensin-II-receptor-blocker (ARB) and a diuretic in patients with CKD, diabetes and micro-albuminuria to 93% for prescribing antihypertensive medication in patients with CKD and hypertension. For the indicators on medication safety, the results ranged from 0.3% for prescribing erythropoiesis-stimulating agent in patients with normal haemoglobin levels to 21% for prescribing metformin in patients with an eGFR <30 ml/min/1.73m² (Table 3.3).

The sensitivity analysis did not yield different results except for the indicator on medication need for statins. Statin prescribing was higher in patients with confirmed CKD (two consecutive eGFR measurements <60 ml/min/1.73m²) compared with patients with unconfirmed CKD (79.5% and 67.5% respectively, p=0.009).

Table 3.2 Patient characteristics at baseline

Variable	N (%)	Mean (\pm SD)
Age (years)	4,706 (100)	77.1 (\pm 8.7)
Male gender	1,859 (39.5)	
<i>Measurements</i>		
eGFR (ml/min/1.73m ²)	4,706 (100)	47.1 (\pm 10.3)
CKD stage		
Stage 3	4,335 (92.1)	50.5 (43.5-55.8) ^a
Stage 4	343 (7.3)	25.5 (22.0-27.8) ^a
Stage 5	28 (0.6)	11.9 (7.8-13.6) ^a
Systolic blood pressure (mmHg)	4,580 (97.3)	141.5 (\pm 19.6)
High systolic blood pressure (>140 mmHg)	2,090 (44.4)	154 (148-165) ^a
Diastolic blood pressure (mmHg)	4,580 (97.3)	75.1 (\pm 10.4)
Low diastolic blood pressure (<70 mmHg)	1,178 (25.0)	63 (60-66) ^a
Albumin/creatinine ratio (mg/mmol)	3,409 (72.4)	1.4 (0.0-4.9) ^a
Micro-albuminuria (3-30 mg/mmol)	884 (18.8)	7.2 (4.5-12.8) ^a
Macro-albuminuria (>30 mg/mmol)	235 (5.0)	70.4 (42.1-121.7) ^a
Phosphate (mmol/l)	156 (3.3)	1.0 (\pm 0.2)
High phosphate level (>1.49 mmol/l)	6 (0.1)	1.6 (\pm 0.1)
Calcium (mmol/l)	290 (6.2)	2.4 (\pm 0.2)
High calcium level (>2.54 mmol/l)	17 (0.4)	2.6 (2.6-2.7) ^a
Low calcium level (<2.10 mmol/l)	21 (0.4)	2.1 (2.0-2.1) ^a
Haemoglobin (mmol/l)	2,264 (48.1)	8.1 (\pm 1.0)
Low haemoglobin level (<7.5 mmol/l)	602 (12.8)	7.0 (6.6-7.3) ^a
<i>Medication</i>		
Antihypertensives	4,075 (86.6)	
Diuretics	2,904 (61.7)	
Beta blocking agents	2,474 (52.6)	
Calcium channel blockers	1,341 (28.5)	
Agents acting on the RAAS system	3,184 (67.7)	
ACE-i	1,937 (41.2)	
ARBs	1,360 (28.9)	
Other agents acting on the RAAS system	13 (0.3)	
Statins	2,858 (60.7)	
Phosphate binders	70 (1.5)	
Calcium containing phosphate binders	65 (1.4)	
Non-calcium containing phosphate binders	6 (0.1)	
Vitamin D	132 (2.8)	
ESA	30 (0.6)	
NSAIDs	438 (9.3)	
Metformin	2,411 (51.2)	

Table 3.2 Patient characteristics at baseline (continued)

Variable	N (%)	Mean (\pm SD)
Digoxin	220 (4.7)	

SD: standard deviation; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; RAAS: renin-angiotensin-aldosterone system; ACE-i: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; ESA: erythropoiesis-stimulating agent; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivatives.

^a Median with interquartile range

DISCUSSION

We developed a set of sixteen PQIs, which is intended for measuring the quality of pharmacotherapy in patients with CKD stages 3-5. The indicators are derived from evidence-based guideline recommendations and were approved by experts in the Netherlands. The PQIs focus on medication need and medication choice for the treatment of hypertension, albuminuria, MBD and statin prescribing, as well as on medication safety. Most of the indicators could be operationalized using routinely collected data from a primary care database. The number of eligible patients needed for reliable estimates was >1,250 for eleven of the indicators. To our knowledge, this is the first validated set of indicators for measuring prescribing quality in patients with CKD.

Our indicator set covers the domains medication need and medication choice for four therapeutic areas relevant for CKD patients (nine indicators), as well as the domains medication safety and optimal prescribing (seven indicators on unsafe combinations, contraindications and dosing). In contrast, previously developed indicator sets for CKD focused mainly on adequate monitoring of risk factors for CKD progression and not on medication treatment.¹⁸ One medication indicator included in several general quality indicator sets measures ACE-i/ARB treatment in patients with albuminuria.^{40,41} This indicator is also included in our PQIs set. Medication safety was extensively covered by the pharmacotherapy assessment in chronic renal disease (PAIR) criteria developed by Desrochers *et al.*¹⁹ However, these criteria are intended for evaluation of individual patient's treatment and have not been converted to quality indicators.

Using a medical record database that includes routinely collected data about physical examination, laboratory measurement, comorbidity and prescribed medication, we were able to make operational definitions for all indicators. To identify patients eligible for treatment, different approaches can be used.⁴² In the development phase, the experts decided to apply a combination of diagnosis codes, clinical measurements and prescribed medication to identify patients

Table 3.3: Assessments in final round of RAND/UCLA method and outcomes from operational validity testing of indicators

Indicator	Final scores		
	Correct reflection of guidelines	Health gain	Necessary aspect
<i>Treatment of hypertension</i>			
1. 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 (<70 mmHg)	8.5	8	8
2a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria [‡] treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic	8.5	8	8
2b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria [‡] and diabetes [§] treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic	8.5	8	8
<i>Treatment of albuminuria</i>			
3a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria [‡] , that is prescribed an ACE-i or ARB	9	9	9
3b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria [‡] and diabetes [§] , that is prescribed an ACE-i or ARB	8.5	8.5	8.5
<i>Prescription of statins</i>			
4. The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin	9	8.5	9
<i>Treatment of MBD</i>			
5. The percentage of patients with CKD stages 3-5 between 18 and 80 years with an elevated phosphate level (>1.49 mmol/l), that is prescribed a phosphate binder	9	8.5	8.5
6. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with an elevated calcium level (>2.54 mmol/l), that is prescribed a non-calcium-containing phosphate binder	9	8.5	8.5

Operational validity				
Outcome score (%) in study cohort	Nominator/denominator (eligible) in study cohort	Percentage of eligible patients in total cohort (n=4,706)	N eligible patients needed for comparison	Minimal number of CKD patients needed for reliable comparison
92.9	92/99	2.1	≥26	1,238
60.5	81/134	2.8	≥92	3,237
58.9	321/545	11.6	≥93	805
81.9	122/149	3.2	≥57	1,804
78.0	495/635	13.5	≥66	490
74.3	271/365	7.7	≥74	956
75.0	39/52	1.1	≥73	6,619
-	0/0	0.0	≥96	- [†]

Table 3.3: Assessments in final round of RAND/UCLA method and outcomes from operational validity testing of indicators (continued)

Indicator	Final scores		
	Correct reflection of guidelines	Health gain	Necessary aspect
7. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with a low calcium level (<2.10 mmol/l), that is prescribed a calcium-containing phosphate binder	8.5	7.5	8
<i>Medication safety</i>			
8. 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)	8.5	9	9
9. The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (>2.54 mmol/l), that is prescribed active vitamin D	9	8.5	8
10. The percentage of patients with CKD stages 3-5 18 years or older with an haemoglobin level above target (≥ 7.5 mmol/l), that is prescribed an ESA	9	9	9
11. The percentage of patients with eGFR <30ml/min/1.73m ² 18 years or older, that is prescribed an NSAID	9	9	9
12. The percentage of patients with eGFR <30 ml/min/1.73m ² 18 years or older with diabetes [§] , that is prescribed metformin	9	8	8
13. The percentage of patients with eGFR <50 ml/min/1.73m ² 18 years or older, that is prescribed high dose digoxin (>0.125 mg/day)	9	8.5	8
14. The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed a combination of NSAIDs, RAAS inhibitors and diuretics	9	9	9

CKD: chronic kidney disease; ACE-i: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; MBD: mineral and bone disease; RAAS: renin-angiotensin-aldosterone system; ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivatives. † Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives.

Operational validity				
Outcome score (%) in study cohort	Nominator/denominator (eligible) in study cohort	Percentage of eligible patients in total cohort (n=4,706)	N eligible patients needed for comparison	Minimal number of CKD patients needed for reliable comparison
-	1/1	0.0	≥96	- [¶]
3.7	117/3,193	67.7	≥1,369 [#]	2,022
17.7	3/17	0.4	≥224	- [¶]
0.3	5/1,662	35.2	≥115 [#]	327
3.0	11/371	7.9	≥1,118 [#]	14,209
21.0	78/371	7.9	≥255	3,241
11.1	16/144	3.1	≥152	4,977
4.6	216/4,706	99.8	≥1,686 [#]	1,690

‡ Micro-albuminuria is defined as albumin/creatinine ratio ≥3.0 mg/mmol and <30 mg/mmol. Macro-albuminuria is defined as albumin/creatinine ratio ≥30 mg/mmol. § Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs. ¶ Not estimated due to low number of eligible patients in this cohort. # Eligible patients calculated using a precision of 1 percentage point due to low outcome of indicator.

having hypertension. Such an approach was deemed necessary since diagnosis coding in medical records is seldom complete⁴²⁻⁴⁴ and a difference in quality of diagnosis registration between healthcare providers can influence the indicator scores. Also, to identify all the patients in need of a phosphate binder, both clinical measurements and prescribed medication were used. Including clinical measurements is expected to increase the sensitivity of identification of poorly treated patients,⁴² whereas including patients with prescribed medication is expected to increase the sensitivity of identification of well treated patients. It is possible, however, that these medications were prescribed for other indications, reducing the specificity of the indicators and leading to overestimating their outcome.

The quality of pharmacotherapy in primary care diabetes patients with CKD was found to be suboptimal, with indicator scores <80% for prescribing ACE-i/ARBs, statins and phosphate binders when needed, and >10% for potentially unsafe prescribing of vitamin D, metformin and digoxin. PQIs are also used to compare healthcare providers. With an estimated prevalence of 4% of CKD patients in primary care,⁴⁵ most of these indicators should not be used to compare scores of individual general practitioners. Moreover, the indicators focusing on treatment of MBD and unsafe vitamin D prescribing may not be relevant for primary care, since <2% of patients from the source population were eligible. These indicators can be more relevant for a secondary care population.¹⁷

Of note, the level of evidence supporting some indicators is higher than for others. In patients with CKD, multiple (cardiovascular and renal) outcomes need to be considered. In addition, many large trials do not exclusively include patients with CKD. For these reasons, we included indicators based on evidence from randomized clinical trials or meta-analysis (level A) and from observational studies, case-control studies and case-report (level B). When assessing the indicators, the expert panel sometimes decided to adapt the definitions of an indicator, based on their knowledge and experience, to make them more useful for practice. For example, indicator 2b was defined during the consensus meeting to differentiate between patients with and without diabetes. As such, the indicators provide insight into prescribing for CKD patients at the level of a healthcare provider or organization but should not be seen as an evidence-based assessment of appropriate care at individual patient level. Also, the focus of our indicators is the prescribing behaviour of a healthcare provider and not the actual use of drugs by patients. This is particularly relevant for indicators that include drugs, such as NSAIDs, that are available over the counter. The PQIs are not intended to signal inappropriate use of such drugs. Furthermore, several of the safety indicators include a large group of CKD patients in the denominator, only excluding patients in whom such drug prescribing is considered safe. As a consequence, the indica-

tor outcome can be close to 0% and appear non-informative. In such cases, the nominator may be more informative, providing the absolute number of patients who may be exposed to medication that should be avoided.

Several strengths and limitations should be considered. First, as is the case with any consensus method, the results may depend on the selected panel. Our expert panel consisted of twelve experts from three relevant disciplines, namely nephrology, general practice and pharmacy, equally represented. Our intention was to reach consensus across these disciplines on indicators intended for primary and secondary care. From general practice, we invited professionals who either contributed to the transmural guideline for the treatment of CKD or who conducted scientific research or training related to this topic. The total number of participants satisfies the requirement according to the RAM to include 7-15 experts to the panel.³⁵ Using more experts may impede the consensus meeting, which is an important round for making essential changes to the indicators. Per discipline, however, the number of experts was limited. Two pharmacists and one nephrologist could not attend the consensus meeting but their comments and suggestions were voiced by the moderator. All indicators were discussed, allowing for consensus, as well as indicators receiving sufficient scores in the first round. In the third round, all experts assessed the final list of indicators. Second, the indicators were based on recommendations from national evidence-based guidelines for clinical practice.^{4,22-24} The recommendations in these Dutch guidelines are similar to those in other international guidelines, such as proposed by the European Renal Best Practice, the Kidney Disease Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative guidelines.^{5-7,25-31} This makes our indicators useful for other countries. The PQIs, however, should be updated when guidelines are updated. Thirdly, we used a single eGFR measurement to define the CKD stage. Using two measurements gives more precision in classifying the CKD stage, thereby decreasing false selection of patients for the indicators.⁴⁶ Our sensitivity analysis showed that similar outcomes were obtained for all but one indicator. Finally, we tested the operational validity of the indicators in a primary care cohort, while some of the indicators, especially those measuring medication need for MBD, may be more relevant for secondary care.

In conclusion, a set of sixteen PQIs for CKD stages 3-5 patients was developed and validated using the RAM method. The indicators focus on medication need and medication choice for hypertension, albuminuria, MBD, statin prescribing and on medication safety. The indicators can be used to point out priority areas for improvement. Due to the small number of patients with CKD stages 3-5 in a primary care practice, these indicators cannot be used for benchmarking of individual healthcare providers in primary care. At practice level, the indicators

can be used for evaluation and for giving feedback to healthcare providers on the quality of prescribing. The safety indicators might also be used by healthcare providers in an alerting system. Further validation of the PQIs usefulness in a secondary care cohort is needed.

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