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

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Chapter 9

General discussion
Introduction

This thesis focuses mainly on three issues. The first was to describe the epidemiology of chronic kidney disease (CKD) and renal replacement therapy (RRT) within Europe over the past two decades, the second was 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, and the third was to examine the association of patient characteristics, treatment characteristics and macroeconomic determinants with survival in children and adults on renal replacement therapy. In this last chapter the main conclusions of this thesis are summarized, integrated and discussed. Further, considerations regarding working with registry data will be described.

Summary of the principal findings

Epidemiology of chronic kidney disease and renal replacement therapy

Chronic kidney disease (CKD) is a growing worldwide health problem, driven by rising rates of diabetes mellitus, obesity, hypertension and ageing [1]. Yet, until recently CKD received scarce attention by the majority of the European governments. The review presented in Chapter 2 showed that information on the epidemiology of CKD within Europe is scarce and fragmented. The available data from European countries were based on information derived from medical databases (such as general practitioners databases) or on population samples representative of the general population of those countries. As it is not feasible to detect all new patients with CKD no data have been published regarding the incidence of CKD within Europe. However, the prevalence of stage 3-5 CKD has been examined in a number of European countries, and ranged from 3.6% (36000 per million population (pmp)) in Norway to 7.2% (72000 pmp) in Germany in males, and from 6.2% (62000 pmp) in Italy to 10.2% (102000 pmp) in Iceland in females.

The epidemiology of renal replacement therapy (RRT) for ESRD within Europe was documented more extensively. For an increasing number of countries within Europe national or regional renal registries annually provide individual data of patients on RRT to the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry [2]. In addition, a number of European national or regional renal registries provided aggregated data on the incidence and prevalence of RRT in their country. Chapter 2 showed that in 2005 the incidence rates of RRT ranged from 57 patients pmp in Estonia to 205 patients pmp in Portugal, while the prevalence of RRT ranged from 321 patients pmp in Romania to 1057 patients pmp in Germany.
Since RRT for ESRD became generally available in Europe in the 1960s, the incidence of RRT has been rising explosively [3,4]. In Chapter 3 data from nineteen national and regional renal registries within Europe providing individual patient data to the ERA-EDTA Registry were combined, and it was demonstrated that the overall age- and gender-adjusted incidence rate of RRT further increased from 110 per million population (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. Nevertheless, trends in the incidence rates of RRT differed widely across countries, ranging from steady increase to substantial decrease, potentially due to differences in the prevalence and progression of CKD and to variable access to RRT.

Determinants for the incidence of renal replacement therapy
In the study described in Chapter 4 it was shown that in 46 countries across the world the 2004 RRT incidence rates ranged from 12 pmp in Bangladesh to 455 pmp in Taiwan. Aggregated data per country were used to study 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). The study showed that a higher gross domestic product (GDP) per capita, a higher health care expenditure as percentage of GDP and a lower dialysis facility reimbursement rate relative to GDP were independently associated with a higher RRT incidence. In addition, in the more developed countries, also a higher private for profit share of haemodialysis facilities was associated with a higher incidence of RRT. This suggests that, except from demand side factors, also supply-side factors contribute significantly to the incidence of RRT.

Determinants for survival on renal replacement therapy
There is a lot of variation in the mortality on dialysis and after transplantation, while determinants for survival on RRT are diverse and multifaceted. The study described in Chapter 5 showed that in 22 countries worldwide the two-year survival on dialysis ranged from 62.3% in Iceland to 89.8% in Romania. It was demonstrated that a higher GDP per capita and a higher health expenditure as percentage of GDP were independently associated with a higher two-year mortality on dialysis, suggesting that macroeconomic factors are important determinants of international differences in mortality on dialysis. Renal service organisational factors appeared to be less important.

Also treatment characteristics are associated with the survival on RRT. All available literature suggests that for patients who start RRT kidney transplantation is the best treatment option, both from the perspective of survival and quality of life [2,5,6]. However, there is a shortage of kidney donors, and consequently most patients will have to start RRT
with dialysis first. When compared to adult patients, children who need to start RRT have a relatively high chance of a transplant since often a parent is willing to donate a kidney and in most countries children get priority on the waiting list for deceased donor kidneys. The study described in Chapter 6, using data from nine European renal registries, showed that the majority (60.4%) of all children who started RRT during childhood and reached the age of 18 had a functioning transplant at their 18th birthday. In addition, this study showed that the survival prospects of these young adults were independent of age at the start of RRT, sex, and cause of renal failure, but highly dependent on having, or not having, a functioning transplant at their 18th birthday. Nevertheless, Chapter 7 showed that in daily practice only 21.2% of the children received a pre-emptive transplant, whereas the remaining 78.8% had to start RRT with dialysis. However, it was found that the potentially negative effect on patient survival of postponing transplantation for a short period of one or two years, taking into account the mortality on dialysis before transplantation, was relatively small and not statistically significant.

Also the far majority of the adult patients starting RRT need to start with dialysis first. In Chapter 8 we used data from sixteen national and regional renal registries within Europe of adult patients who received a first kidney transplant between 1 January 1999 and 31 December 2008. We found that the choice for the pretransplant dialysis modality (haemodialysis (HD) or peritoneal dialysis (PD)) was likely not associated with the patient and graft survival after transplantation.

**General points of discussion**

In light of the findings described in this thesis, some general points of discussion are put forward.

**Epidemiology of CKD**

For planning future public health policy and the development of meaningful screening strategies and prevention programs it is of importance to get further insight in all the factors that could help to decrease RRT incidence rates and also to be able to dissect the relative contributions of these factors. As demonstrated in this thesis both demand side factors (i.e. factors contributing to the incidence of ESRD, such as the general population health status) and supply-side factors (i.e. factors contributing to the availability of RRT and access to RRT, such as macro economic factors) contribute to the incidence of RRT. The incidence of ESRD is a result of the prevalence of CKD and of the progression rate of CKD. To gain more insight in the prevalence of CKD, including the earlier stages, and the differences between countries across Europe, research based on national representative population samples is needed. Although these population based surveys have been held in a number
of countries (Chapter 2), and several other studies have been published recently [7,8], the information on prevalence of CKD in Europe is still scarce. It is therefore important that also other European countries set up population based surveys, preferably in close collaboration to increase the use of similar methods. These cross-sectional survey studies would, however, not be suitable to study factors associated with the progression of CKD. For that it is essential that cohorts are composed of patients with CKD who can be followed for multiple years. These patients could be selected from the population-based studies, or one could extract the patients for whom CKD is confirmed from the medical databases of nephrologists or general practitioners. However, as only a part of all patients with CKD visit the general practitioner or are referred to a nephrologist these patients comprise a potentially biased selection of the total group of patients with CKD.

Macroeconomic indicators and the variation in the incidence of RRT and the survival on dialysis

RRT incidence rates vary widely across the world, as well as within Europe. Although in many countries within Europe the incidence of RRT has started to stabilize during the last decade, or even decreased, it will probably continue to increase in many of the developing countries. Moreover, as every year new patients are entering the RRT programs, and as the survival on RRT is still improving, the total number of patients on RRT is expanding rapidly, with about 2.7% per year in Europe (Chapter 3) with the fastest growth occurring in the elderly. However, considering the fact that RRT is an expensive treatment, estimated to cost per patient per year (except for the first year) €40,600 for haemodialysis, €20,500 for peritoneal dialysis and €12,900 after transplantation [9], it is anticipated that the costs of RRT will increase almost proportionally. It is therefore likely that the wealth in a country and the amount of money that is available for health care are associated with the acceptance of new patients for RRT. Chapter 4 showed that indeed macroeconomic factors were associated with RRT incidence rates: a higher GDP per capita, a higher health expenditure as percentage of GDP and a lower dialysis facility reimbursement rate relative to GDP were associated with higher incidence rates of RRT. However, as the study design was cross-sectional we could not establish the direction of the relationship. In 1998 McKenzie [10] published the results of a questionnaire which was distributed among nephrologists in the US, the UK and Canada, showing that the non-referral to RRT in the UK and Canada was often motivated by a belief that there were insufficient resources to fund RRT for all patients who might have benefited from it. Contrary, almost no US nephrologists reported that lack of funding had caused them to withhold dialysis from patients. This suggests that countries with more money available for health care have more resources available to accept more patients for RRT. Alternatively, the countries with more money available for health care could have spent their money in a different way, for example by putting more emphasis on treatment of ESRD than on the prevention of ESRD. Hallan et al. [11] examined the
prevalence of CKD and the incidence of RRT in both Norway and the US. They demonstrated that although the prevalence of CKD was similar in both countries, the incidence rate of RRT was three times higher in the US, indicating that the higher risk for ESRD in the US may be due to a higher rate of progression of CKD. They argued that competing cardiovascular mortality was not a factor of importance and that the large difference in the incidence of RRT between the US and Norway lay in the management of patients with CKD due to suboptimal pre-ESRD care.

Mortality rates on dialysis vary considerably across the globe. Although factors such as age, sex, primary renal disease, co-morbidities, and general population mortality rates explain a part of this variation [12-15], a major part of the variation in dialysis mortality across countries is still unexplained. However, Chapter 5 showed that a higher GDP per capita and a higher percentage of GDP per capita spent on health care were associated with a higher mortality of a country’s dialysis population. This counter-intuitive finding is in line with the findings regarding the association of macroeconomics and the incidence of RRT. It supports the idea that having more money available for health care is associated with the acceptance of a wider range of patients for RRT (including those with a poor health condition). A complementary explanation could be that higher spending does not necessarily result in more effective care. Moreover, if having more money available implies more focus on the treatment of ESRD rather than on prevention of it, it could well be that patients start RRT in a worse health condition, with more comorbidities and a worse nutritional status. Within both EVEREST studies presented in this thesis the US is among the extremes. It has the second highest incidence of RRT (Chapter 4), whereas it has third highest mortality on dialysis (Chapter 5). When compared to Europe, patients in the US start dialysis with a higher number of comorbidities [16]. Nevertheless, incident dialysis patients in the US are not much older than those in other countries, which is also reflected in their moderate intrinsic age- and sex-related mortality risk of their dialysis population. On the other hand, several studies have suggested that practice patterns account for some of the differences in survival across countries [17,18]. In the US the rates of arteriovenous fistula use are much lower than within Europe, with suggested explanations including (1) an decreased priority during the pre-ESRD period for establishing a permanent access, (2) more difficulties encountered in creating a vascular access that successfully matures to be functional for the start of HD, and (3) a more frequent failure of pre-ESRD evaluations to accurately estimate onset of ESRD [19]. Nevertheless, the exact pathways through which having more money available for health care and a higher mortality on dialysis are associated are still unknown. The explanations given here should be considered “hypothesis generating”, and should encourage further investigation. For example, we examined the association of general macroeconomic determinants and the incidence of RRT and the survival on dialysis, however, future studies could focus on health care spending within the specific area of nephrology. How much money is invested in prevention versus that spent on dialysis and
what and for whom is it used for? Is it used for large groups of very old and very ill patients who die after a short period on dialysis? In addition, as the aims of dialysis are to improve survival and quality of life, future research could focus on whether there are groups of patients for whom dialysis does not improve prognosis, and if starting dialysis for these groups is rational, or not. Furthermore, a study on the number and characteristics of patients who reach ESRD but do not start RRT may provide further insight into the different selection of patients for RRT across countries and resulting international differences in outcomes.

Working with registry data
All studies presented within this thesis were performed using data from the ERA-EDTA Registry. Via national and regional renal registries in Europe the ERA-EDTA Registry annually collects core data on patients with ESRD who are treated with RRT. These data include a patient identifier, the patient's date of birth, sex, cause of renal failure, date of start of first RRT, history of RRT with dates and changes of modality, treatment centre, date and cause of death and information concerning transfer from or to other renal registries. Currently the database contains individual patient data from 26 national and regional renal registries from 14 countries, and this number is growing. Most registries reported to cover 100% of the general population within their country or region over the period studied in this thesis, with the exception of the UK of which the coverage has increased from 16% in 1997 to 100% in 2007. The majority of the registries provided data which is complete and reliable for patients who started RRT from the 1990s, and some even for patients who started RRT from the 1960s.

To minimize missing data and data errors extensive checks are performed, both at the national / regional registry and at the ERA-EDTA Registry. In a number of countries / regions internal inconsistency checks are performed through the data entry system that dialysis and transplantation centres use to enter their new patients and other changes into a national database, while in other countries / regions centres periodically send a dataset to the national / regional renal registry and inconsistency checks are performed only after arrival in the national / regional registry. After the receipt of the entire dataset, including the data of all previous years, at the ERA-EDTA Registry office in Amsterdam standardized inconsistency checks are performed. These include the detection of missing and invalid values, range checks, the detection of duplicates, and checks regarding the sequence of dates and event types (for example, a dialysis event can not directly be followed by a transplant failure event). The results of these extensive checks are reported back to the registries. Finally, when the data is approved the entire dataset will be imported in the ERA-EDTA Registry database, thereby replacing all previous data of that country / region. Changes in the data sets made by the national and regional registries are in this way adopted by the ERA-EDTA Registry. However, although this procedure results in most of the errors to be detected, some of them will remain unnoticed. For example, when the day and month are exchanged,
this will only be noticed when the day has a value larger than 12. As only a limited number of variables are collected, missing values are infrequent: within the ERA-EDTA Registry database there are no missing values for date of birth, gender and date of event, and only a few for some of the other variables (date of start RRT: 0.2%; event type: 1.1%; cause of renal failure: 1.7%). For cause of death the percentage of missing values is 17.2%. To ensure the completeness of death events, some registries have reported that they check the status of all registered patients with the national death certificate registry [20]. This is especially important for patients who are living with a functioning transplant.

Using data from the ERA-EDTA Registry provides some important advantages. The availability of data from multiple countries and regions provides the possibility to carry out analyses in patient groups where numbers in individual national or regional renal registries are usually small. More focused studies using data from a sub cohort of the entire RRT population could be carried out with the aim of answering specific questions, for example when studying rare diseases [21]. In Chapter 6 and 7 studies were performed examining the survival of children on RRT. Cohorts were composed existing of 1777 and 2091 children respectively, which is far more than could be studied by single countries or single centres.

Another advantage is that the registry data provide a powerful tool to build up a demographic picture of treated ESRD within and across countries. As for most countries and regions all patients attending RRT programs are included in the registry (i.e. a 100% coverage of the general population) incidence and prevalence numbers represent true numbers and do not need to be estimated based on a sample of a country’s RRT population.

Although the limited number of variables that are collected by the ERA-EDTA Registry ensures high data quality, it also restricts the research that can be done, and extensive adjustment in multivariable analysis is often not possible. However, the intensive collaboration between the national / regional renal registries and the ERA-EDTA Registry has provided the possibility for additional data collection, for example resulting in studies on residual renal function [22] and comorbidities [23,24]. Also for the studies described in Chapter 4 and 5 within this thesis such additional data have been collected from all renal registries worldwide that were known to have reported on RRT incidence and survival. Furthermore, in the NephroQUEST project clinical performance indicators have been selected, standardized and proposed for future data collection by renal registries in Europe [25]. This list includes items such as vascular access and haemoglobin. The collection of such data will start at the end of 2011.

Registry data can only be used for observational studies, and when using observational data to study treatment effects a drawback is the risk of confounding by indication: those who receive the treatment generally differ from those who do not, according to the medical indication for which the treatment was prescribed [26]. A randomized controlled trial (RCT) is considered the gold standard study design to investigate the effect of an intervention, with
the random allocation of treatment avoiding confounding by indication. However, in some situations an RCT may be unnecessary, inappropriate, impossible, or inadequate, for example when an outcome is rare or when randomization is unethical [27,28]. Moreover, RCTs are time-consuming and very expensive. As the registry data are already available, they provide the possibility to perform multiple observational studies, without extra costs, and often without additional data collection. Moreover, also with observational data there are ways to approximate randomization [27,29]. The instrumental variable method [27,30], which has already been used for many years [31,32], is a method that at least partially accounts for both observed an unobserved (or unmeasured) confounding. Using this method a variable is chosen - the instrumental variable - that can be considered to be allocated to a patient at random, and then the association of this instrumental variable and the outcome is studied. In Chapter 8 the aim was to compare the survival after transplantation for patients who were on HD or PD before transplantation. However, as patients may have been selected to start with HD or PD because of observed or unobserved prognostic factors, this association suffers from confounding by indication. As it can be assumed that patients tend to visit a treatment centre in the direct neighbourhood of their homes, in principle treatment centre can be considered to be allocated to the patient at random and independently of prognostic factors. Therefore in this study we chose the case-mix adjusted percentage of PD patients in the patient's treatment centre as the instrumental variable. This provided the possibility to study the association of dialysis modality and the survival after kidney transplantation, in a pseudo-randomized setting.

Concluding remarks

Within this thesis the first aim was to describe the epidemiology of chronic kidney disease and renal replacement therapy within Europe. Although information on the epidemiology of CKD within Europe was scarce, we showed that the prevalence of stage 3-5 CKD was reasonably similar across Europe. Furthermore, we demonstrated that the incidence of RRT within Europe is stabilizing, but that the trends of the incidence rates of RRT differ across Europe. The second aim was to examine to what extent general population characteristics, macroeconomic determinants and renal service indicators contributed to the worldwide variation in the incidence of renal replacement therapy across countries around the world. We showed that countries with more money available for health care had higher incidence rates of RRT. The third aim was to examine the association of patient characteristics, treatment characteristics and macroeconomic determinants with survival in children and adults on renal replacement therapy. Within this thesis we demonstrated that dialysis populations in countries with more money available for health care had higher mortality rates. Furthermore we showed that patients who started renal replacement therapy during
childhood have the best survival prospects when living with a functioning graft at their eighteenth birthday. Yet, for children postponing kidney transplantation for one of two years, and start renal replacement therapy with dialysis first did seem to be an acceptable option from the perspective of patient survival. For adult patients we showed that there was no association between haemodialysis or peritoneal dialysis before kidney transplantation, and the survival after kidney transplantation.

The ERA-EDTA Registry data provided a powerful tool to study the epidemiology of RRT, as well as the association of different determinants with the incidence of RRT and the survival on dialysis and after transplantation. Nevertheless, for planning future public health policy and the development of meaningful screening strategies and prevention programs it is of the utmost importance to further unravel the mechanisms that cause international differences in incidence of RRT and mortality on dialysis. Future studies could focus more on the specific flows of money within the field of nephrology, and on the epidemiologic characteristics of CKD stages 1-4 to identify which patients progress to later stages of CKD and who will finally need dialysis or renal transplantation.
References


