Starting renal replacement therapy in end-stage renal disease patients
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Chapter 1

Introduction, aims and outline
INTRODUCTION

End-stage renal disease
Kidneys are essential to a person’s health, as these organs are responsible for many processes in the human body. The three most important functions of the kidneys are to remove (toxic) waste products and excess water from the body, to regulate the blood pH, and to produce hormones to regulate the production of red blood cells and blood pressure.\(^1\)

A patient’s kidney function can be determined by estimating the glomerular filtration rate (GFR), which indicates the rate of filtering fluids through the kidneys. For healthy adults the level of GFR is between 90 and 140 ml/min/1.73m\(^2\), but GFR decreases progressively with age in all adults.\(^1-3\) Several factors like the presence of diabetes mellitus or an untreated high blood pressure may cause a more rapid decline in kidney function.\(^1;4\)

There are several markers to be used in the clinical assessment of kidney disease. These markers include albuminuria, abnormalities in urine sediment, electrolyte and other abnormalities due to tubular disorders, and abnormalities detected by histology or imaging techniques.\(^4;5\) All individuals with abnormalities of kidney structure or function, i.e. markers of kidney damage or a GFR <60 mL/min/1.73 m\(^2\), for at least three months with implications for health, are classified into one of the five stages of chronic kidney disease.\(^4\)

The severity of the disease increases with every stage. There is a small proportion of patients who eventually progress towards stage 5 chronic kidney disease. The GFR in this stage has decreased to 15 ml/min/1.73 m\(^2\) or lower and patients and their nephrologists need to consider starting with renal replacement therapy.\(^6\) From the moment that renal replacement therapy is required to sustain the patient’s life, stage 5 chronic kidney disease is being referred to as “end-stage renal disease”.

Renal replacement therapy
Once renal replacement therapy is required, there are two options; treatment with dialysis or kidney transplantation. The latter is regarded as the optimal treatment for the patient, because it results in the best survival, best preserves the patient’s autonomy and enables the patient to live a life that is as normal as possible.\(^7\) This is reflected in the patient’s quality of life, which is rated higher by transplanted patients than by patients receiving dialysis treatment.\(^8;9\)

However, not all patients are considered eligible for a kidney transplantation, for example those with severe cardiovascular or peripheral vascular disease or with disseminated malignancy.\(^10\) Furthermore, since there are extensive waiting lists due to a shortage of donor kidneys, most patients start renal replacement therapy with dialysis.\(^11\) The average waiting time for transplantation differs between countries due to differences in factors such as legislation, transplant system organisation, and infrastructure. In addition, waiting time varies with patient characteristics like blood type, HLA classification and medical urgency. In the Netherlands, the average time on dialysis before receiving a kidney transplant is currently 3.7 years.\(^12\)

Starting renal replacement therapy
Over the last decade there has been a trend towards starting dialysis at higher levels of estimated GFR (eGFR), a measure frequently used to evaluate kidney function.\(^13-15\) It has been suggested that this results in a start before the development of severe signs and symptoms, when the patient still has a good nutritional status and a substantial residual kidney function, and can make a so-called healthy start.\(^16;17\) However, as soon as dialysis
treatment is initiated the GFR may further deteriorate.\textsuperscript{18} Since residual kidney function is associated with a better nutritional status and has an important contribution to the overall health of dialysis patients, the patient's quality of life decreases with a decline in residual kidney function.\textsuperscript{19,20}

Several studies suggested that starting renal replacement therapy at higher levels of kidney function is associated with worse patient survival.\textsuperscript{21-23} The results of a randomised controlled trial aiming to explore the relationship between starting dialysis with a high (10-14 mL/min/1.73 m\textsuperscript{2}) versus a low (5-7 mL/min/1.73 m\textsuperscript{2}) eGFR were published in 2009.\textsuperscript{24} However, for the patients randomised to start at a low eGFR the study protocol permitted starting dialysis before reaching 7 ml/min/1.73m\textsuperscript{2} if the treating nephrologist considered this necessary. The trial results did not show a difference in survival between patients who started dialysis with high or low eGFR levels. Nevertheless, 76% of patients randomly assigned to start at low levels of eGFR actually started at higher levels because of the presence of uraemic signs and symptoms. Although the patients who were randomised to start at low levels of eGFR started six months later than the patients randomised to start at higher levels, there only was a relatively small difference in eGFR between the groups. This emphasizes the importance of the patient’s clinical status in the decision-making by nephrologists regarding the timing of renal replacement therapy.

Better knowledge on other factors involved in the decision-making process by nephrologists is important to inform future studies aiming to relate the patient’s kidney function and clinical status to patient prognosis.

Not starting renal replacement therapy - a conservative approach

Although dialysis is life sustaining, the burden of the treatment is substantial. The dialysis sessions are time consuming and afterwards patients often feel very tired.\textsuperscript{25} In addition, dietary restrictions to control fluid, salt and protein intake are necessary in order to prevent a further decline of the kidney function and an accumulation of waste products in between dialysis sessions. On top of the symptom burden of the kidney disease itself and of treatment burden, patients will need to adapt their daily life drastically.\textsuperscript{26}

Not all patients actually start dialysis, for example patients themselves may choose not to pursue treatment with dialysis.\textsuperscript{27,28} For other patients, such as vulnerable elderly or very ill patients, dialysis treatment may further worsen their health status and/or quality of life and the nephrologist’s advice may be not to start this treatment.\textsuperscript{29,30} The benefits of receiving dialysis may not outweigh its burden for these patients, and therefore in some cases providing conservative care may be a good alternative.\textsuperscript{31,32}

Without providing renal replacement therapy, conservative care focuses on slowing the decline in renal function, but additionally on achieving the best possible quality of life by relieving suffering and controlling symptoms. It involves advance care planning as well as the provision of appropriate end-of life care in the context of physical, social and psychological beliefs of the patient.\textsuperscript{33}

Over the last decades the acceptance rate for renal replacement therapy and the patients’ age at the start of dialysis has increased. As a result, the proportion of older end-stage renal disease patients with comorbidity at the start of renal replacement therapy has increased.\textsuperscript{34} The life expectancy of those older and sicker patients may be very limited.\textsuperscript{35} Dialysis treatment will sustain life for a certain period of time, but patients may have to spend an important part of this prolonged survival time on dialysis days or hospital admissions.\textsuperscript{31} Epidemiological studies on the provision of conservative care in Europe and knowledge
about which factors are considered important in the decision-making process regarding not starting with renal replacement therapy are currently lacking.

Providing dialysis treatment – the initial dialysis modality choice
As soon as the decision to start with dialysis has been made, the patient and nephrologist need to decide upon the optimal dialysis modality for this individual patient: haemodialysis (HD) or peritoneal dialysis (PD).

For treatment with HD, the patient visits a dialysis centre three or four times per week, for a dialysis session of three to eight hours. During a dialysis session, the patient is connected to a dialysis machine (Figure 1). The patient’s blood circulates through this machine to be filtered by diffusion across a non-biological membrane. Small molecules like waste products and excess water will cross the membrane and be removed, while larger molecules such as proteins cannot cross this membrane and will remain in the blood. If the medical condition of the patient permits, this treatment can be performed at home. This also depends on whether the patient is living alone or with a partner, and on the patient’s willingness and capability to be responsible for each dialysis session.1,36

With PD a dialysis solution (1.5 to 3 liter) is infused in the patient’s abdominal cavity, where it remains for four to six hours. The peritoneum, a membrane lining the abdominal cavity, acts as the filtering membrane (Figure 1). The small blood vessels in the peritoneum allow waste products and excess fluid to pass from the blood into the dialysis solution and by emptying the abdominal cavity these products and fluids will leave the patient’s body. The process of emptying and filling the abdomen should be performed manually three or four times per day or by a machine overnight. Treatment is usually performed by the patients themselves at home.1

Fig 1: Schematic overview of HD (left) and PD (right).

Only for specific patient groups substantial survival benefits for HD or PD have been suggested.37-39 Therefore, if medical contraindications are absent, modality choice mainly depends on factors like the patient’s and physician’s preference, social support, and capacity in the dialysis centres.40
The ERA-EDTA Registry

A large share of the work in this thesis is based on data from the registry of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA). On a yearly basis, the ERA-EDTA Registry collects data on European end-stage renal disease patients receiving renal replacement therapy. The ERA-EDTA Registry was established in 1965. Since June 2000 the Registry office has been housed in the Department of Medical Informatics in the Academic Medical Center in Amsterdam, The Netherlands. The Registry collects aggregated and individual patient from national and regional registries in the ERA-EDTA area. An annual report is produced to present and summarize these data.

For the research in this thesis we used the data from countries providing the ERA-EDTA Registry with individual patient data. These include the patient's date of birth, sex, cause of renal failure, history of renal replacement therapy with dates of start and changes in treatment modality, treatment centre, and date and cause of death.

OBJECTIVES

The research reported in this thesis aims to contribute to the knowledge related to the start of renal replacement therapy in patients with end-stage renal disease. The objectives are threefold;
1) To examine opinions of European nephrologists about which clinical, social, or logistical factors influence their decision on whether and when to start renal replacement therapy.
2) To investigate the association of medical and non-medical factors with dialysis modality choice. These factors include demographic and co-morbid factors, as well as macroeconomic factors and renal service indicators.
3) To study dialysis modality specific patient survival and its trends in relation to contemporary changes in dialysis modality choice, technique survival and (pre-emptive) transplant rates in Europe.

OUTLINE OF THIS THESIS

Chapter 2 comprises a summary paper of the 2009 ERA-EDTA Registry Annual Report and provides an overview of the epidemiology of renal replacement therapy in Europe.

For Chapter 3 we performed an online survey to evaluate nephrologists' opinions on when to start renal replacement therapy. The results show which social, clinical and logistical factors are considered important in the decision-making by nephrologists.

Chapter 4 presents the second part of this online survey and focused on which factors are taken into account by nephrologists when they decide not to start renal replacement therapy but to provide conservative care instead. This study also describes the occurrence of conservative care in Europe and the patient involvement in the decision-making process.

In Chapter 5 we examined dialysis modality choice for subgroups of patients based on age, sex, and the presence of diabetes, cerebro- or cardiovascular disease, ischaemic heart disease, or malignancy at the start of dialysis. We additionally evaluated whether dialysis modality choice was in line with patient survival in these groups of patients.

In Chapter 6 we compared the survival of patients with diabetes as primary cause of renal failure (diabetic nephropathy) with that of patients with diabetes as co-morbid condition.
Chapter 7 presents the patient characteristics, macroeconomic factors, and renal service indicators that are associated with the proportion of patients in a country starting dialysis on PD. For this study we used data from the EVEREST study (Explaining the Variation in Epidemiology of RRT through Expert opinion, Secondary data sources and Trends over time).

Chapter 8 describes the temporal trends in dialysis modality specific patient survival and discusses them in relation to changes in technique survival, transplantation activity and modality choice over the same period. These changes are then put in the perspective of trends in dialysis modality specific incidence and prevalence.

Finally, the results of all chapters are summarised and discussed in the general discussion in Chapter 9. This final chapter additionally puts the results in a broader perspective and elaborates on ideas for future research.
References


