Epidemiology and outcomes of renal replacement therapy: results from the ERA-EDTA registry
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Citation for published version (APA):
Chapter 1

General introduction and outline
Introduction

Functions of the kidney

The main functions of the kidney include: (1) the excretion of metabolic wastes and excess water through urine; (2) the regulation of the volume, the mineral composition and acidity of the blood; and (3) the production of enzymes and hormones, including renin, erythropoietin, and vitamin D. [1]

Chronic kidney disease and renal replacement therapy

Chronic kidney disease (CKD) is defined as either kidney damage or decreased kidney function, as reflected by a reduction of the glomerular filtration rate (GFR), for 3 or more months [2]. Although several measures can be taken to slow down the progression and to prevent complications of CKD, for example by controlling diet and blood pressure and use of medication, usually the decrease in kidney function can not be stopped. The severity of CKD is classified in five stages. Stage 1 is the mildest category, including patients showing signs of kidney damage (pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies), but with a normal GFR level (≥ 90 mL/min per 1.73 m²). Stage 5 is a severe illness with poor life expectancy, and is characterized by a GFR level less than 15 mL/min per 1.73 m². Signs and symptoms of CKD include high blood pressure, anaemia, malnutrition, bone disease, neuropathy, and decreased overall functioning and well-being. As risk factors for CKD include older age, diabetes mellitus, hypertension and a family history of kidney disease, in most patients CKD occurs during adulthood. [2,3]

If the kidney function is no longer adequate to sustain life the patient has end-stage renal disease (ESRD). At this stage renal replacement therapy (RRT) is required, which can be either dialysis or kidney transplantation. Dialysis is the process of cleaning the blood from toxins and removing excess water. There are two main types of dialysis: haemodialysis and peritoneal dialysis. [3]

In haemodialysis the blood is pumped into a dialysis machine through an artificial filtering device, where waste products and excess water are removed from the blood by passing through a membrane into a dialysis solution. Each dialysis session takes three to eight hours, and needs to be performed at least three or four times a week. Most frequently haemodialysis is performed at a dedicated outpatient dialysis centre, but it can also be done at home. [3]

In peritoneal dialysis a dialysis solution (dialysate) is infused into the patient’s abdominal cavity. The fluid is held within the abdomen for a prescribed period of time. Small blood vessels running through the peritoneum, a thin membrane surrounding the outside of the organs in the abdomen, allow waste products and excess fluid to pass from the blood
into the dialysis solution. The process of emptying and filling the abdomen for each exchange can be performed manually four or five times throughout the day (continuous ambulatory peritoneal dialysis - CAPD), or at night by a machine (automated peritoneal dialysis - APD). Both forms can be performed at home. [3]

For most patients with ESRD kidney transplantation is the preferred form of RRT, since patient survival and quality of life are often better than on dialysis [4-6]. A kidney transplantation can be performed with a kidney from a deceased donor, or from a living (related or not-related) donor. As there is a shortage of kidneys available for transplantation, most patients initiate RRT with dialysis while they are put on a transplant waiting list.

**European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry**

In Europe a renal registry for the epidemiology of RRT was set up in 1965: the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry. Nowadays, on an annual basis the ERA-EDTA Registry collects individual patient data via national and regional renal registries. For each patient on RRT the following variables are collected: a national patient identifier, sex, date of birth, cause of renal failure, date of start of first RRT, history of RRT with dates and changes of treatment modality, treatment centre, date and cause of death, and information concerning transfer to or from other renal registries [7]. Datasets received from national and regional renal registries are validated and stored in a relational SQL database. Annually the ERA-EDTA Registry publishes a report [8] containing information on the incidence (number of new patients per year) and prevalence (number of existing patients at a certain moment in time) of RRT within Europe, as well as statistics regarding the survival on RRT. In the 14 European countries that participated in the 2009 annual report the total number of patients who started RRT in 2009 was 34,064. The population covered in these 14 countries was 257.1 million, resulting in an overall incidence of 132.5 per million population (pmp). On December 31st in 2009 the total prevalence of RRT was 239,612 in the 14 countries, corresponding with 932.1 pmp. When compared with the general population the average life expectancy was much lower for prevalent dialysis and transplant patients. For persons aged 50 to 54 years the expected remaining lifetimes was 29.1 years in the general population, whereas it was only 7.7 and 19.0 years for dialysis and transplant patients respectively.

In children RRT is even more rare than in adults. In 2009 the incidence and prevalence of RRT among persons aged 20 years and over were 168.6 and 1187.3 per million age-related population (pmarp) respectively, whereas in those younger than 20 years of age these were 8.5 and 53.0 pmarp respectively. When compared to adult patients, children have a very different pattern of causes of renal failure and treatment modalities. Kidney failure is more often a consequence of an inherited, or congenital disease such as hereditary nephropathy and hypoplasia or dysplasia, rather than causes of renal failure frequently seen
in adult patients like diabetes and hypertension [9]. Furthermore, even more than in adult patients kidney transplantation is the preferred treatment modality, as growth and cognitive development are better in children after transplantation than on dialysis [10,11]. For children high transplant rates are reached [12], due to parents (or other family members) donating their kidney to a child, and the priority that children have on the waiting list for deceased donor kidney transplantation. Within nephrology, children comprise a special group, with their own specialised nephrologists (paediatric nephrologists) and nephrology services.

Aims of this thesis

Although studies have been published examining the epidemiology of CKD and RRT, as well as the determinants for survival on dialysis or after transplantation, still many questions remain and there is a continuing need for updated information. Therefore, the aims of the research presented in this thesis were:

1. to describe the epidemiology of chronic kidney disease and renal replacement therapy within Europe over the past two decades;
2. to examine the association of general population characteristics, macroeconomic determinants and renal service indicators with the incidence of renal replacement therapy across countries around the world;
3. to examine the association of patient characteristics, treatment characteristics and macroeconomic determinants with survival in children and adults on renal replacement therapy.

Aims 1 and 2 are addressed in the first part of this thesis (Part I) and aim 3 is addressed in the second part of this thesis (Part II).

Outline of this thesis

The first part of this thesis (Part I) describes the epidemiology of CKD and RRT as well as determinants for the incidence of renal replacement therapy.

CKD is becoming a worldwide public health problem, with an increasing incidence and prevalence, poor outcomes, and high costs [2,13]. Yet, until recently this chronic disease received scarce attention from the public and policy makers. The aim of the first study (Chapter 2) was to give an overview of the epidemiology of stages 3-5 CKD within Europe, together with a summary of the current health care policies on CKD that exist in the different countries.

Since it became possible to keep ESRD patients alive by dialysis and kidney transplantation in the 1960s and early 1970s both the incidence and prevalence of RRT for
ESRD have been rising [14,15]. Also the patient survival on dialysis and after transplantation has improved over time, especially in the 1970s and 1980s [16], but also in the 1990s considerable improvements were established [7]. The aim of our second study (Chapter 3) was to describe the current trends in the incidence and prevalence of RRT and the survival on RRT between 1997 and 2006, within a European cohort of RRT patients.

Worldwide there are substantial differences in the incidence rates of patients starting RRT for ESRD [13,17]. It has been speculated that not only “demand side” factors, such as prevalence of diabetes mellitus and CKD, contribute to this variation, but possibly also “supply side” factors. As RRT is an expensive treatment [18] macroeconomic, healthcare system and renal service organisational factors might be associated with the availability of and access to RRT, and thus with the incidence of RRT. The aim of the study described in Chapter 4 was to examine the association between general population indicators, macroeconomics and renal service characteristics and RRT incidence rates across the broad range of 46 countries around the world.

The second part of this thesis (Part II) describes the association of specific determinants of the survival on dialysis and after kidney transplantation.

Not only incidence rates, but also survival probabilities of patients on dialysis vary extensively across the world, even after adjustment for age and cause of renal failure [19], the presence of comorbidities [20], and general population mortality rates [21]. In Chapter 5 the aim was to study the independent association between macroeconomic indicators and country-specific survival rates of the incident dialysis patient population.

The availability of individual patient data within the ERA-EDTA Registry provided the opportunity to examine factors influencing survival at the level of the patient, instead of at the level of the country. Moreover, the large number of patients on RRT within the European countries contributing with data to the ERA-EDTA Registry offered the possibility to select specific cohorts of patients.

Young adults who started RRT during childhood comprise a special group of patients as they transfer from paediatric to adult nephrology services. Whereas the paediatric nephrologist looses sight of his or her patients, the adult nephrologist gets to treat a patient with a sometimes already long treatment history. The aim of Chapter 6 was to describe the patient demographics, treatment history and survival after reaching the age of 18 years, within a European cohort of young adults who started RRT during childhood and turned 18 between 1985 and 2004.

Many studies have examined differences in survival of patients on different RRT modalities [4,22]. However, within this thesis we have examined if and how dialysis before transplantation is associated with the survival after transplantation within two cohorts of patients.
Due to parents or other relatives willing to donate their kidney to a child and priority rules on the transplant waiting list children have higher chances of kidney transplantation than adult patients. Nevertheless, in practice transplantation at the start of RRT only happens in about 10 to 20% of the children starting RRT. In Chapter 7 we aimed to estimate the effect of postponing transplantation for one or two years, and start with dialysis first, on the patient survival, within a European cohort of paediatric patients who needed to start RRT between 1988 and 2007.

Also most adult ESRD patients need to initiate dialysis while awaiting a donor kidney. There has been discussion if the choice of dialysis modality (haemodialysis or peritoneal dialysis) may affect prognosis of patients receiving their first kidney transplantation. In Chapter 8 the aim was to study the association of dialysis modality before the first kidney transplantation with the patient and graft survival after transplantation, within a European cohort of adult patients who received a kidney transplant between 1999 and 2008.

Finally, in the general discussion (Chapter 9) we elaborate on our major results and their implications. In addition, we discuss some issues related to working with registry data and provide suggestions for future research.
References


