Summary
Chronic kidney disease (CKD) is defined as either kidney damage or decreased kidney function for 3 or more months. The severity of CKD is classified in five stages. Stage 1 is the mildest category, including patients showing signs of kidney damage but having a normal kidney function, and stage 5 is a severe illness with poor life expectancy. In patients with end-stage renal disease (ESRD) the kidney function has decreased to the level that it is no longer adequate to sustain life. 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 (HD) and peritoneal dialysis (PD).

The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry annually collects individual patient data for patients on RRT. For each patient 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.

Within this thesis the following objectives were addressed:
1. to describe the epidemiology of chronic kidney disease and renal replacement therapy within Europe over the past two decades (Chapter 2 and 3);
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 (Chapter 4); and
3. to examine the association of patient characteristics, treatment characteristics and macroeconomic determinants with survival in children and adults on renal replacement therapy (Chapter 5 to 8).

CKD is becoming a worldwide health problem, with an increasing prevalence and poor outcomes. The aim of Chapter 2 was to give an overview of the epidemiology of CKD stages 3-5 within Europe. Data on prevalence of CKD was based on medical databases (such as databases from general practitioners) and on representative samples from the general population. In the twelve European countries of which the prevalence of CKD stage 3-5 has been examined it ranged from 3.6% (Norway) to 7.2% (Germany) in males, and from 6.2% (Italy) to 10.2% (Iceland) in females. The epidemiology of RRT for ESRD within Europe is being documented by the ERA-EDTA Registry. In 2005 in the 26 countries participating, the incidence rates of RRT for ESRD ranged from 57 per million population (pmp) in Estonia to 205 pmp in Portugal, and the prevalence of RRT ranged from 321 pmp in Romania to 1057 pmp in Germany.

Chapter 3 describes the trends in the epidemiology of RRT between 1997 and 2006 within Europe, using data from nineteen European national or regional renal registries. Incidence
and prevalence trends were analysed with Poisson and Joinpoint regression. Cox regression methods were used to examine patient survival. It was demonstrated that the overall age- and gender-adjusted incidence rate of RRT increased from 110 pmp in 1997 to 120 pmp in 2000 with 2.9% per year. However, starting from 2000 there was a trend towards stabilisation of the overall incidence rate, with an average increase of only 0.6% per year. This change was largely due to a stabilisation in the incidence rates of RRT for females aged 65-74 years, males aged 75-84 years and patients receiving RRT for ESRD due to hypertension / renal vascular disease. The overall adjusted prevalence in Europe continued to increase with 2.7% per year. Between the periods 1997-2001 and 2002-2006, the risk of death decreased for all treatment modalities, with the most substantial improvement in patients starting PD (a decrease of 19%) and in patients receiving a kidney transplant (a decrease of 17%). We concluded that the annual rise of the overall incidence rate of RRT for ESRD has been reduced and that the survival on RRT has continued to improve.

Incidence rates of RRT for ESRD vary considerably worldwide. In Chapter 4 the aim was to examine the extent to which this variation was associated with supply-side factors (macroeconomic, healthcare system and renal service organisational factors) rather than with demand-side factors (general population demographics and health status). RRT incidence data for patients starting RRT between 2003 and 2005 were obtained from 46 renal registries worldwide. General population age and health, macroeconomic indices and renal service organisation data were collected through secondary sources and questionnaires. Linear regression models were built to establish the factors associated with RRT incidence. The incidence of RRT ranged from 12 pmp in Bangladesh to 455 pmp in Taiwan. It was found that a higher Gross Domestic Product (GDP) per capita (incident rate ratio (IRR): 1.019 per 1000 USD (95% CI: 1.005-1.033)), a higher percentage of GDP spent on healthcare (IRR: 1.112 per % (95% CI: 1.053-1.173)) and a lower dialysis facility reimbursement rate relative to GDP (IRR: 0.755 per GDP per capita-sized increase in reimbursement rate (95% CI: 0.646-0.883)) were associated with a higher RRT incidence. In more developed countries, also a higher private for-profit share of HD facilities was associated with higher incidence of RRT (IRR: 1.009 per % (95% CI: 1.005-1.014)). We concluded that macroeconomic and renal service factors are more often associated with RRT incidence rates than demographic or general population health status factors.

Also the survival of patients on dialysis varies extensively across the world. In Chapter 5 the aim was to study the association between macroeconomic indicators and country-specific dialysis survival rates and to explore potential explanations through renal service indicators, the incidence of dialysis and the characteristics of the dialysis population. Survival probabilities were obtained from 22 renal registries across the world for patients starting dialysis in 2003-2005. Linear regression models were built to establish the factors
associated with survival. Two-year dialysis survival ranged from 62.3% in Iceland to 89.8% in Romania. Remarkably, a higher GDP per capita (hazard ratio (HR): 1.023 per 1000 USD (95% CI: 1.002-1.045)) and a higher percentage of GDP spent on healthcare (HR: 1.103 per % (95% CI: 1.035-1.175)) were associated with a higher mortality on dialysis. Also a higher intrinsic mortality risk (general population mortality, age- and sex-"standardized" to the dialysis population) was associated with a higher mortality on dialysis (HR: 1.038 per death per 10000 person years (95% CI: 1.009-1.069)). We concluded that macroeconomic factors and the intrinsic mortality of the dialysis population are associated with survival on dialysis, whereas renal service organisational factors and RRT incidence are less important.

Little is known about the group of children on RRT who reach the age of 18 years and are transferred from paediatric to adult nephrology services. Chapter 6 describes patient demographics, treatment history and survival after reaching the age of 18 years, within a European cohort of 1777 young adults who started RRT during childhood and turned 18 between 1985 and 2004. The chi-square test was used to test differences between patient groups and Cox regression analysis to examine patient survival. It was found that the annual number of children on RRT turning 18 increased between 1985 and 2004 from 71 to 116 per age-related million population (pmarp). Also there was an increase in the percentage of young adults who started RRT at a very young age, a greater number of children with hypoplasia/dysplasia and cystic kidneys and more young adults who started RRT with PD or pre-emptive transplantation. The 5-year patient survival from the 18th birthday was 95.1%, and the average life expectancy was 63 years for young adults with a functioning graft and 38 years for those remaining on dialysis. We concluded that the number pmarp of young adults on RRT has increased over time, and their characteristics and treatment history changed. Their survival prospects are good, especially for kidney transplant recipients.

Although kidney transplantation provides the best outcomes for children on RRT, controversy exists concerning the timing of the first kidney transplantation. 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. We used a European cohort of 2091 children who needed to start RRT between 1988 and 2007. A multistate model was used to simulate patient survival assuming the following treatment scenarios: a) pre-emptive transplantation; b) transplantation after one or two years on dialysis; and c) remaining on dialysis. It was found that the highest eight-year survival probabilities were achieved in children transplanted pre-emptively (living donor (LD): 95.9% (95% CI: 93.1-98.8), deceased donor (DD): 95.3% (95% CI: 90.9-99.9)) rather than after two years of dialysis (LD: 94.2% (95% CI: 91.6-96.8), DD: 93.4% (95% CI: 91.0-95.9)), although these differences were not statistically significant. We concluded that even after taking mortality on dialysis into account, the
potentially negative effect of postponing transplantation for one or two years on mortality was relatively small.

Most adult ESRD patients need to initiate HD or PD while awaiting a donor kidney. 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. We used a cohort of 29088 adult patients from sixteen European renal registries who received a kidney transplant between 1999 and 2008. We applied standard multivariable Cox regression analyses with the pre-transplant dialysis modality as variable of interest. In addition, to decrease confounding by indication through unmeasured factors also the instrumental variable method was used, with the case-mix adjusted centre percentage of PD as variable of interest. The results of the standard analyses suggested that PD before transplantation was associated with better patient survival (HR: 0.83 (95% CI: 0.76-0.91)) and better graft survival (HR: 0.90 (95% CI: 0.84-0.96)) when compared to HD. In contrast, the instrumental variable analysis showed that a 10% increase in the case-mix adjusted centre percentage of patients on PD was neither associated with post-transplant patient survival (HR: 1.00 (95% CI: 0.97-1.04)) nor with graft survival (HR: 1.01 (95% CI: 0.98-1.04)). We concluded that results from standard Cox regression analyses using individually assigned pre-transplant dialysis modality may have suffered from confounding by indication. The instrumental variable method suggests that there is likely no association between pre-transplant dialysis modality and patient and graft survival after transplantation.

Finally, in **Chapter 9** we elaborated on the major results of the research described in this thesis. In addition, the methods used for data processing after receipt of the data by the ERA-EDTA Registry were described. We also described the advantages of the ERA-EDTA Registry database for research projects, such as the high coverage of the general population, the possibility to carry out analyses in patient groups where numbers in individual renal registries are usually small, and the possibility to make a demographic picture of treated ESRD within and across countries. Furthermore, the instrumental variable method was discussed as a method to account for confounding by indication arising from the use of observational data. Finally, we discussed recommendations for further research that include epidemiological studies into CKD stages 1-4 and more detailed study of the flows of funds specifically in the field of nephrology.