English summary

Chronic kidney disease (CKD) and type 2 diabetes (T2D) are conditions with a (potentially) high burden of disease worldwide, in terms of prevalence, suffering of individual patients, and costs for society. These conditions also carry a high burden of treatment. Pharmacotherapy is a major pillar of chronic disease management in these conditions to control multiple intermediate targets, including blood pressure, dyslipidaemia, glycaemic control, proteinuria and electrolyte imbalances. To achieve the overall treatment aims of risk reduction and better quality of life of the patient, the quality of prescribing should be optimal. One way of assessing the quality of prescribing is by the use of prescribing quality indicators (PQIs). PQIs assess whether patients are prescribed according to the guidelines and give insight in the prescribing behaviour of healthcare providers. PQIs which are properly developed and validated can be used in assessing the quality of prescribing. This thesis is focused on the development and validation of two sets of PQIs: one for CKD and one for T2D care.

Part I: Quality of prescribing in chronic kidney disease

The aims of the first part of this thesis are to (I) give an overview of existing quality indicators to assess processes of CKD care with a systematic literature review, (II) develop and validate a set of PQIs for CKD care and (III) apply this set to assess the current quality of prescribing in CKD patients.

The review of existing process quality indicators used in research and daily practice showed that many indicators exist already (**Chapter 2**). The indicators found focused on monitoring of kidney function and vascular risk factors, treatment, drug safety, adherence and referral to a specialist. None of these indicators was sufficiently validated on all four assessed validities, i.e. content, face, operational and predictive validity. A few indicators were sufficiently validated on content, face and operational validity. These included some indicators focusing on monitoring of kidney function and vascular risk factors in patients with CKD, and some regarding prescribing focusing on underprescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors and inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs), nitrofurantoin and bisphosphonates.

In the second project (**Chapter 3**), we describe the process of development steps of a set of sixteen PQIs with an expert panel of general practitioners, nephrologists and pharmacists. This set is intended for assessing the quality of prescribing in both primary and secondary CKD care. The PQIs focus on prescribing of antihypertensives, RAAS inhibitors, statins and phosphate binders when recommended and the potential inappropriate prescribing of dual RAAS

blockade, erythropoiesis-stimulating agents (ESA), metformin, active vitamin D and NSAIDs. Some PQIs were discarded during the development phase. These included PQIs focusing on preferred prescribing of RAAS inhibitors among antihypertensives (without the presence of albuminuria), start of phosphate binders, underprescribing of vitamin D, iron supplements and ESA, monitoring of potassium when RAAS inhibitors and diuretics are used simultaneously and prescribing of an fixed-combination pill. After the development, the set was tested using the data of primary care patients with T2D and CKD from the Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT) database. The results showed that it was feasible to calculate all sixteen PQIs using the available data derived from a primary care database, although for some PQIs information was available of only a small number of patients. After this structured development process and based on these results, we concluded that this set of PQIs for CKD care has content, face and operational validity for primary care (table ES.1).

In a next step, the current quality of prescribing in a secondary care population was assessed by these new PQIs using data from three nephrology outpatient clinic, of which two are academic and one is non-academic (**Chapter 4**). The indicators on non-calcium containing or calcium-containing phosphate binders were not assessed, due to the limited number of included patients. Furthermore, due to limited availability of albumin/creatinine ratios, the indicators focusing on prescribing of RAAS inhibitors in the presence of diabetes and micro-albuminuria were not assessed, and proteinuria was used as a proxy for macro-albuminuria. The results showed low prescribing rates of RAAS inhibitors and statins when recommended, and high prescribing rates of active vitamin D when potentially inappropriate. Besides, several differences were observed between CKD stages. We observed less prescribing of recommended RAAS inhibitors in patients with CKD stage 5. On the other hand, in patients with CKD stage 3 we observed less prescribing of statins, but also less prescribing of potentially inappropriate active vitamin D and ESA. In addition, we also observed several differences between the outpatient clinics, even after stratification for CKD stage. This study showed it was feasible to calculate these PQIs using the available data derived from Hospital Information Systems. Therefore, we can conclude that this adapted set of PQIs also has operational validity in secondary care (table ES.1).

Table ES.1: Developed prescribing quality indicators for chronic kidney disease and their validity

	Validity				
			Operational		
Prescribing quality indicator	**Content**	**Face**	**1st†**	**2nd†**	**Predictive**
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)	√	√	√	√	0
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	√	√	√	√¶	0
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	√	√	√	-	0
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	√	√	√	√¶	0
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	√	√	√	-	0
4. The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin	√	√	√	√	0
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	√	√	√††	√	0
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	√	√	√††	0	0
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	√	√	√††	0	0
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)	√	√	√	√	0
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	√	√	√††	√	0
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	√	√	√	√	0

Table ES.1: Developed prescribing quality indicators for chronic kidney disease and their validity (continued)

	Validity				
			Operational		
Prescribing quality indicator	**Content**	**Face**	**1st†**	**2nd†**	**Predictive**
11. The percentage of patients with eGFR <30ml/min/1.73m^2 18 years or older, that is prescribed an NSAID	√	√	√	√	0
12. The percentage of patients with eGFR <30 ml/min/1.73m^2 18 years or older with diabetes#, that is prescribed metformin	√	√	√	√	0
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)	√	√	√	√	0
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	√	√	√	√	0

CKD: chronic kidney disease; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug.
† 1st: primary care, 2nd: secondary care. ‡ 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. ¶ These indicators were tested using proteinuria (>0.5 g/l urine) as a proxy for macro-albuminuria, since the albumin/creatinine ratio was only limited available. # Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs. †† These indicators showed operational validity, but included <2% of the source patient population and are therefore mainly suitable for internal evaluation. Content validity: √ = developed based on guidelines. Face/operational/predictive validity: √ = tested and valid; - = not valid; 0 = not tested.

Part II: Quality of prescribing in type 2 diabetes

The aims of the second part of this thesis are to (I) develop and validate a new set of PQIs for T2D in primary care with a focus on clinical action indicators, (II) test for possible associations between these PQIs and related intermediate patient outcomes and (III) test for possible associations between these PQIs and health-related quality of life in T2D patients.

A set of twenty PQIs for diabetes care was developed with an expert panel of internists and general practitioners (**Chapter 5**). The set includes PQIs focusing on treatment with glucose lowering drugs, antihypertensives, RAAS inhibitors and statins when recommended, and on potential inappropriate prescribing of

Table ES.2: Developed prescribing quality indicators for type 2 diabetes and their validity

	Validity			
Prescribing quality indicator	**Content**	**Face**	**Operational**	**Predictive[†]**
1. The percentage of patients with T2D between the ages 18 and 70 years with elevated HbA_{1C} level (>53 mmol/mol) in the previous year that started with glucose lowering drugs or that reached the HbA_{1C} target level (≤53 mmol/mol)	√	√	√[‡]	√
2. The percentage of patients with T2D between the ages 18 and 70 years on monotherapy metformin and an elevated HbA_{1C} level (>53 mmol/mol) in the previous year, that is intensified or that reached the HbA_{1C} target level (≤53 mmol/mol)	√	√	√	√
3. The percentage of patients with T2D between the ages 18 and 70 years with two or more non-insulin glucose lowering drugs and an elevated HbA_{1C} level (>53 mmol/mol) in the previous year that started with insulin or that reached the HbA_{1C} target level (≤53 mmol/mol)	√	√	√	√
4. The percentage of patients with T2D that started with metformin among all starters of oral glucose lowering drugs	√	√	√	0
5. The percentage of patients with T2D treated with metformin among all patients treated with glucose lowering drugs	√	√	√	0
6. The percentage of patients with T2D treated with metformin and an SU-derivative among all patients treated with two non-insulin glucose lowering drugs	√	√	√	0
7. The percentage of patients with T2D that started with gliclazide among all starters of an SU-derivative	√	√	√	0
8. The percentage of patients with T2D between 55 and 80 years old that is treated with statins	√	√	√	√
9. The percentage of patients with T2D between the ages 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	√	√	√	√
10. The percentage of patients with T2D between the ages 18 and 80 years treated with simvastatin and an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	√	√	√	√
11. The percentage of patients with T2D between the ages 18 and 70 years of age and an elevated systolic blood pressure (>140 mmHg) in the previous year that started with antihypertensives or reached the systolic blood pressure target level (≤140 mmHg)	√	√	√	√

Table ES.2: Developed prescribing quality indicators for type 2 diabetes and their validity (continued)

	Validity			
Prescribing quality indicator	**Content**	**Face**	**Operational**	**Predictive†**
12.The percentage of patients with T2D between the ages 18 and 70 years treated with monotherapy antihypertensives and an elevated systolic blood pressure (>140 mmHg) in the previous year, that is treatment was intensified or that reached the systolic blood pressure target level (≤140 mmHg)	√	√	√	√
13. The percentage of patients with T2D and treated with two or more antihypertensives that is treated with an ACE-i or ARB	√	√	√	-
14. The percentage of patients with T2D between the ages 18 and 70 years with micro- or macro-albuminuria§ in the previous year that started with an ACE-i or ARB or that returned to normo-albuminuria§	√	√	√‡	√
15. The percentage of patients with T2D treated with antihypertensives and micro- or macro-albuminuria§ that is treated with an ACE-i or ARB	√	√	√	-
16. The percentage of patients with T2D that started with an ACE-i among all patients that started with RAAS treatment	√	√	√	0
17. The percentage of patients with T2D that is treated with glibenclamide among all patients treated with SU-derivatives	√	√	√	0
18. The percentage of patients with T2D and an eGFR <30 ml/min/1.73m^2 that is treated with metformin	√	√	√‡	0
19. The percentage of patients with T2D 80 years or older and a normal HbA_{1c} level (<53 mmol/mol) that is treated with two or more glucose lowering drugs	√	√	√	0
20. The percentage of patients with T2D that is treated with a combination of an ACE-i and an ARB (dual RAAS blockade) among all patients with RAAS treatment	√	√	√	0

T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; SU-derivative: sulphonylurea derivative; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate.

† Predictive validity with intermediate patient outcomes. ‡ These indicators were operational valid, but included <2% of the source patient population and are therefore mainly suitable for internal evaluation. § Micro-/macro-albuminuria is defined as albumin/creatinine ratio ≥2.5 mmol/l for males and ≥3.5 mmol/l for females. Normo-albuminuria is defined as albumin/creatinine ratio <2.5 mmol/l for males and <3.5 mmol/l for females. Content validity: √ = developed based on guidelines. Face/operational/predictive validity: √ = tested and valid; - = not valid; 0 = not tested.

glibenclamide, metformin, dual RAAS blockade and potential overtreatment with glucose lowering drugs. Eight of the PQIs in the set are clinical action indicators focusing on timely start or intensification of recommended treatment. During the development, several PQIs were discarded. Those excluded were volume-indicators on the use of glucose lowering drugs and PQIs on appropriate prescribing of glucose lowering drugs in elderly T2D patients, preferred use of simvastatin, start of antihypertensives stratified to age and blood pressure level, potential inappropriate prescribing of a combination of pioglitazone and insulin and intensification of antihypertensives in elderly patients, monitoring of potassium when RAAS inhibitors or diuretics are prescribed, flu vaccination and treatment adherence for glucose lowering drugs, lipid lowering drugs and antihypertensives. After development, the set was tested in two databases of patients with T2D from primary care (GIANTT and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC)). The results showed that all twenty PQIs were feasible to assess the quality of prescribing using the available data, although some PQIs included a small number of patients due to limited availability of data. Following these results and their structured development, we concluded that this set of PQIs for T2D care has content, face and operational validity in primary care (table ES.2).

Thereafter, the associations of several PQIs with intermediate patient outcomes were tested (**Chapter 6**). For this study, eleven PQIs were selected which were assumed to have an influence on levels of glycated haemoglobin (HbA_{1c}), low-density lipoprotein-cholesterol(LDL)-cholesterol, blood pressure or prevalence of albuminuria. The tested PQIs were the eight clinical action indicators, one indicator on current prescribing of statins and two on current prescribing of RAAS inhibitors. The results showed that the clinical action indicators on glucose lowering drugs were significantly associated with lower HbA1c levels one year later. Similarly, both the clinical action indicators and the indicator on current prescription of statins, both clinical action indicators on antihypertensive treatment and the clinical action indicator on RAAS inhibitor treatment showed significant associations with respectively lower LDL-cholesterol levels, lower blood pressure and lower risk of albuminuria. The two indicators on current prescription of RAAS inhibitors were not associated with the risk of albuminuria one year later. Therefore all tested PQIs except for the ones on current prescription of RAAS inhibitor showed predictive validity with intermediate patient outcomes (table ES.2).

Finally, we assessed possible associations of guideline-adherent prescribing and disease-specific medication burden with health-related quality of life (HRQoL) in T2D patients (**Chapter 7**). To assess guideline-adherent prescribing, seven PQIs were selected. This selection was based on the data availability of the patients within the e-Vita/ZODIAC study. For most of them, data of multiple years were un-

available and calculating the clinical action indicators was therefore not feasible. The selected PQIs were three indicators on current prescribing of statins and RAAS inhibitors when recommended and four PQIs on potential inappropriate prescribing of glibenclamide, metformin and dual RAAS blockade and potential overprescribing of glucose lowering drugs in the elderly T2D patients are used. Disease-specific medication burden was assessed using a modified version of the Medication Regimen Complexity Index. The disease-specific medication included glucose lowering drugs, statins and antihypertensives. HRQoL was assessed through both the Euroqol 5 dimensions 3 levels (EQ5D-3L) questionnaire and the World Health Organization Well-Being Index. Both questionnaires are short, including five questions, which gives an indication of the general and mental HRQoL respectively. A large proportion of the patients scored high on the EQ5D-3L and the outcome was therefore dichotomized. Guideline-adherent prescribing assessed by the seven PQIs was not significantly associated with HRQoL in T2D patients. Also, no significant association was found between disease-specific medication burden and HRQoL. The power of detecting an association with HRQoL, however, was limited by low numbers of included patients. Moreover, the dichotomization of the EQ5D-3L may also have reduced the power to detect associations. Therefore, we concluded that at this time, there was no evidence for guideline-adherent prescribing or medication burden influencing the quality of life in T2D patients.

Conclusion

This thesis resulted in two sets of valid PQIs for assessing the quality of prescribing in CKD and T2D care. Several of these PQIs are ready for implementation in quality improvement initiatives, such as audit-and-feedback programs. Some of the PQIs need more testing, especially for predictive validity (table ES.1 and ES.2). Nonetheless, this thesis denotes important steps towards a better assessment of the quality of prescribing and optimal pharmacotherapy in patients with CKD or T2D.