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GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Chronic kidney disease

Healthy kidneys remove waste products and excess water from the body, regulate mineral composition and acidity of the blood, and produce enzymes and hormones. When there are abnormalities in the kidney structure or function for at least three months, with implications for health, patients are diagnosed with chronic kidney disease (CKD).[1] With a worldwide prevalence of 13.4% CKD is a major public health problem.[2]

CKD is classified based on cause, estimated glomerular filtration rate (eGFR) category, and albuminuria category.[1] In general, we define five CKD stages. In stage 1 patients are asymptomatic, have a normal eGFR and only a mildly increased albuminuria, while stage 5 CKD is characterized by kidney failure with an eGFR<15ml/min/1.73m^2. Stage 5 CKD is also called end-stage renal disease (ESRD) and in this stage renal replacement therapy (RRT) can become necessary to replace the function of the kidney and thereby improve quality of life and postpone death. RRT consists either of receiving a kidney transplantation, or dialysis. Although kidney transplantation is the best treatment for ESRD, not all patients can receive a donor kidney due to waiting lists, severe cardiovascular morbidity, or unsuitability to undergo surgery.[3, 4] These patients depend on dialysis for survival.

There are two dialysis treatment modalities; hemodialysis and peritoneal dialysis. During hemodialysis, waste products and excess water are removed from the body by using a non-biological membrane in an artificial kidney (hemodialysis machine) outside the body. Patients undergo this treatment approximately three times a week for several hours. Peritoneal dialysis is a treatment that uses the peritoneum as an endogenous membrane to remove waste products and excess water. This is done via a catheter implanted in the abdominal cavity of the patient, through which fluid has to be instilled and refreshed several times a day. Peritoneal dialysis in general takes place at home opposed to hemodialysis which most often takes place at the hospital.

Pre–dialysis stage

Ideal preparation for RRT starts with referral to a multidisciplinary team when reaching CKD stage 4 (eGFR<30 ml/min/1.73m^2), for so-called pre-dialysis care, to optimize care and slow down CKD progression. During pre-dialysis, patients are in the care of a nephrologist, nurse, dietician, and a social worker at an outpatient clinic. This team tries to retard kidney function decline by treating risk factors for kidney function decline, prevents and treats complications of CKD, and educates patients with regard to RRT. This approach has shown to be effective in multiple studies.[5-7] Patients on pre-dialysis care for example, have a lower risk of starting dialysis as compared with patients on regular care. After starting dialysis, patients who have received pre-dialysis care have a lower mortality as compared with patients on regular care.[5]

In this advanced stage of CKD, biological processes are changing and therefore treatment effects are changing too. Unfortunately, trials and large cohort studies, both in general and in CKD patients, often exclude pre-dialysis patients or include a very small proportion of

these patients for whom results are not analysed separately.[8-10] As a consequence there is a lack of knowledge on the optimal treatment of several risk factors for kidney function decline in pre-dialysis patients. More knowledge could positively affect the prevention and postponing of negative outcomes in this patient group.

Health related quality of life

Traditional outcomes in patients with CKD are mortality, morbidity, start of dialysis, and kidney function decline. However, patients with CKD suffer from a great range of physical and psychological symptoms and are known to have a lower health related quality of life (further referred to as quality of life), especially in the later stages of CKD.[11, 12] Focus is shifting from only attempting to improve prognosis (the traditional outcomes) in CKD stage 4-5 patients, towards also improving symptom burden and quality of life. Although these latter outcomes seem more subjective and may seem less specific as compared with traditional outcomes, for patients, especially with chronic conditions, these are very relevant outcomes representing the burden of their disease in daily life. Insights in these outcomes can increase the understanding of treatment effects and will improve patient care.[13, 14] In addition, a low quality of life in CKD stage 4-5 patients is associated with an increased risk of ESRD and mortality.[15, 16] In dialysis patients a low quality of life is associated with hospitalization, lower residual kidney function and mortality.[17, 18]

Quality of life can be defined in many ways, but a very common definition is “the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient” which is determined by an individual’s capacity to cope and to adapt.[19, 20] Quality of life can be measured with questionnaires completed by patients. Currently, several measurement tools are used, of different sizes and with different content. Not all of them are developed for the same population. Therefore, these questionnaires should be validated before using them in a population that differs from the original population in which the questionnaire was developed (**chapter 3**).

Several clinical variables are considered to be determinants of quality of life.[12, 21-24] However, kidney function, the most important biological factor in CKD and determinant for many treatment choices, does not influence quality of life as much as expected.[12, 25] A possible explanation for this can be found in the conceptual model by Wilson ***et al***. which portrays quality of life as the result of a chain of consecutive elements, passing from biological variables through symptom status to quality of life.[26] From this model it could be inferred that factors earlier in the chain – affecting quality of life through more intermediate variables – will have a weaker effect. The effect of biological factors, such as kidney function, is mediated by symptoms, which may thus be more important determining quality of life (**chapter 2**).

Cardiovascular risk factors and traditional outcomes

Even though there appears to be a careful shift of focus towards quality of life, treatment is still primarily aimed at delaying progression of the disease, and thus delaying kidney function decline and trying to prevent the need for a kidney transplant or start of dialysis.[27] Treatment is aimed at risk factors that are associated with disease progression as well as general lifestyle changes. With hypertension and diabetes mellitus causing over 50% of all CKD cases, many interventions are aimed at these diseases and their associated risk factors.[28]

As a result, many of the treatment targets in CKD address cardiovascular disease. As CKD progresses there is an increasing risk of cardiovascular disease and mortality. For example, patients with CKD stage 4 have a three times higher cardiovascular mortality risk as compared with individuals without CKD.[28] It is thought that addressing cardiovascular risk factors may directly and indirectly slow down CKD progression. Important treatment targets and thus risk factors for CKD and cardiovascular disease are blood pressure, the renin-angiotensin system (RAS), metabolic parameters (blood sugar, uric acid, and acidosis), and dyslipidemia (**chapter 4, 5 and 6**).[27] Non-traditional risk factors, such as FGF-23 and hyperhomocysteinemia, are beyond the scope of this thesis.

When a patient has reached ESRD, the treatment aim shifts towards preventing cardiovascular morbidity and postponing death. During dialysis, mortality rates are up to eight times higher as compared with persons without ESRD in the same age range and of the same sex.[28-30] With increasing age the difference in mortality rate becomes smaller but remains substantial. Cardiovascular events are the main cause of death, and the incidence of coronary artery disease, congestive heart failure, and left ventricular hypertrophy is elevated in these patients.[31] Therefore, research into cardiovascular risk factors remains an important topic in dialysis patients (**chapter 7**).

Aims of this thesis

The aims of this thesis were firstly to provide insight in quality of life as an outcome in pre-dialysis patients by investigating appropriate ways to measure this construct and by investigating factors affecting quality of life, and secondly to increase the understanding of the different associations between several cardiovascular risk factors and traditional outcomes in pre-dialysis and dialysis patients. The results can improve pre-dialysis patient care directly, provide supporting evidence for current guidelines for pre-dialysis and dialysis patients, or provide information to change current guidelines.

Description of the cohorts used in this thesis

EQUAL

The European Quality study on treatment in advanced chronic kidney disease (EQUAL), is a prospective cohort study performed in elderly patients with CKD progressing towards

ESRD in six European countries (the Netherlands, Sweden, Germany, United Kingdom, Italy, Poland). Study enrolment started in 2012 end will continue until 2020. Patients aged ≥65 years and an eGFR ≤ 20 ml/min/1.73m^2 (stage 4 and 5 CKD) for a maximum of six months are included in this study. These patients are followed for at least 4 years. A subset of the included patients (1500 patients, all patients included before December 2015) was used to perform the study in **chapter 2**.

PREPARE

The PREdialysis Patient Record (PREPARE) study is a multicenter follow-up study in 1049 patients aged ≥18 years, starting specialized pre-dialysis care in the Netherlands. The PREPARE study consists of a retrospective and a prospective part. In the retrospective part (PREPARE-I), incident patients who started pre-dialysis care (stage 4 CKD) in one of eight participating nephrology outpatient clinics between 1999 and 2001 were included. In the prospective part (PREPARE-II), incident patients who started pre-dialysis care in one of 25 participating nephrology outpatient clinics between 2004 and 2011 were included. The PREPARE-II population was used in **chapter 3, 4 and 5**. The entire PREPARE study was used for **chapter 6**.

NECOSAD

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective Dutch multicenter study in 38 dialysis centers, which included incident ESRD patients, aged ≥18 years, starting dialysis between January 1997 and January 2007. Over 2000 dialysis patients were included. After inclusion, patients were followed over time during which events of death and censoring due to other reasons were recorded. Follow up of events of death are continued to this day via the national registry. The NECOSAD population was used in chapter 7.

Outline of this thesis

In **chapter 2** we determined the relation between symptoms and quality of life in pre-dialysis patients.[12] The association of quality of life with negative outcomes, such as an increased risk of ESRD and mortality, emphasizes its importance and thereby the need to investigate determinants of quality of life in CKD patients.[15-18]

Since quality of life is an important outcome there is a need for adequate and efficient questionnaires to measure this. The most frequently used questionnaire to assess quality of life is the Short Form 36 (SF-36). The SF-36 measures health on eight dimensions as well as overall physical- and mental component scores.[32] However, the SF-36 can take up to 12 minutes to complete and is often considered too long for inclusion in large scale monitoring efforts. Therefore, shorter questionnaires are needed. In **chapter 3** we validated two of the most often used shorter quality of life questionnaires, the Short Form-12 (SF-12) and the EuroQol questionnaire (EQ-5D), in pre-dialysis patients.

In **chapter 4** we focused on the traditional outcome start of dialysis. We investigated the association between dyslipidemia and start of dialysis. This is one of the main risk factors aimed at in the treatment to delay CKD progression, although knowledge on the effects of dyslipidemia in pre-dialysis patients is lacking.

In **chapter 5 and 6** we investigated associations with the traditional outcomes start of dialysis and kidney function decline in pre-dialysis patients. In **chapter 5** the association with the risk factors angiotensin converting enzyme inhibitor use or/and angiotensin II receptor blocker use was investigated, which influence the RAS, an important target in the treatment to delay CKD progression. In **chapter 6** we investigated the association between vitamin K antagonists and start of dialysis and kidney function decline in pre-dialysis patients.

In **chapter 7** we shift focus from pre-dialysis to dialysis patients. We investigated the risk factor vitamin K antagonist again, but this time we investigated the association with mortality in dialysis patients.

In **chapter 8** the results of the previous chapters are discussed and summarized.

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