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General introduction

This doctoral thesis is about ethnic differences in survival on chronic dialysis treatment in Europe. This introductory chapter provides background information on chronic kidney disease (CKD) and chronic dialysis treatment, describes the rationale for studying ethnic differences in survival on dialysis and describes the general objective and outline of this thesis. Finally, it gives an overview of the data that were used to perform the analyses.

CHRONIC KIDNEY DISEASE

CKD is a major public health problem: up to 11% of the general adult population has some degree of CKD and the proportion of the population affected by CKD is increasing rapidly.^{1,2} CKD is defined as either sustained kidney damage or decreased kidney function for at least three months.³ The kidneys are paired retroperitoneal organs situated in the posterior part of the abdomen. They perform the essential functions of (1) removing waste products and excess water from the body, (2) regulating the volume, mineral composition and acidity of the blood, and (3) producing enzymes and hormones.⁴ The main causes of CKD are diabetes mellitus, hypertension/renal vascular disease and glomerulonephritis.⁵

The severity of CKD is classified into 5 stages based on markers of kidney damage and level of kidney function.³ Only a small proportion of patients with CKD reach the final stage of CKD (CKD stage 5 or end-stage renal disease (ESRD)).⁶ In the final stage of CKD, kidney function is decreased to below 15 mL per min per 1.73 m² (normal kidney function ≥ 90 mL/min per 1.73 m²) and renal replacement therapy is needed to sustain life.³ In 2008, the incidence rate and prevalence of renal replacement therapy for ESRD in Europe were 122 per million population (pmp) and 644 pmp, respectively.⁵

Renal replacement therapy is either given by kidney transplantation or chronic dialysis treatment. Kidney transplantation is regarded as the optimal renal replacement therapy.^{7,8} However, not all ESRD patients are treated with kidney transplantation, due to waiting lists for matching kidneys⁹, graft failure after kidney transplantation¹⁰, or ineligibility to undergo surgery.¹¹ For these ESRD patients without a functioning transplanted kidney, survival depends upon chronic dialysis treatment.

CHRONIC DIALYSIS TREATMENT

Chronic dialysis treatment is given by hemodialysis or peritoneal dialysis. Patients on hemodialysis are treated approximately three times a week for three to eight hours. During hemodialysis, waste products in plasma diffuse across the non-biological membrane of an artificial kidney outside the body. These waste products and excess water are removed from the body.⁴ In peritoneal dialysis, the peritoneum is used as an endogenous dialysis membrane to remove waste products and excess water. For this type of dialysis, a catheter is implanted in the abdominal cavity of the patient, through which fluid has to be instilled and refreshed several times a day.⁴

Dialysis treatment was introduced in the 1960s.¹² Since then, several factors have been identified that are associated with mortality in dialysis patients, such as underlying renal disease, the presence of comorbid conditions, metabolic abnormalities, nutritional status, adequacy of dialysis, dialysis session length and psychosocial factors.¹³⁻¹⁸ These insights have led to the identification of modifiable risk factors for mortality and consequently to the improvement of dialysis treatment.¹⁹

Although great progress has been made in medical and technical aspects of dialysis treatment, mortality rates of dialysis patients remain high. One and five years after the start of dialysis treatment, respectively, 20% and 60% of the patients have died.²⁰ Compared with the general population, dialysis patients between the age of 25 and 35 years have a 500-fold increased risk of death and patients aged ≥ 85 years have a 5-fold increased risk.^{21;22} Thus, the improvement of dialysis treatment warrants further scientific attention.

ETHNIC DIFFERENCES IN SURVIVAL ON DIALYSIS

In 1987, Held et al. described that black American patients had a lower risk of death than non-black Americans while on dialysis.²³ Since then, numerous North-American studies have reported on ethnic differences in survival on dialysis. These studies showed that black and Asian patients have a better survival compared with white patients.²⁴⁻³³

Possible explanations for ethnic survival differences on dialysis have been studied extensively, but are far from understood.²⁴⁻³³ Identifying factors responsible for ethnic differences in survival on dialysis is of great importance for two reasons. Firstly, this may result in the identification of specific risk factors for mortality in the whole dialysis population. Secondly, this could raise new ideas or have implications for improved renal replacement therapy for specific ethnic groups. Such a development is important because (1) Western societies are becoming increasingly ethnically diverse^{34;35}, and (2) non-white individuals are overrepresented among dialysis patients due to their increased incidence of ESRD compared with whites.³⁶

The majority of studies exploring ethnic differences in survival on dialysis derive from the North-American subcontinent; scant data exist from Europe. However, there are important differences between the North-American subcontinent (particularly the US) and Europe, such as differences in ethnic composition and migration history³⁷⁻³⁹, access to health care facilities⁴⁰⁻⁴², incidence rates for ESRD^{5;20}, comorbid conditions⁴³, and mortality in the general population and dialysis population.^{44;45} Therefore, it is unclear whether ethnic differences in survival on dialysis also exist in European countries. Information on this topic is important as it may help to identify factors responsible for ethnic differences in survival on dialysis.

OBJECTIVE AND OUTLINE OF THIS THESIS

The general objective of this thesis is to investigate to what extent and why ethnic differences in survival on dialysis exist in countries in Europe. Special emphasis is put on the role of demographic, clinical and psychosocial factors in ethnic differences in survival on dialysis.

In **chapter 2**, an overview is provided of studies on non-white dialysis patients within Europe. Special emphasis is placed on the proportion of non-whites among patients on dialysis compared with the general population, patient characteristics and survival.

In **chapter 3**, differences in survival are addressed between immigrant and native Dutch dialysis patients who started chronic dialysis treatment in an urban medical center in the

Netherlands. It is investigated whether possible survival differences could be explained by demographic and clinical characteristics.

Based on the results presented in chapter 3, we hypothesized that ethnic differences in survival on dialysis could be explained by psychosocial factors. Before investigating this, we studied whether the 5-item mental health inventory (MHI-5), which is a subscale of the SF-36 quality of life questionnaire⁴⁶, is a valid screening instrument for depressive symptoms in dialysis patients. The results of this study are presented in **chapter 4**. Furthermore, we studied the association between depressive symptoms, as measured by the MHI-5, and short-term, medium-term and long-term mortality in incident dialysis patients. The results of this study are presented in **chapter 5**.

In **chapter 6**, we explored whether psychosocial factors indeed play a role in ethnic differences in survival on dialysis. To this end, we compared the survival of white, black and Asian incident chronic dialysis patients in a multicenter setting in the Netherlands and investigated whether ethnic differences in survival could be explained by patient characteristics, including psychosocial factors.

In the studies presented in chapters 3 and 6, non-white groups were relatively small and therefore effect modification could not be tested. Consequently, it was assumed that the effect of a covariate on mortality was equal among ethnic groups. Therefore, an analysis was done in a much larger series of patients from the United Kingdom Renal Registry (UKRR). In **chapter 7**, we report on this study exploring whether the association between mineral metabolism disorders and mortality is equal among white, black and South Asian patients initiating dialysis treatment.

To gain further insight into the mechanisms underlying ethnic differences in survival on dialysis, it is important to know whether duration of residence in the adopted country before the initiation of dialysis is associated with mortality on dialysis. Therefore, in **chapter 8** we investigated ethnic differences in survival within a group of patients starting dialysis in Denmark and explored whether duration of residence in Denmark before the start of dialysis is associated with mortality on dialysis.

In **chapter 9**, ethnic differences in the trajectory prior to the start of dialysis are studied. In this chapter, we explored differences in progression to ESRD between black and white incident patients on pre-dialysis care in the Netherlands.

In **chapter 10**, the results presented in the previous chapters are discussed in a broader context. The findings are translated into implications and recommendations for future research. Finally, in **chapter 11**, the results presented in this thesis are summarized.

DATA USED IN THIS THESIS

The studies described in **chapter 3** and **chapter 4** are based on data collected from the dialysis departments of the Sint Lucas Andreas Hospital (chapter 3 and 4) and the VU University Medical Center (chapter 4), two large hospitals in Amsterdam, the Netherlands.

For the studies described in **chapter 5** and **chapter 6**, data from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) are used. NECOSAD is a prospective, longitudinal, observational multicenter cohort study that was performed among 2,051 incident dialysis patients aged 18 years or above in 38 dialysis centers in the Netherlands between 1997 and 2008.

For the study described in **chapter 7**, we collaborated with the UKRR. The UKRR provides a focus for the collection and analysis of standardized data relating to the incidence, clinical management and outcome of patients on renal replacement therapy in the United Kingdom.⁴⁷ We used data of 34,639 adult incident chronic dialysis patients who started dialysis treatment between 1997 and 2008.

For the study described in **chapter 8**, we collaborated with the Danish Nephrology Registry (DNR). The DNR collects data on all ESRD patients treated with renal replacement therapy in Denmark.⁴⁸ We used data of 9,109 adult incident chronic dialysis patients who started dialysis treatment between 1995 and 2010.

For the study described in **chapter 9**, we used data from the PREdialysis Patients Record (PREPARE) study. The PREPARE study is a multicenter follow-up study of 1,049 incident patients aged 18 years or above 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 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.

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