GENERAL INTRODUCTION
Prevention and treatment of diseases and disease complications are central in healthcare. Evidence-based clinical guidelines describe certain processes of healthcare, including diagnosing, monitoring and treating patients. These guidelines are based on previous research showing the benefits and risks of these processes of care and, in absence of scientific evidence, clinical expertise or opinions. To evaluate whether guidelines are followed and to assess the quality of healthcare, quality indicators are used. These indicators can be used both for internal and external evaluation. Quality indicators can be classified into structure, process and outcome indicators. Structure indicators focus on organizational aspects, such as staff availability, equipment and policies. Process indicators focus on the actual care delivery, such as the conduct of physical examinations, laboratory measurements and prescribing. Outcome indicators focus on these health outcomes, such as risk factor levels, disease complications or quality of life. Structure aspects can influence the likelihood of a process to occur. These processes can in turn have an influence on the health outcome of patients.

Quality of prescribing

One important process of care is the prescribing behaviour of healthcare providers. The quality of prescribing comprises of several elements. Some important elements are underprescribing, overprescribing, use of preferred drugs and medication safety.

Underprescribing means that based on guidelines, patients should (be recommended to) receive a certain treatment, but are not receiving the treatment. Over-prescribing on the other hand, means that patients receive a certain treatment which is unnecessary. Moreover, some drugs are preferred over others within the same drug class, because of health benefits or economic reasons. Medication safety is an element that includes avoiding certain potentially unsafe or inappropriate drugs or dosages and avoiding drug-drug interactions.

To assess these elements of prescribing behaviour, prescribing quality indicators (PQI) are used. PQIs are ‘measurable elements of prescribing performance for which there is evidence or consensus that they can be used to assess the quality.’ PQIs can be drug-, disease- or patient-oriented. Drug-oriented PQIs assess quality of prescribing based only on drug prescribing/dispensing data without taking into account any other aspects such as indications or comorbidities. These kinds of PQIs focus on the use of preferred drugs within a drug class or the occurrence of drug-drug interactions. Disease-oriented PQIs take into account indications and comorbidities of patients and assess to what extent the patients are under-
overprescribed with recommended treatment or whether inappropriate drugs are prescribed. Patient-oriented PQIs go a step further and take into account patient-specific information such as age and severity of the disease to assess treatment suitable for a specific patient.

As with all quality indicators, PQIs must be validated before being used in daily practice. Several types of validation are considered essential, including content, face, operational and predictive validity. Content validity reflects whether the definitions of the PQI correctly follow clinical guidelines. Face validity reflects whether a group of experts in the field accepts the PQI as being valid. Using an expert panel representative of the field during the development stage of the indicators will assure face validity. Operational validity reflects whether the PQIs can be measured using available data from clinical practice. Finally, predictive validity reflects whether the PQI is predictive of a relevant clinical outcome. In other words, calculating PQIs with predictive validity and improving on the PQI scores is beneficial for the patient. This can be shown when there is a positive relationship between better PQI scores and improved intermediate or hard clinical endpoints. Previous research has shown that using PQIs to give feedback to the healthcare providers has led to increased quality of prescribing.

Chronic kidney disease

Chronic kidney disease (CKD) is a condition with a potentially high burden of disease. Clinical guidelines for CKD recommend monitoring of disease progression and factors such as kidney function, blood pressure and albuminuria. In addition, these guidelines include recommendations on treatment with blood pressure and albuminuria lowering drugs, statins, and phosphate binders. Furthermore, several types of drugs should be avoided in certain situations. Adhering to these guidelines should reduce the risk of end-stage renal disease, cardiovascular morbidity and mortality, but also the risk of adverse drug reactions.

In CKD care, assessing the quality of care is relatively new with few quality assessment initiatives compared to fields with more experience such as type 2 diabetes. Previously, a set of quality indicators has been developed for CKD care and some quality indicators are used in audit-and-feedback programs. These quality indicators are mainly focused on monitoring kidney function and risk factor levels. Although quality of prescribing is an important aspect of quality of care, up to now only a few indicators focus on prescribing. The PQIs include disease-oriented indicators focusing on underprescribing of anaemia treatment and albuminuria lowering drugs and inappropriate prescribing of non-steroidal
anti-inflammatory drugs and bisphosphonates. These PQIs have been developed and validated through a structured process,\textsuperscript{12,14} but many areas of prescribing are still not covered. Therefore, it is evident that a comprehensive and properly validated set of PQIs to assess quality of prescribing in patients with CKD is lacking and needed.

**TYPE 2 DIABETES**

Like CKD, type 2 diabetes (T2D) is a chronic condition with a potential high burden of disease, and its prevalence is increasing worldwide.\textsuperscript{15} Clinical guidelines for T2D recommend monitoring of risk factors such as blood glucose levels, blood pressure, cholesterol levels and albuminuria.\textsuperscript{16,17} In addition, stringent start and intensification of treatment steps for glucose, blood pressure, and albuminuria lowering drugs and statins are recommended in certain patients; furthermore, recommendations are made as well with regards to the avoidance of certain drugs in certain situations. Adhering to these recommendations should reduce the risk of developing cardiovascular, renal and other diabetes complications and mortality as well as reduce the risk of adverse drug reactions.

The development of quality indicators for T2D started in the 1990s.\textsuperscript{18} Since then, many quality indicators have been developed, validated and used in audit-and-feedback programs. Most quality indicators to assess quality of T2D care are focused on monitoring risk factors and achieving target levels, whereas few focus on the quality of prescribing.\textsuperscript{19} Previously, specific PQIs have been developed to assess quality of prescribing in patients with T2D.\textsuperscript{20} These PQIs focus on prescribing glucose, blood pressure and albuminuria lowering drugs, statins and acetylsalicylic acid, but none of the PQIs focus on medication safety. Moreover, quite often, such PQIs have not been implemented in practice nor updated to the most recent guidelines and recommendations.

PQIs have different structures with regard to the time aspect; most of the currently used PQIs are cross-sectional indicators, using data from one point in time to assess quality of prescribing. On the other hand, some of them are clinical action indicators, i.e. whether healthcare providers act adequately in patients with elevated risk factor levels. These indicators “award” actions of healthcare providers when the patient reaches a target level with or without clinical action, or when the healthcare provider takes the appropriate clinical action, while excluding patients for whom the action is inappropriate.\textsuperscript{18,21} Clinical action indicators are patient-oriented indicators and have shown to be more clinically meaningful than cross-sectional indicators.\textsuperscript{22} These clinical action indicators also fit into the
current views on individualizing healthcare. Previous research showed that improvements in clinical action indicators for treatment of T2D were also associated with better patient outcomes. A new and updated set should therefore incorporate individualized care, including the preferred clinical action indicators whilst also taking into account patient differentiation.

**RESEARCH AIMS AND OUTLINE OF THE THESIS**

PQIs are the central focus of this thesis. The thesis will describe different aspects of the development, validation and application process of PQIs. The aim of the first part of this thesis is to provide an overview of existing process quality indicators for CKD care, and to develop a new set of PQIs for CKD care. This set will be tested for content, face and operational validity and applied to assess the current quality of prescribing in CKD care.

The aim of the second part of this thesis is to develop and validate a new set of PQIs for T2D care. Besides the testing for content, face and operational validity, the second part will also focus on testing the predictive validity of the newly designed PQIs. With these sets, the current quality of prescribing in CKD and T2D care can hopefully be assessed. This information, when validated as being of consequence, can in turn be used in audit-and-feedback programs to identify priority areas of improvement and improve the quality of prescribing.

**PART I: QUALITY OF PRESCRIBING IN CHRONIC KIDNEY DISEASE**

Chapter 2 presents a systematic literature review of studies focusing on process quality indicators for CKD care. The objectives of this review are to (I) identify existing quality indicators intended for assessing processes of care in patients with CKD and (II) identify the quality indicators that have sufficient content, face, operational and predictive validity. Chapter 3 describes the development and operational validation of a set of PQIs for CKD care. The set is developed by means of a structured process based on clinical guidelines and expert experience. After development, the set is tested for operational validity in patients with CKD using a large database of primary care patients with T2D, the Groningen Initiative to Analyse Type 2 diabetes (GIANTT). In chapter 4, this set of PQIs for CKD is used to assess the quality of prescribing in outpatient clinics in the Netherlands. This study uses data from two academic and one non-academic clinics. In particular, differences in quality of prescribing among different stages of CKD and different clinics are examined.
PART II: QUALITY OF PRESCRIBING IN TYPE 2 DIABETES

Chapter 5 describes the development and operational validation of a set of PQIs for T2D care. In addition to PQIs focusing on current prescribing, also clinical action indicators focusing on the start and intensification of treatment are included in this set. This set is also developed using a structured method based on clinical guidelines and expert experience. For operational validity testing, the GIANTT and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) databases are used. In chapter 6, several of the developed PQIs are tested on possible associations with intermediate patient outcomes. The focus of this chapter is on the clinical action indicators regarding timely start and intensification of glucose, blood pressure and albuminuria lowering drugs and statins and the clinical outcomes glycated haemoglobin, systolic blood pressure, albuminuria and low-density lipoprotein-cholesterol. The association between guideline-adherent prescribing and health-related quality of life is assessed in chapter 7 using data from the e-Vita/ZODIAC study. In this chapter, besides PQIs focusing on current use of albuminuria lowering drugs and statins, PQIs on medication safety are also tested. In addition, the association between medication burden and health-related quality of life is assessed.

Finally, the main findings of these studies are discussed in light of their implications for research and clinical practice in chapter 8.
Chapter 1

REFERENCES


Part I
QUALITY OF PRESCRIBING IN CHRONIC KIDNEY DISEASE