Determinants of outcome dialysis
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Summary
End-stage renal disease can be due to many different conditions. If left untreated, it will lead to death. The removal of waste products and excess fluid from the blood, functions that are normally fulfilled by the kidneys, can be taken over by dialysis. Because of the shortage of organ donors, most ESRD patients will for at least a part of their lives be dependent on dialysis treatment.

In Chapter 1 it is outlined that the number of dialysis patients in the Netherlands keeps growing. Currently, more than 1300 patients start dialysis therapy each year. The growth in the number of dialysis patients was accompanied by increasing mortality rates. This has led to the initiative of the Dialysis Group Netherlands (DGN) to start the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a prospective multicenter study. The first aim of this study was to prospectively investigate the association of patient and therapy characteristics at 3 months after the start of dialysis with outcome. The second aim of this study was to define adequate dialysis and to develop treatment guidelines applicable to the Dutch dialysis population. This thesis deals with the first NECOSAD cohort and its outcome.

In Chapter 2 the characteristics of these patients at 3 months after the start of dialysis (baseline) are reported. Chapter 2.1 provides a description of their clinical condition and puts this patient population in a European perspective. Two hundred and fifty consecutive new patients from 13 centers were included. Their mean age was 57 years and 58% were male. Renal vascular disease was the most frequent cause of ESRD; comorbid conditions were present in 51%, diabetes mellitus in 18%, and cardiovascular disease in 28%. Multivariate linear regression showed that decreased protein intake was related to diminished residual renal function. Blood pressure was associated with age and ESRD. Our patients did not seem to have more comorbidity than Dutch patients participating in a European study some years earlier. Comparison with other European studies was complicated by the use of different definitions of comorbidity and of selected patient populations.

It is concluded that the patients starting dialysis in the Netherlands have become older and that the incidence of diabetic nephropathy has increased. From this study no conclusions could be drawn on a concomitant increase in comorbidity. However, our patient group was representative for new dialysis patients in our country in the period 1993-1995 and may therefore serve as a reference population to study future changes in patient case-mix within the Netherlands. Furthermore, it was stressed that the use of common international definitions of comorbidity is needed to be able to make comparisons of survival data.

In Chapter 2.2 details on the quality of life at baseline are provided and put into the perspective of the quality of life of a Dutch general population sample.
addition, the relationship of quality of life with demographic, clinical, renal function and dialysis characteristics is identified. Patient's self-assessment of quality of life was measured by the SF-36, a 36-item questionnaire encompassing eight dimensions: physical functioning, social functioning, role-functioning physical, role-functioning emotional, mental health, vitality, bodily pain and general health perceptions. With multiple linear regression analysis we identified the independent explanatory variables of the quality of life dimensions. One hundred and twenty hemodialysis and 106 peritoneal dialysis patients completed the SF-36. Their quality of life was substantially impaired in comparison to the general population sample, particularly with respect to role-functioning physical and general health perceptions. Hemodialysis patients showed lower levels of quality of life than peritoneal dialysis patients on physical functioning, role-functioning emotional, mental health and pain. However, on the multivariate level, we could only demonstrate an impact of dialysis modality on mental health in favor of peritoneal dialysis. A higher number of comorbid conditions, a lower hemoglobin level and a lower residual renal function were independently related to poorer quality of life. The variability of the SF-36 scores explained by selected demographic, clinical, renal function and dialysis characteristics was highest for physical functioning (29.7%). Explained variability of the other SF-36 dimensions ranged from 6.9% for general health perceptions to 15.4% for vitality.

We conclude that the quality of life of new ESRD patients is substantially impaired. Comorbid conditions, hemoglobin and residual renal function could explain poor quality of life only to a limited extent. Further research exploring determinants and indices of quality of life in ESRD is needed. From a clinical perspective we conclude that quality of life should be considered in the monitoring of dialysis patients.

In Chapter 3 treatment and mortality are reported. The first part, Chapter 3.1, deals with case-mix differences among the participating centers and with dialysis treatment over time. A comparison is made with current US guidelines on the adequacy of dialysis. Mortality, hospitalization and the time course of renal function and blood pressure are described and outcome in the elderly subgroup is reported separately.

There were considerable differences in patient populations among dialysis centers with respect to age, comorbidity and residual renal function at baseline. Approximately 40% of the hemodialysis patients and more than 50% of the peritoneal dialysis patients received adequate dialysis according to guidelines currently advised in the US. In hemodialysis patients this percentage increased over time, but in peritoneal dialysis it decreased. Patient survival was 76% at two years. With Cox proportional hazards regression we demonstrated that a higher age, the presence of comorbidity, a higher systolic blood pressure and low serum albumin levels were risk factors for mortality. There was no survival difference between the
dialysis modalities. Technique survival was higher in hemodialysis. Hospitalization rates decreased from 25 days between 3 to 12 months to 19 days per patient year in the third year. Residual renal function decreased at a similar rate in both modalities, but blood pressure tended to increase in females receiving peritoneal dialysis.

We concluded that outcome was predominantly dependent on patient characteristics at 3 months after the start of dialysis. In the light of the increasing age of patients starting dialysis, increasing mortality can be expected. Furthermore, if outcome is to play a role in the quality assessment of dialysis centers, it is essential to know the characteristics of their patient populations.

In Chapter 3.2 we present the determinants of mortality and technique failure in patients who started peritoneal dialysis. While other studies have shown an association between small solute clearance and patient survival, little attention has been paid to the potential effects of fluid overload. In this study Cox proportional hazards regression was used to determine the risk factors for mortality and technique failure in patients starting peritoneal dialysis. There were 33 deaths and 44 technique failures. Two-year patient survival was 77% and two-year technique survival was 64%. A higher age, a higher systolic blood pressure and a lower absolute quantity of small solutes removed at baseline were independent risk factors for mortality. A one-year increase in age was associated with a relative risk (RR) of death of 1.05 (95% CI, 1.01 to 1.09) and a 10 mm Hg rise in systolic blood pressure with a RR of 1.42 (95% CI, 1.17 to 1.73). The removal of 1 mmol/week/1.73m² of urinary and dialysate creatinine were associated with a RR of death of 0.95 (95% CI, 0.92 to 0.98) and 0.93 (95% CI, 0.89 to 0.98). The removal of urea had a similar association with the RR of death. Risk factors for technique failure were a low urine volume, a low peritoneal ultrafiltration and a high systolic blood pressure.

From this study it is concluded that dialysate solute removal is an independent predictor of mortality. Furthermore, the association between systolic blood pressure and mortality shows that the maintenance of fluid balance and small solute removal deserve equal attention.

The subject of Chapter 4 is nutritional status. It is known that malnutrition is a risk factor for mortality in the dialysis population. So far, prospective studies comparing the time course of nutritional status in incident hemodialysis and peritoneal dialysis patients have not been published. The aims of this study were to compare the time course of nutritional status in patients starting hemodialysis or peritoneal dialysis and to identify the baseline determinants of that time course. Data were collected up to 24 months after the start of dialysis. Repeated-measures analysis of variance was used to establish the changes in nutritional status over time. Differences between groups were adjusted for baseline characteristics.
Univariate analysis demonstrated a decrease in serum albumin in hemodialysis and an increase in peritoneal dialysis patients. Body fat increased, lean body mass did not change. The protein equivalent of nitrogen appearance (PNA) normalized to ideal weight, decreased in peritoneal dialysis after one year. In multivariate analysis, serum albumin at 2 years was 2.0 g/l (95% CI, 0.3 to 3.8) higher in patients who started on peritoneal dialysis. The increase in body fat was 3.2 kg (95% CI, 1.6 to 4.9) higher in females on peritoneal dialysis than in others. Diabetics gained 2.3 kg (95% CI, 0.6 to 4.1) more fat than nondiabetics. Kt/V_urea did not affect the time course of nutritional status, but a higher Kt_urea was associated with a higher serum albumin at 24 months.

Mostly, dialysis modality choice is made on the basis of patient preference and medical criteria. We conclude that the results of this study may implicate that the nutritional status at the start of dialysis, together with the patient's sex and diabetic status, are among the factors to consider when a choice for one of the dialysis modalities is made. Patients whose energy stores are low, may benefit to a larger extent from peritoneal dialysis, whereas this treatment may have undesirable effects in overweight or obese females and diabetics. In addition, the results of this study indicate that Kt_urea may be a better measure of dialysis dose than Kt/V_urea and that the patient's protein metabolism may be improved by providing a higher Kt_urea.

In Chapter 5 the time course of quality of life over the first 18 months after the start of dialysis treatment is studied. Repeated measures analysis of variance was used to establish changes in quality of life over time, differences in quality of life between dialysis modalities and interaction between changes over time and dialysis modality. Patient's self-assessment of quality of life was measured with the SF-36 at 3, 6, 12 and 18 months after the start of dialysis treatment. Out of 230 patients who completed the questionnaire at least once, 139 patients stayed on their initial dialysis modality, 26 patients switched dialysis modality, 35 patients received a kidney transplant, 28 patients died and in 2 patients renal function recovered. The quality of life of patients who died during the study period was considerably worse at baseline and worsened at a faster rate than in the other patient groups. In patients who stayed on their initial dialysis modality, the physical quality of life decreased over time, whereas the mental quality of life tended to remain stable. After adjustment for the initial value of quality of life and comorbidity, a consistently favorable effect of hemodialysis on the physical quality of life over time was found compared to peritoneal dialysis, whereas the mental quality of life remained similar. Parameters of adequacy of dialysis were not associated with quality of life over time.

We conclude that this prospective cohort study indicates that the decrease in the physical quality of life over time in peritoneal dialysis patients may be faster than in hemodialysis patients.
The purpose of the general discussion, Chapter 6, is to integrate our findings where possible and to put them into the context of recent literature. In Chapters 1 to 5 outcomes were reported together with their determinants. In Chapter 6 the determinants are taken as a starting point and their influence on several outcome measures is discussed. It is concluded that NECOSAD-1 has shown that, in general, patient factors are the most important determinants of outcome in dialysis. The larger sample size of NECOSAD-2 will allow the further study of the effects of dialysis on outcome in the entire cohort and in subgroups. Finally, suggestions for future research are provided.