Starting renal replacement therapy in end-stage renal disease patients
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Chapter 9
General discussion
Chapter 9

GENERAL DISCUSSION

The research reported in this thesis aimed to contribute to the knowledge on three themes related to the start of renal replacement therapy in patients with end-stage renal disease. Our first objective was to examine which clinical, social or logistical factors influence the decision-making of European nephrologists on whether and when to start renal replacement therapy. The second one was to assess the associations of medical and non-medical factors with dialysis modality choice in different patient groups. Finally, we aimed to examine dialysis modality specific patient survival and its trends in relation to changes in technique survival, dialysis modality choice and (pre-emptive) transplant rates in Europe.

This chapter summarises the results of previous chapters and puts them in a broader perspective. To this end we elaborate on the implications for clinical practice and provide guidance for future research.

Starting renal replacement therapy

Chapter 3 showed that the majority of the European nephrologists reported to use an estimated GFR (eGFR) of 10 ml/min/1.73m² as the target level of kidney function to start renal replacement therapy. They also reported that this start is brought forward in the presence of chronic clinical conditions or important uraemic signs and symptoms, whereas the preference of the patient and the presence of vascular dementia were reasons for them to postpone the start.

In the most recent guideline of the European Renal Best Practice it is stated that dialysis should be considered for all patients with a GFR <15 mL/min/1.73m² when one or more of the following factors is present: symptoms or signs of uraemia, inability to control hydration status or blood pressure or a progressive deterioration in nutritional status. As an additional note it is stated that the majority of patients will be symptomatic and need to start dialysis with a GFR between 6-9 mL/min/1.73m². The results in Chapter 3 therefore suggest that the European nephrologists make an effort to act in line with the recent guidelines providing recommendations for the start of dialysis.

Over the last decade, there has been a tendency to start dialysis at higher levels of eGFR compared to earlier years. Several factors may explain this trend, including a change in characteristics of the dialysis population. Nowadays, a larger proportion of patients are older than 75 years of age at the start of renal replacement therapy. Additionally, patients more often present themselves with diabetes mellitus and renal vascular disease as primary cause of kidney failure as well as with a higher comorbidity burden. Both a higher age and comorbidity burden are associated with higher levels of eGFR at the start of dialysis. Furthermore, in the US it has been suggested that nephrologists in recent years have put a stronger reliance on eGFR levels in determining the best moment to start dialysis, instead of on the clinical condition of the patient.

In clinical practice the patient’s kidney function is usually estimated by equations. However, these were not developed in patients with advanced kidney disease and only validated in a limited number of patient groups. Additionally, most equations are based on serum creatinine levels that are highly affected by the patient’s age, weight, muscle mass and dietary intake. In patients with advanced kidney disease the equations are highly inaccurate and should therefore be considered unfit for decision-making.
Instead of using equations to estimate the GFR, it is also possible to measure a patient’s kidney function. This can be established by intravenously injecting an exogenous marker like inulin or iohexol, which are freely filtered by the kidneys. After injection, blood samples should be drawn at certain time intervals. Subsequently, the inulin or iohexol concentration in these samples is determined by using high-pressure liquid chromatography. Based on this assay, plasma elimination curves can be generated to calculate the concentration of inulin or iohexol as filtered by the kidneys. \(^{14}\) However, since measuring GFR is a time-consuming, invasive and expensive method this is not often performed in clinical practice.

**Not starting renal replacement therapy – a conservative care approach**

The European nephrologists who participated in our survey estimated that in 2009 up to 15% of the referred patients with end-stage renal disease were treated conservatively. The need for offering and optimizing conservative care for specific patients with end-stage renal disease is increasingly recognised. \(^{15}\) Ellwood et al. recently found that patients who initiated dialysis at an eGFR >10.5 ml/min/1.73m\(^2\) were 17% more likely to withdraw from dialysis. They additionally observed that even after adjustment for eGFR at initiation patients who started dialysis in more recent years were more likely to withdraw from dialysis. \(^{16}\) Old and sicker patients are often brought forward as a group of patients who may not always benefit from dialysis and may therefore be considered for conservative care. \(^{17};^{18}\) Our results in Chapter 4 showed that in the considerations of nephrologists the presence of severe clinical conditions prevailed over a higher age. Moreover, the nephrologists considered patient preference as extremely important in the decision-making about providing conservative care instead of dialysis.

**Choosing between haemodialysis and peritoneal dialysis as initial dialysis modality**

We explored the association between patient survival and initial dialysis modality choice for several subgroups of patients in Chapter 5. Overall, there was a survival benefit of starting with peritoneal dialysis (PD). However, with an increasing number of comorbid conditions and in the presence of diabetes mellitus, ischaemic heart disease, peripheral vascular disease or cerebrovascular disease the survival benefit disappeared and we found similar survival outcomes for patients starting with haemodialysis (HD) or PD. For patients with diabetes mellitus there were differences by sex. Male patients with or without diabetes mellitus showed survival benefits on PD, whereas diabetic female patients showed an increased mortality when treated with PD as initial treatment, especially if they were 70 years and older. We further explored patients with diabetes mellitus in Chapter 6, where we found that patients with diabetes mellitus as primary cause of kidney failure showed a worse patient survival than patients with diabetes mellitus as comorbid condition. For most patient groups the dialysis modality choice was in line with survival outcomes: there was a lower likelihood to receive PD in groups where a start on HD was associated with a survival benefit. However, in patients of 70 years and older, non-diabetic patients and those with a malignancy, survival benefits on PD were found, whereas these patients were less likely to receive PD as initial dialysis modality. Finally, in Chapter 8 we showed that since 2001 PD use has decreased, whereas since 2009, HD use has stabilized. We related these trends to patient and technique survival, to pre-emptive and non-pre-emptive transplant rates as well as to trends in incidence for both dialysis modalities. We found that the PD and HD patient survival and technique survival for
PD has improved. Also the probability to receive a transplant while on dialysis did not increase. Therefore, our data suggest that the only cause for the decrease in PD use was a decrease in its incidence since 2000. Dialysis modality choice is affected by multiple factors, including patient preference and the preference and experience of the nephrologist. Also country-level factors, like macro economic factors or renal service indicators play an important role in dialysis modality choice. In Chapter 7, we showed that the following factors contribute to a smaller proportion of PD as initial dialysis modality choice: a higher proportion of patients with diabetes mellitus as primary renal disease, higher health care expenditures, larger share of private-for-profit centres, and higher costs of PD consumables relative to staffing costs. The latter two factors suggest that it may be possible to influence dialysis modality choice through healthcare organization and funding.

Methodological issues
A large part of the research was performed using data from the ERA-EDTA Registry. Because of the large number of patients for whom the core dataset is available and the high completeness of the data, using registry data enables to perform analyses in subgroups of patients yielding effect estimates with high precision. Additionally, the ERA-EDTA Registry has a high geographical coverage in Europe, hereby enabling to examine country differences and produce results that are generalizable to Europe. In Chapters 3 and 4 we used a cross-sectional web-based survey to capture the opinions of European nephrologists. Surveys have the important advantage of collecting topical data in a limited time period. An important drawback is however that the results are mainly descriptive in nature and several forms of bias like volunteer bias and non-response bias may occur. Volunteer bias occurs when people with a high personal interest in the survey topic and those with strong or distinct opinions are more eager to respond. Non-response bias may occur when individuals choose not to participate in a survey. Characteristics from these non-respondents are often not known, and therefore the results of the survey may not be generalizable to the entire population of potential respondents. Also, as the topic of the survey had been recently highly debated, there is a possibility that respondents provided socially acceptable answers. The studies presented in this thesis are all observational in nature. An important limitation of observational studies is that they cannot prove causality. For studying causal associations between therapeutic interventions and outcomes the optimal study design is a randomized controlled trial (RCT). In this design included subjects are randomly assigned to a specific treatment or other exposure to strive for an equal distribution of all (un)measured confounders over the study groups and to avoid confounding by indication. Confounding by indication arises when factors like the patient's or physician's preferences influence treatment decisions and it may result in an over- or underestimation of the actual effects of therapy. Due to several barriers, including ethical concerns and patient preference, not all research questions can be studied by using an RCT. This especially holds true for treatment decisions that affect a patient's daily life to an important extent. For example, an RCT which aimed to determine which dialysis modality would yield the best results in terms of quality of life and patient survival, showed that randomisation was not possible as the far majority of patients either had medical or social contra-indications for PD or HD or had a preference for
For specific research purposes and when performing an RCT is challenging, properly performed observational studies are the best available alternative, as long as their limitations are taken into account when interpreting the results. Several methods are available to reduce confounding in observational studies, for example multivariable adjustment and propensity score risk adjustment. However, only with pseudo-randomization methods like the instrumental variable method it is possible to address insufficiently measured or unmeasured confounders. The instrumental variable method attempts to reduce confounding by indication by mimicking randomization. The use of this and similar methods should therefore be further explored for use in registry studies.

Future research

Decision-making around starting dialysis or conservative care for end-stage renal disease

The survey described in the Chapters 3 and 4 focused on nephrologists’ opinions on the decision whether and when to start dialysis. Its results showed that in this decision the preference of the patient is considered as one of the most important factors. Whereas our survey focused on the opinion of the nephrologists, future research should include an additional focus on the patient’s perspective. In addition, the factors pointed out as important in the survey may be relevant for new studies exploring which factors are actually involved in decision-making in clinical practice.

The proportion of patients older than 75 years of age at the start of renal replacement therapy for the incident population of the ERA-EDTA Registry increased from 16% in 2000 to 31% in 2011. As a result, geriatric problems are currently more often encountered in the end-stage renal disease population, which brings along difficult challenges for nephrologists. Several complications like multimorbidity, malnutrition, cachexia, and cognitive impairment are related to older age, and may affect the decision-making and treatment protocols for the patient’s kidney disease. Also, for several specific comorbidities like hypertension, diabetes, and cardiovascular disease treatment protocols may be different for elderly patients compared to their younger counterparts. Future studies on decision making in elderly patients approaching end-stage renal disease should therefore incorporate geriatric principles that focus not only on assessment of kidney function, but also on disabilities, comorbidities, and geriatric problems (e.g. multimorbidity, frailty, dementia, delirium, depression, falls, malnutrition, polypharmacy).

The EQUAL study (European Quality study on treatment in advanced chronic kidney disease), initiated by the ERA-EDTA Registry, is expected to contribute to our knowledge by addressing several of these issues. This prospective observational cohort study is currently recruiting patients of 65 years and older in a large number of renal centres in Germany, Italy, Poland, Sweden, The Netherlands and the United Kingdom. The study includes patients whose kidney function has dropped below 20 mL/min/1.73m² for the first time within the last six months, while being under the care of a nephrologist. Patients will be followed during their routine care for a maximum period of four years. The results of this study will amongst others inform the nephrology community about what patients consider as important in deciding if and when to start dialysis and on the optimal decision-making process for elderly patients. In EQUAL, survival outcomes and quality of life will be compared between patients starting dialysis with a higher versus lower kidney function and between patients starting dialysis with fewer versus more signs and symptoms. Another important research focus will
lie on the assessment of kidney function, specifically in terms of determining which method provides the best information for deciding when to start dialysis for these elderly patients.30

Comparing benefits of HD and PD as initial dialysis modalities.
We found survival differences between HD and PD for several subgroups of patients (Chapters 5 and 8), but these differences were limited in terms of absolute survival time. This relatively small difference may be important to take into account for a more efficient organization of the healthcare system, especially considering the increased pressure on healthcare budgets worldwide. When comparing the economic impact of HD and PD treatment, we can conclude that PD is a more affordable treatment option than HD.31,32 Besides the lower costs of PD treatment and its consumables, lower staffing costs are required since PD is often performed at home. However, such economic considerations should be in balance with the preference of the individual patient and the presence of (medical) contraindications.

Conclusions
When combining the results of all studies in this thesis we can draw the following conclusions. According to the opinions of European nephrologists, the preference and clinical condition of the patient are the two most important factors in decision-making on whether and when to start dialysis. Patient-centered studies are required to further explore which factors are considered important by the patients themselves, to integrate such knowledge in the shared decision-making process. It is estimated that conservative care in Europe was provided to up to 15% of the patients in 2009. We may expect a further increase of this proportion because of the larger share of elderly patients with a high prevalence of geriatric problems.

Once it has been decided to initiate dialysis, also dialysis modality choice should rely mainly on patient preference, provided that important medical contra-indications for the modality choice of their preference are absent. Over the years, patient survival has improved, especially for patients starting dialysis on PD. As a consequence currently the best available evidence suggests that starting on PD provides many patients with the best survival prospects. Although the improved outcomes and the current burden on health care budgets plead for the expansion of PD use, the prevalence of PD has decreased in Europe since 2001. These results merit further investigation on how to stimulate the use of PD as initial dialysis modality in patients with end-stage renal disease.
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