



Netherlands Cooperative Study
on the Adequacy of
Dialysis

Final report

Final report Necosad

**Netherlands Cooperative Study
on the Adequacy of
Dialysis**

Naarden, October 2003

Foreword

This is the final report of Necosad, the **NE**therlands **CO**operative **S**tudy on the **A**dequacy of **D**ialysis. This study was initiated by the Dialysis Group Netherlands and was largely financed by the Dutch Kidney Foundation.

This final report provides a survey of the activities that were carried out within the framework of the study. However, the Necosad project has not only yielded scientific results, but has also significantly promoted the interest in the quality of dialysis. "Necosad one step ahead" was the slogan with which the project began. This step could only be made thanks to the commitment of a large number of enthusiastic parties involved.

The study would not have been possible without the almost 2000 patients who rendered their assistance and gave permission for the use of their medical data. They collected urine and donated extra blood samples. Time and again they proved to be prepared to fill in questionnaires and to cooperate in the assessment of their nutritional status.

The assessments in the participating dialysis centers were largely carried out by dialysis nurses. Their enthusiastic involvement was the motor of the study that was steered by the nephrologists in the centers.

Many nurses and doctors participated in the annual Necosad symposiums. The Necosad Newsletter was published three times a year on average, providing information on the progress of the study. In this way Necosad has also managed to make a contribution with respect to "quality thinking".

Necosad has not remained limited to the Netherlands. During international conferences presentations were and still are given about the study. The Necosad publications are quoted regularly. Researchers from abroad seek cooperation with respect to the development of guidelines and the determination of factors that might be relevant to the outcome of dialysis therapy. The Necosad database and the frozen samples prove to have great value for future research as well. Research groups wishing to use the database can approach the Hans Mak Institute, where the Necosad data have been stored. Like the Renine database, the Necosad database is not freely accessible, but on request aggregated data can be made available in an anonymous form.

Therefore it may be concluded that although Necosad has stopped, it has not entirely finished. In the next few years Necosad is bound to be mentioned often in publications and presentations alike.

Naarden, 14 October 2003

Dr. E.W. Boeschoten
Hans Mak Institute
Koningin Wilhelminalaan 29 B
1411 EL Naarden

Tel. +31-35-678 30 00
e-mail: info@hansmakinstituut.nl

TABLE OF CONTENTS

Introduction

Patients and methods

- Patients
- Randomized trial
- Data collection
- Validation of parameters
- Performance of the study

Results

- Chief factors determining the outcome of dialysis
- Tests and development of guidelines for optimal dialysis
- Contributions to the quality of the therapy inter alia through feedback of center-specific results and the development of benchmarks for clinical and therapy characteristics
- Other research

Future possibilities

Necosad Publications

Introduction

Renal replacement therapy by means of dialysis has been possible since the late 1960s. Due to the small number of dialysis centers a strict selection was initially applied for this life-saving treatment. People over 40 did not qualify for dialysis.

Adequate planning of this scarce and costly provision was thus one of the main reasons why in 1971 dialysis was ranged under the regulations of Article 18 of the Hospital Provision Act [*Wet ziekenhuisvoorzieningen*]. In order to steer the planning to a certain extent, the annual DGN (Dialysis Group Netherlands) enquiry was set up in 1983, whereby patients who were treated with dialysis and transplantation were registered in all Dutch centers. This registration of demographic data and data on the type of renal function replacement therapy merged in 1986 into Renine (REgistratie NIervervangende behandeling NEderland; i.e. registration of kidney-replacing therapy Netherlands). In the past few years the Renine database has not only been used for the development of scenarios within the context of planning sufficient dialysis capacity, but also as a benchmark in the assessment of dialysis centers during the site visits by nephrologists and dialysis nurses that are conducted within the framework of certification and accreditation.

The first ideas for a Netherlands Cooperative Study on the Adequacy of Dialysis (Necosad) arose in 1991, when the medical profession came to realize that despite all the efforts made (such as improvements of dialysis equipment, dialysis liquids, expansion of the possibilities for additional medicinal treatment), the mortality of dialysis patients had not decreased in the past decade. Was this because increasingly older and sicker patients were admitted to therapy or was the adequacy of the treatment insufficient? Could the outcome of dialysis be improved by developing evidence-based guidelines for this treatment?

To investigate this, it would be necessary to collect data of a large number of Dutch dialysis centers: not only clinical and biochemical patient-specific data, but also data on modalities and doses of dialysis. It became a large prospective study, whose data could be used for clinical epidemiological analyses and the development of guidelines for an optimal treatment, as well as for expansion of the benchmark by clinical and treatment data.

Necosad was started in 1993, as a feasibility study for a two-year period of 250 patients from 13 centers, and was financed by the Dutch Kidney Foundation. On the basis of this pilot study, Necosad-1, a more extensive study involving 1500 patients was started in 1997, Necosad-2. 38 out of the 50 Dutch dialysis centers participated in this study. Necosad was an initiative of the Dialysis Group Netherlands, which towards the end of 2002 was absorbed by the Netherlands federation for Nephrology (NfN).

Objectives of Necosad.

1. Analysis of the factors determining the outcome of dialysis. Were the disappointing results caused especially by patient characteristics (such as age and comorbidity) or was it particularly the dialysis therapy itself that was to blame?
2. Tests and development of guidelines for optimal dialysis
3. Contributions to the quality of therapy, for instance through feedback of center-specific results and the development of benchmarks for clinical and therapy characteristics

Patients and methods

Patients

Only adult (older than 18) incident dialysis patients qualified for participation in Necosad who had not been treated before with any form of kidney-replacing therapy. Written consent was a requirement. In the participating centers the treatment was conducted in the way customary for each individual center. The influx of consecutive patients in a center was 2 years, but inclusion of new patients after that period remained possible. Initially the follow-up period after closing

the inclusion was to be 2 years. In order not to lose the possibility of analyzing the effects of long-term treatment, this period was extended by another 2 years. And in order to be able to analyze shifts of trends in treatment, the influx was continued in a number of centers.

Randomized trial

To allow analysis of the actual differences between hemodialysis and peritoneal dialysis, a randomized trial of hemodialysis versus peritoneal dialysis was conducted within the Necosad cohort. This trial was financed by the Health Insurance Fund Council. Patients without clear contra-indications for one of the two modalities of dialysis were asked in the predialysis phase to take part in the trial. Patients who had been included via randomization were subsequently treated in the same manner as patients in the cohort. The gathering of data was also identical. At the request of the renal patient association (LVD) an ombudsman was appointed so as to exclude wrongful pressure on patients.

Data collection

The following data were registered in patients 4 to 0 weeks before the start of dialysis: demographic data (date of birth, sex, ethnic origin), initial therapy and the reason for choosing this, predialysis care, primary renal disease (EDTA code), comorbidity (both its incidence and its seriousness), smoking habits, height, body weight, blood pressure, medication, laboratory investigations (albumin, urea, creatinine), renal function (average creatinine and urea clearance), quality of life.

Subsequently registration of the following data took place at 3, 6, 12, 18 etc. months after the initiation of dialysis: modality of dialysis, therapy changes (including kidney transplantation) and reasons for this, registration on a waiting list for kidney transplantation, target weight, actual weight (in case of hemodialysis before and after dialysis), blood pressure (in case of hemodialysis before and after dialysis), diet, nutritional status, assessed as Subjective Global Assessment (SGA) and BMI (until 2002 anthropometry as well), medication, hospitalizations, duration and reasons for this, laboratory investigations (Hb, Ht, ferritin, Na, K, bicarbonate, Ca, PO₄, alkaline phosphatase, PTH, cholesterol), urea and creatinine kinetics, residual renal function, Karnofsky index, quality of life.

At all intervals of the assessment, samples of serum, dialysate and (if there was still any urine production) urine were taken and frozen. It was possible to collect DNA material from the majority of patients.

The questionnaires relating to the quality of life were filled in by the patients themselves, whilst the dialysis nurses in the centers performed the assessment of the nutritional status.

Considering that the first assessments in patients taking part in the pilot, Necosad-1, were performed only three months after the start of the treatment, no data about the residual renal function and quality of life for these patients are available from the time when dialysis was started.

Validation of parameters

Before the study was started a number of parameters to be used had to be checked for their usefulness and had to be validated for the dialysis population.

Quality of life

Quality of life was used within the Necosad study as one of the outcome measures of the study. Measuring the quality of life has its own methodological problems. Indeed, the quality of life is strongly determined by the case-mix, i.e. the composition of the patient population researched, in which comorbidity is an important factor. On the basis of an extensive literature survey [1] it was concluded that a combination of a generic and a disease-specific measuring instrument would suit the purpose best. The choice was made for the KDQOL-SF, a combination of a generic (SF-36) and a disease-specific instrument for measuring the quality of life in renal patients that is also relatively easy to fill in for patients. The suitability of this measure for the dialysis population was examined in a separate study [2]. This study showed that the KDQOL-SF also has excellent psychometric characteristics for dialysis patients. The

dialysis-specific dimensions proved to be informative, possessed a high degree of reliability and validity and the different patient groups could be distinguished clearly. The added value of renal-disease- and dialysis-specific questionnaires was investigated three months after the start of the treatment in HD and PD patients [3]. Fatigue (HD 82% and PD 87%) and itch (HD 73%, PD 68%) were the most frequent complaints. In HD patients mild to serious comorbidity proved to be associated with the severity of the complaints, in PD patients this proved to be related also to a lower percentage of fat-free mass, a reduced residual renal function and episodes of dehydration. The total variance of complaint scores accounted for by these variables was 12% for HD and 21% for PD. By adding a complaints analysis to demographic and clinical data, it became possible to account for over one third of the score variance of the quality of life experienced.

Comorbidity

Patient selection is an essential problem in epidemiological research. One can only adjust for factors that are known. This is the reason why randomized trials are regarded as the “golden standard”. Comorbidity is a familiar problem. Different measuring instruments (Kahn, Davies, Charlston) measure the presence or absence of diseases. Obviously, the seriousness of the condition may be relevant as well. The various methods for measuring comorbidity in the dialysis population were investigated. As the severity of the conditions had been inquired into within Necosad as well, it was possible to develop a new index for dialysis patients in which the severity of the additional disease could be weighed as well. Considering that the predictive value of this new index turned out to be hardly any better than existing measuring methods, it was concluded on the basis of this study that the existing methods were sufficient [4, 5]. The predictive values of the Kahn, Davies and Charlston scores were similar.

Nutritional status

Which is the best method to apply for assessing the nutritional status in a large multi-center study of dialysis patients? It is a known fact that the usefulness of anthropometric measuring methods is limited. In a Canadian-American study of peritoneal dialysis patients (the CANUSA study) “subjective global assessment” (SGA) was the measure used. Thereby researchers had deviated from the original 3-point scale and used a finer-meshed 7-point scale. This method had not been validated in dialysis patients, however. The validity of the 7-point SGA was studied and demonstrated in the Necosad cohort [6].

Renal function

Calculation of the (residual) renal function, expressed as (r)GFR or as Kt/V-urea, requires data about the urea concentration in the urine. Occasionally this information is absent from clinical practice, but also in the cohort study, whereas the creatinine clearance is known. For this reason a formula was developed by means of which the (r)GFR could be calculated precisely from the creatinine clearance and the 24-hour urine volume. Determination of the Kt/V-urea from the creatinine clearance yielded less reliable values [7].

Performance of the study

Upon the start of Necosad a foundation: “Stichting Necosad” was created. The project leaders formed the executive committee, while the Supervisory Board consisted of two members on behalf of the Dutch Kidney Foundation and two members on behalf of the DGN. The performance of the study took place from the Necosad office that was accommodated in Amsterdam-Buitenveldert. The researchers were supervised by staff members from the departments of nephrology and clinical epidemiology and biostatistics of the Academic Medical Center in Amsterdam and the Leiden University Medical Center.

In the centers the research forms were filled in by the dialysis nurses from the centers that had been earmarked for the performance of the Necosad study. They also conducted the assessments of the nutritional status of the patients. These “Necosad nurses” cooperated closely with the research nurses of Necosad. The research nurses provided explanation and instructions in the centers, collected the frozen samples, were responsible for the correct entry

of data in the database and were always available for questions and suggestions. Together with the researchers and the research nurses the project leaders formed the project group. The supervisory committee, consisting of nephrologists from the participating centers, was convened for advice at least once every year, but usually more frequently.

The check for completeness of the patient file was conducted by comparing the included population with the patients who had been reported at Renine in the same period. A check for the accuracy of the data collected by Necosad was made by the research nurses of Necosad monitoring these data in the centers.

Once every year, and more often on request, the data at patient level were forwarded to the centers. In addition, centers that had included 20 or more patients received outcomes annually at the center level, with other (anonymous) centers as a benchmark.

Results

Table 1 shows the patients included in the Necosad study from 1997 to March 2003. The average age of these incident dialysis patients had increased by 2.4 years in comparison with the Necosad-1 cohort (1993-1995). This tendency was also observed in the Renine registrations. Patients starting on hemodialysis (HD) were more than 10 years older on average than patients in whom peritoneal dialysis (PD) was started. HD patients also had higher comorbidity and their physical condition, measured by the Karnofsky score, was worse. In patients starting on HD the underlying renal disease was more often related to vascular suffering than in PD patients. In the latter group the incidence of glomerulonephritis was relatively greater. The incidence of diabetes mellitus as the cause of the renal insufficiency was equal in both groups. The GFR in PD patients at the start of dialysis was slightly higher on average.

Table 1 Patient characteristics Necosad-2 (1997-2003) at the start of the treatment

		All Patients	HD	PD
Number of patients		1708	1094	614
Age (av. (SD))		59.4 (15.1)	63.3 (13.9)	52.9 (14.9)
Sex (% male)		61	59	66
Davies's comorbidity score	Low	45	38	57
	Medium	45	50	35
	High	10	12	8
Karnofsky (physical functioning) (av. (SD))		79.1 (15.5)	76.0 (16.1)	84.5 (13.0)
Primary Renal Disease (%)	Diabetes	16	15	16
	Glomerulonephritis	13	10	20
	Renal Vascular Conditions	19	22	13
	Other	52	53	51
Residual renal function GFR (ml/min/1.73 m ²) (av. (SD))		5.12 (3.10)	4.75 (3.26)	5.57 (2.87)
Renal Kt/V-urea (/wk) (av. (SD))		0.8 (0.6)	0.7 (0.6)	0.8 (0.6)

The inclusion of patients did not proceed equally rapidly in all centers, which was mainly due to a delay in obtaining permission for the study from the medical ethics committees of the participating centers. It is remarkable that by the middle of 2003 there were still 36 centers participating in Necosad, usually by continuing the measurements in patients who had been included in preceding years (figure 1).

The influx and efflux of patients per year can be seen in figure 2. The efflux, due to death and kidney transplantation, exceeded the influx as from 2000.

The result of an efflux exceeding the influx is a decreasing patient number (figure 3).

On 1 July 2003 there were still 596 patients participating in Necosad; 167 of these patients had been on dialysis for longer than five years.

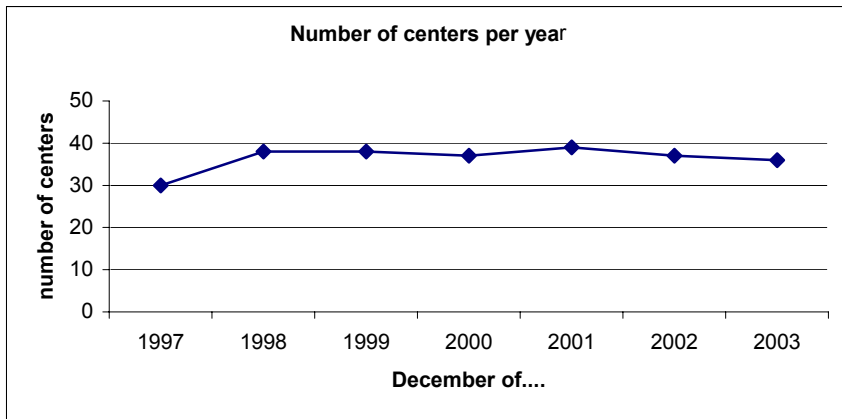


Fig. 1 Number of participating centers

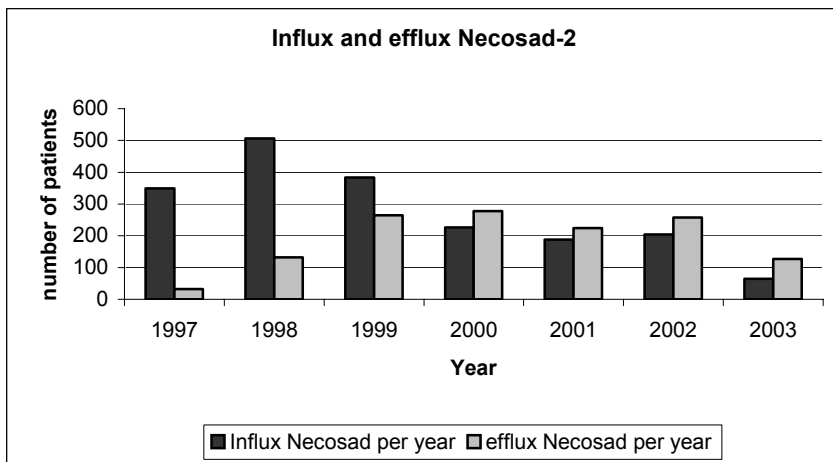


Fig. 2 Influx and efflux of patients on an annual basis (2003 incl. June)

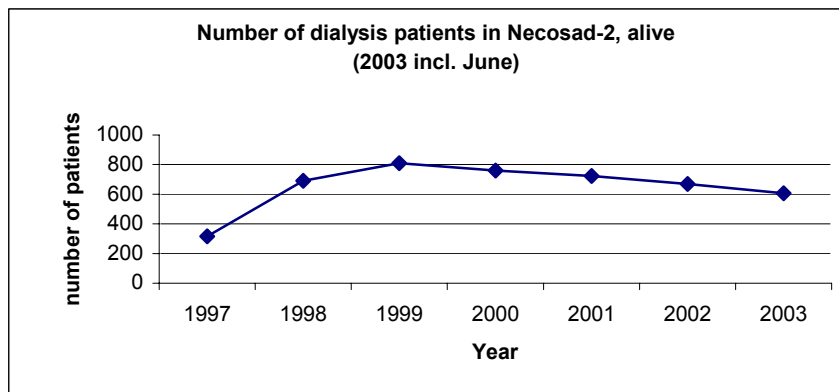


Fig. 3 Number of dialysis patients in Necosad-2, alive (2003 incl. June)

Objective 1. Chief factors determining the outcome of dialysis

The outcome parameters used in the investigation of the factors determining the outcome of the treatment were mortality, morbidity (number of hospitalizations and days of admission) and quality of life. First of all the patient population was described. To what extent did it differ from dialysis populations in other European countries? It appeared that comparison with other European studies is complicated by the use of different definitions of comorbidity and because different patient populations are studied [8]. If the treatment results of dialysis populations are to be compared, common definitions, for instance of comorbidity, are required.

In another analysis of the Necosad cohort the quality of life of the dialysis patients was compared with that of the Dutch population. Furthermore, the relation between quality of life and demographic, clinical (for instance residual renal function) and dialysis characteristics was studied [9]. It is hardly surprising that even at the start of dialysis the quality of life of patients in comparison with the average population was considerably reduced. This was the case especially for the dimensions of physical functioning, role constraints resulting from emotional problems, mental well-being and pain. Comorbidity, hemoglobin and residual renal function could account for the lower quality of life to a limited extent only.

The importance of adjustment for differences between patient groups existing already at the initiation of therapy with respect to quality of life was shown in a group of patients of whom demographic data, clinical data, GFR and HRQOL had been registered 0 to 4 weeks prior to the start of dialysis. After adjusting for age, sex, comorbidity, albumin, nPNA and residual renal function, patients who were about to start on HD had a poorer quality of life compared to patients that were starting on PD [10]. This means that if one wants to study differences in outcome between the two treatments, it is essential to adjust for these baseline differences.

The importance of baseline adjustments for quality of life was shown in an analysis of the course of the quality of life during the first 18 months of dialysis. In this study it appeared that the quality of life of patients who died during the observation period was already significantly worse at the start of the dialysis than that of patients who stayed alive longer. An opposite pattern was seen in patients who were transplanted during follow-up. In them the quality of life at the start of dialysis was even better than with the other dialysis patients [11]. After adjustment for differences in quality of life and comorbidity at baseline a consistently favorable effect of HD – in comparison with PD – on the physical quality of life was observed, while the mental quality of life remained equal. The dose of dialysis, measured as Kt/V-urea, proved not to be associated with the course of the quality of life over time.

An interesting question is whether a poor outcome of dialysis can be predicted in some way or other. For this a composed measure was developed, a measure for poor outcome, which comprises information on survival, morbidity and quality of life [12]. By means of multivariate logistical regression the baseline patient characteristics and the treatment characteristics were identified that predicted this poor health outcome one year after the start of chronic dialysis. Moderate to serious comorbidity, a serum albumin ≤ 30 g/l, a low physical and mental quality of life (≥ 2 SD below the standard value) and an (r)GFR ≤ 2.5 ml/min at the start of the treatment proved to be associated with a chance of a poor health outcome.

What is the significance of the residual renal function in dialysis patients? Does a certain clearance of small molecular substances by the kidney have a similar effect as the same clearance by means of dialysis? A number of publications, including the DOQI-guidelines for an adequate dose of dialysis, assume that there is equivalence between dialysis and renal clearance. The incorrectness of this assumption could be demonstrated in the Necosad study [13]. The clearance of small molecular substances was measured in predialysis patients without dialysis and in PD patients without residual renal function. Predialysis patients with only renal clearance proved to be in a better nutritional status than anuric PD patients. In these patients there were fewer signs of uremic anorexia. What had already been assumed proved to be true: the kidney does more than a dialysis membrane can replace.

In dialysis patients the preservation of the renal function could be relevant for a good outcome. Possible chief predictors of the decline rate of the renal function in dialysis patients were investigated [14]. Similar to results from earlier studies, it was found that the renal function in patients receiving PD treatment is preserved better than in HD patients. A high diastolic blood pressure, proteinuria, hypotension during dialysis and dehydration were the factors that proved to be most directly related to a decline of the residual renal function. All these factors may be prevented or treated by a good therapy.

A poor (residual) renal function is related to a poor nutritional status. The fact that when the renal function of predialysis patients declines the appetite decreases, explains why according to the American DOQI-guidelines a poor clearance of small substances (measured as Kt/V-urea) as well as a reduced protein intake (< 0.8 g protein/kg/day, measured as nPNA) formed a reason for starting dialysis. The relation between Kt/V and nPNA was examined in Necosad patients shortly before they started dialysis treatment [15]. It was evident that the relation between renal function and nutritional status in Necosad patients was different from findings in the United States. Given an identical Kt/V, Dutch patients proved to have a higher nPNA than patients from the USA [15]. This indicates that evidence-based guidelines are only valid for the population in which they have been developed.

What is the course of the nutritional status in the Necosad population? Is it affected by the modality and dose of dialysis? The course of the nutritional status was investigated over a 24-month period in the first 250 Necosad patients [16]. In HD patients the serum albumin dropped, whereas it rose in PD patients. The percentage of body fat increased, while the lean body mass did not change. The body fat increased especially in women treated with PD and in patients suffering from diabetes mellitus. The Kt/V-urea had no effect on the course of the nutritional status. This study suggested that Kt urea could be a better measure for the dose of dialysis than the Kt/V-urea. With Kt/V-urea the body weight is incorporated into the formula via the V (volume of distribution of urea), which may lead to malnourished patients with low body weights having a higher Kt/V than well-nourished patients. Not Kt/V-urea but Kt urea proved to be associated with a higher serum albumin at 24 months after the start of dialysis.

There appeared to be considerable differences between the patient populations of the Dutch dialysis centers with respect to age, comorbidity and residual renal function at the beginning of the treatment [17]. Two years after the start of dialysis the patient survival rate was 76%. It was shown that a higher age, the presence of comorbidity, a higher systolic blood pressure and a lower serum albumin were risk factors for mortality. There was no difference in survival between the two modalities of dialysis. Technique survival was higher with HD. The number of days of admission dropped from 25 days between 3 and 12 months to 19 days per patient per year in the third year. It could be concluded from this study that the result of dialysis in the short term (three years) depends especially on the patient characteristics at the start of dialysis.

The determinants of mortality and technique failure were investigated further in patients starting on PD [18]. A higher age, a higher systolic blood pressure and a lower absolute quantity of removed waste products at baseline were independent risk factors for mortality. In this study, too, the total clearance of urea (Kt urea) proved to be a better predictor than the Kt/V-urea. Risk factors for technique failure were a low urine volume, a low peritoneal ultrafiltration and a high systolic blood pressure.

Several years later it was possible to analyze the effect of the dose of dialysis and the residual renal function on the outcome of the treatment of PD patients in a larger cohort of patients [19]. In this study no effect of peritoneal clearance could be shown on survival, nor on quality of life. However, the residual renal function had a positive effect because it was associated with a better survival and a better quality of life.

A similar study was conducted in HD patients [20]. In this patient group a positive effect of the preservation of residual renal function was established as well. In contrast to the findings in PD patients, it was possible in HD patients to demonstrate an effect of the clearance of small molecular substances with dialysis. Particularly in HD patients without residual renal function a positive effect on survival and quality of life could be shown. Moreover, the prevention of fluid overload and dehydration proved to be relevant to survival.

Effects of the dose of dialysis could not be demonstrated in dialysis patients keeping their jobs [21]. At the start of dialysis only 35% of the dialysis population younger than 65 turns out to have a job. This is considerably less than is the case for the ordinary Dutch population (61%). More PD patients had jobs at the start of treatment than HD patients (48% versus 31%), but in either group the number of people employed dropped by a similar percentage. The quality of life experienced was important to keeping one's job. The modality and dose of dialysis proved to have no influence on this.

Differences in the dose of dialysis between HD and PD are evident, but does this lead to a difference in outcome between the two modalities? Various studies have come up with different results. In some the result with PD was better, in others a better result was found with HD, whilst yet another study showed no difference in results. A problem in most studies is that different patient populations are observed and that different statistical analyses are used. In addition, censoring is applied in different ways for patients who changed modalities. The advantage of the Necosad study is that both HD and PD patients were followed from the start of treatment and that it was possible to adjust for a large number of patient characteristics. In the analysis of Necosad, PD patients tended to have a better survival for the first two years compared to HD patients [22]. However, this difference was not significant. After this period the mortality rate in PD patients began to increase, which resulted in a decrease in the relative risk in HD patients. The higher mortality rate of PD as against HD was found especially in patients who were older than 60 and who were treated longer than two years.

Although the Necosad study allows adjustment for a large number of patient characteristics, the problem remains that it is impossible to do so for unknown factors. For this reason a randomized trial of HD versus PD was carried out. Particularly because a modality of dialysis has a great influence on the life of patients, it turned out to be impossible to achieve the set target: inclusion of 100 randomized patients. Nonetheless it was possible to draw some interesting conclusions from the analysis of the randomized patients (18 HD and 20 PD) [23]. The QALY (quality adjusted life years) was used as an outcome measure, whereby one considers not only mortality, but also the quality of life during the treatment. With respect to the QALY no difference between the two modalities was shown. In patients starting on PD the 5-year survival rate proved to be better than in HD patients. The number of patients that changed modality was larger in PD (7) than in HD (2). Upon censoring for therapy change the difference was no longer statistically significant.

Summary: which are the chief factors determining the outcome of dialysis?

It may be concluded from the results of the Necosad study that the survival rate, particularly in the short term (up to 2 years) is determined mainly by patient characteristics: age, comorbidity, (residual) renal function, and blood pressure. PD patients tended to have a better survival for the first two years compared to HD patients. With regard to quality of life HD had a more favorable effect on physical functioning than PD. No differences in the mental quality of life could be established. In the longer term (especially after 3 years) the differences between the modalities of dialysis turn out to become more distinct. HD yields a better survival rate in older patients in particular. Starting on PD and subsequently changing to HD has a favorable effect on survival. There may be a relation to the longer preservation of residual renal function in PD patients. The preservation of residual renal function is relevant to an optimal outcome anyhow. This means an optimal treatment of blood pressure, avoiding dehydration, counteracting proteinuria and avoiding nephrotoxic medicines. An increase in mortality at a low dose of dialysis can only be shown for HD and is especially evident in anuric patients. As yet it was

impossible to establish in the Necosad population whether increasing the dose of dialysis to values far above what is customary in clinical practice improves the survival rate of dialysis patients. Apart from the dose of dialysis, measured as the clearance of small molecular substances, the avoidance of fluid overload and dehydration is also important to a good outcome. A proper blood pressure control by realizing an optimal water balance, possibly supported by drug therapy, is an essential component of optimal dialysis treatment.

Objective 2: Test and development of guidelines for optimal dialysis

The development of evidence-based guidelines for optimal dialysis is a field that is getting more and more attention internationally also. Well-founded guidelines are an essential part of a quality system. These guidelines must be adjusted continuously, on the basis of new insights and techniques.

A problem in the development of guidelines from observational studies is that the treatment is constantly adjusted on the basis of clinical findings. This renders a correct interpretation of established relations more difficult. Results from observational studies may serve as a starting point for generating hypotheses in the setting up of randomized trials. In areas where no randomized research is possible or practicable (see the randomized trial HD versus PD) the accurate statistical analysis of observational material will have to supply the evidence for clinical guidelines.

In order to obtain sufficient evidence in the development of new guidelines and to test existing guidelines for their usefulness, a long follow-up is necessary. Indeed, it takes a number of years before sufficient events such as deaths and hospitalizations have taken place to be able to measure the effect of guidelines on the outcome of the treatment.

Not long after 1997 when the first patient had been included in Necosad-2 the first version appeared of the American DOQI-guidelines for adequate dialysis treatment. These guidelines were mainly opinion-based and represented the opinions of experts, in the absence of well-founded studies. The material that was collected in the Necosad study presented an opportunity to test the guidelines against (Dutch) reality.

Start of dialysis

One of the guidelines published in 1997 concerned the moment of initiating the dialysis. The DOQI working party recommended starting at a Kt/V-urea lower than 2.0 per week (~ creatinine clearance 14 ml/min). Starting at a lower Kt/V was possibly acceptable when the nPNA was higher than 0.8 g/kg per day.

In Necosad patients who had been treated by a nephrologist in the predialysis phase and in whom the renal function had been established before the start of dialysis treatment the value of this guideline was investigated [24-26]. It appeared that 37% of the patients had started later than should have been the case according to the guideline. Three years after the initiation of dialysis the survival rate in the group that had started dialysis in time was 2.5 months longer than in the group of the late starters. However, this favorable effect disappeared when the time by which the patients had started on dialysis earlier (6 months on average) was taken into account. A timely start of dialysis resulted in a better quality of life during the first three months of the treatment. This effect had already disappeared again one year later, though. One conclusion that may be drawn from this study is thus that the time at which dialysis treatment is usually initiated in the Netherlands – as directed by a combination of laboratory data, complaints and symptoms of the predialysis patient – appears to be adequate. The results of the treatment are not improved when the American guideline of an early start of dialysis treatment is followed.

Guidelines for an adequate dose of dialysis

Even though the DOQI-guidelines for the time of starting and for the dose of dialysis were not evidence-based, and based on the situation in the United States, they have influenced the clinical practice in the Netherlands nevertheless. This could be investigated through analysis of the renal function three months after the initiation of dialysis and of the dose of dialysis that was

prescribed in consecutive years, from the introduction of Necosad in 1993, until 2000 [27]. The average renal Kt/V-urea at three months rose from 0.5 to 0.8, from which it could be concluded that the patients had to have started the dialysis at an earlier moment. In the same period the dose of dialysis increased, both in HD and in PD patients: from an average of 3.3 to an average of 3.7 per week for HD, and from an average of 2.0 to an average of 2.3 per week for PD.

The effect of the DOQI-guideline for peritoneal dialysis (total Kt/V \geq 2.0 per week; total creatinine clearance $>$ 60 L per week) on mortality and on quality of life was investigated. A follow-up of 4.5 years meanwhile made it possible also to analyze effects of the dose of dialysis on the medium-term outcome [19, 28]. In establishing the DOQI-guideline the authors had assumed that for the determination of the total clearance, one could simply add up the renal and peritoneal clearances. Positive effects of the total clearance may be attributed in particular to the renal component. Future guidelines for peritoneal dialysis will need to take these different components into account. Besides, attention will have to be devoted to guidelines for an optimal water balance. The required dose of dialysis and the effects of ultrafiltration were researched further in anuric peritoneal dialysis patients [29]. In these patients it turns out that mortality increases at a weekly Kt/V-urea below 1.5. The necessary daily ultrafiltration proves to be 1.0 L. In patients who lose less water per day the mortality increases.

The residual renal function and water balance are also relevant to the outcome of the hemodialysis treatment [20]. In contrast to what was seen at PD, an effect of the dose of dialysis can be established at HD, but here, too, this relation is clear particularly in anuric patients. Below the recommended Kt/V of 3.3 per week the mortality rate in this patient group increases rapidly. Due to the lack of sufficient patients with a very high Kt/V ($>$ 4.0 per week) the additional effect of prolonged daily dialysis, as is applied in NOCTURNE (daily-nightly hemodialysis), could not be investigated.

Guideline for the treatment of anemia in dialysis patients

Over the past few years the DOQI working party and the ERA-EDTA have also published guidelines for an adequate dialysis treatment, among other things. Due to the lack of clear evidence, these guidelines are also based on the opinions of experts. There is a recommendation of a hemoglobin concentration in the blood (Hb) of 11 g/l (6.8 mmol/l) or higher. On the basis of Necosad data it could be demonstrated that this target value was well-chosen [30]. Patients with an Hb $<$ 9 g/l have a clearly increased mortality risk in comparison with the reference group (13 g/l). Hb values higher than 10.5 g/l are associated with a mortality risk that is comparable to that of the reference group. Above 11 g/l no further gain in quality of life can be found either. Below an Hb of 9 g/l the quality of life of patients is clearly reduced.

Summary: test and development of guidelines for optimal dialysis

By means of data from Necosad it was possible to establish so far that: (1) an earlier start of treatment than is customary in everyday practice will not lead to an improved outcome; (2) in the development of guidelines for an optimal dose of dialysis separate guidelines must be developed for patients with and without residual renal function; (3) in anuric PD patients the peritoneal clearance must be respectively Kt/V-urea \geq 1.5 or creatinine clearance \geq 40 L per week; (4) in PD patients one must strive for a minimum peritoneal ultrafiltration of 1.0 L per day; (5) in anuric HD patients a dialysis Kt/V-urea of at least 3.3 per week appears to be an adequate guideline; (6) in dialysis patients one must strive for an Hb \geq 11 g/l (6.8 mmol/l).

Objective 3: Contributions to the quality of therapy inter alia through feedback of center-specific results and the development of benchmarks for clinical and therapy characteristics

It is only useful to establish guidelines if they are adhered to. This does not only require consensus about the contents among the parties involved, but it is also essential that there should be regular feedback to the centers. By means of a national benchmark the centers can

compare their results with those in other centers. In visitations and later certification and accreditation, only benchmarks of demographic data have been used so far, as they had been registered by Renine. Data from Necosad render it possible to supplement these demographic data with the clinical characteristics of the dialysis population in a center. Figure 4 shows that there are substantial differences among the centers with respect to the percentage of patients suffering from additional diseases. Thus, the percentage of patients with cardiovascular diseases may vary among the centers from 13 to 50%. With regard to the nutritional status of patients large differences among the centers are found as well.

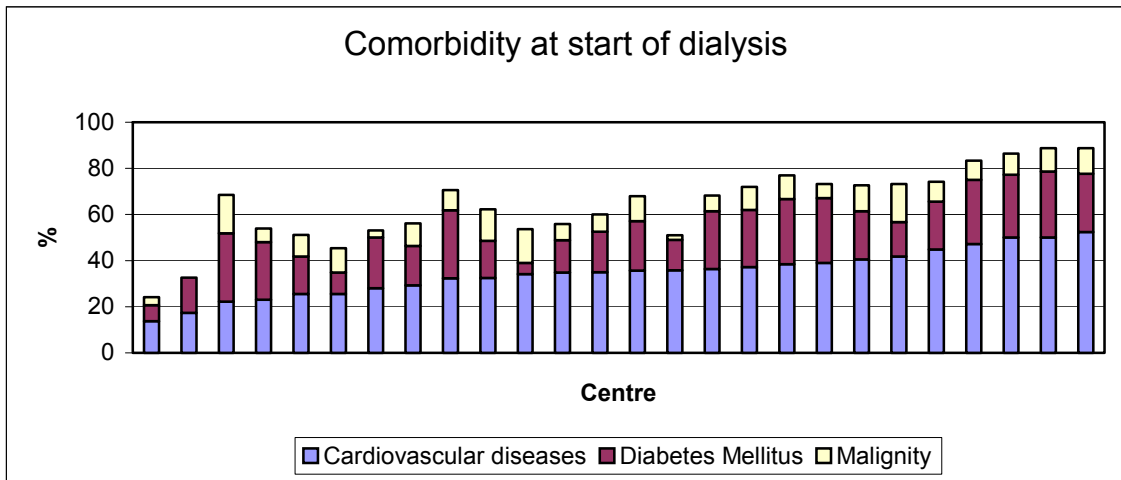


Figure 4. Comorbidity at the start of dialysis

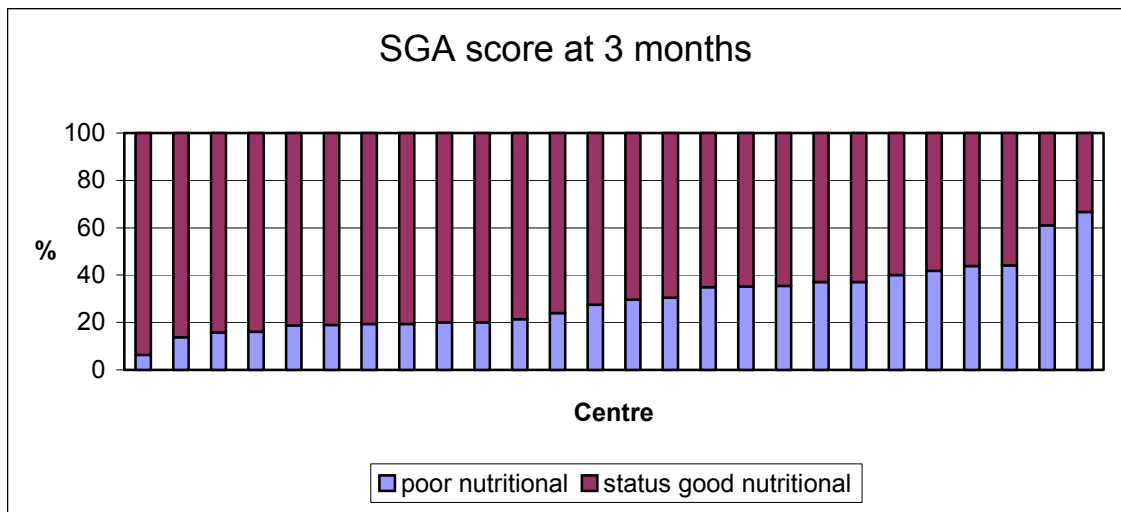


Figure 5. SGA score three months after the start of dialysis

The testing of the use of guidelines calls for benchmarks relating to those guidelines. By means of the data gathered by Necosad it was possible to develop a number of clinical benchmarks. Figure 6 shows the differences among the centers with respect to the weekly total Kt/V three months after the start of dialysis. In almost 50% of the centers the dose of dialysis, measured as Kt/V-urea, is lower than the DOQI-guideline.

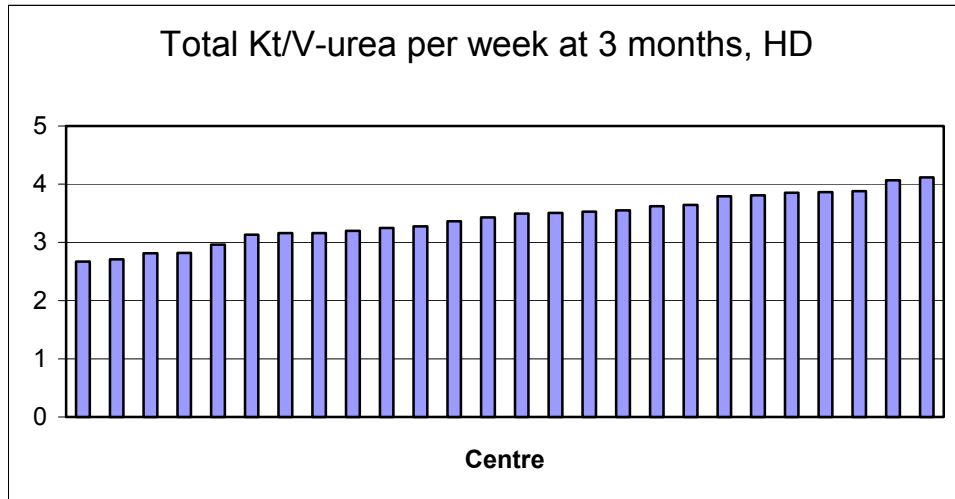


Figure 6. Total Kt/V-urea at 3 months after the start of hemodialysis

The total Kt/V-urea in peritoneal patients also shows great differences among the centers (figure 7). It may be stated that, in contrast to hemodialysis, in peritoneal dialysis the average dose 3 months after the start of the therapy lies at or above the DOQI-guideline.

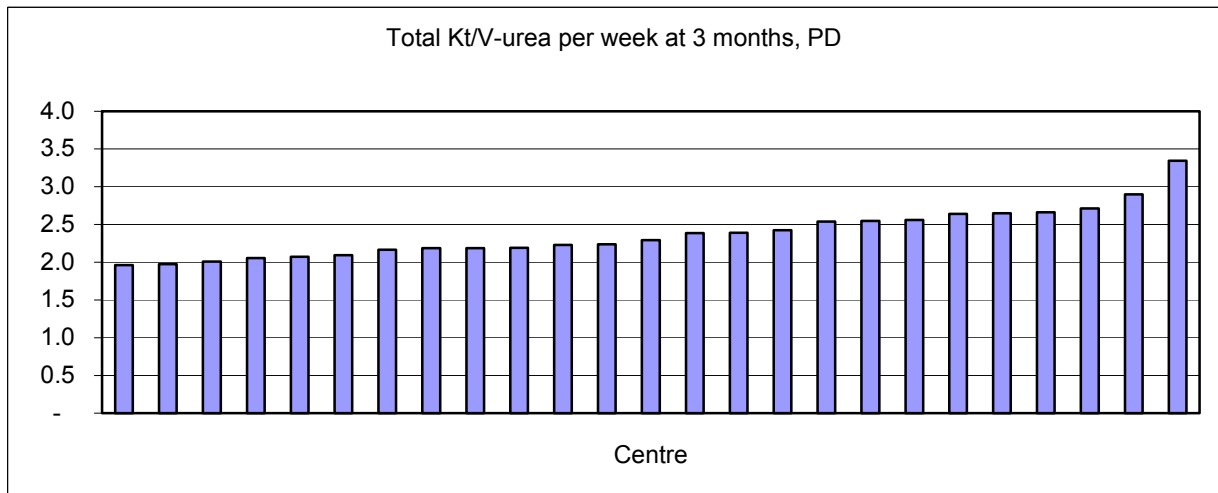


Figure 7. Total Kt/V-urea at 3 months after the start of peritoneal dialysis

Another way of representing the benchmark is as a percentage of the patients satisfying the values recommended in the guideline. By way of example, figure 8 shows the guideline for anemia treatment. The European guideline for an adequate treatment of anemia says that at least 85% of the patients in the centers must reach the target. Figure 8 shows that the percentage of patients satisfying the guideline differs enormously among the centers. It turned out that none of the Dutch centers satisfied the European guideline, which has meanwhile been taken over by the NfN.

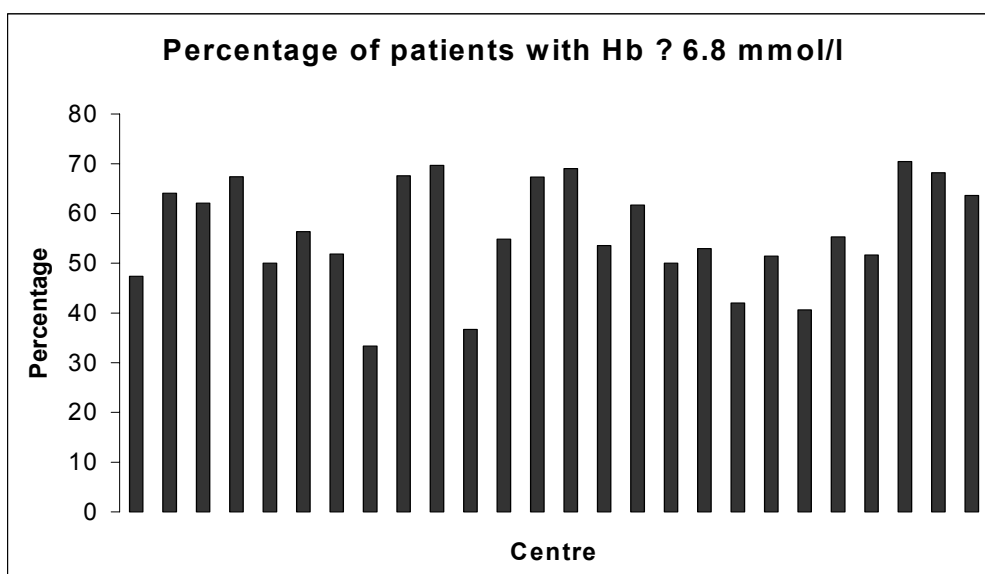


Figure 8. Percentage of patients in the different centers satisfying the recommended Hb guideline (≥ 11 g/l resp. ≥ 6.8 mmol/l)

This form of benchmarking with clinical and treatment data supplementing Renine is very time-consuming, however, and is not feasible on a large scale in the long run. For this it will be necessary to computerize the registrations. Furthermore, it is essential that all registrations for visitation, certification and accreditation should be carried out by one registration. In order to make all of this possible, the Renine database will be computerized and expanded by patient-specific and treatment data: Renine-plus. This undertaking is now in progress, with assistance from the Dutch Kidney Foundation. The system must be operational by the end of 2003. To ensure that no data are lost about the long-term effects of dialysis, the Necosad data will be linked to Renine-plus. An effort will be made to continue the gathering of data within Necosad until this can be realized.

Other matters

Data from Necosad are not only valuable for answering the original questions. The database can be used and is also being used for other studies in dialysis patients. Thus, within the framework of a doctoral research at Erasmus University in Rotterdam, data from Necosad patients were used to calculate the social cost in the Netherlands [31] and for a comparative study into the quality of life of patients on CAPD or automatic PD [32]. The Necosad population was also used as a reference in research into the quality of life of adult patients who had started kidney-replacing treatment in childhood [33, doctoral research Emma Children's Hospital – AMC]. For a number of studies the frozen material was used. In this way it was possible to screen the Dutch dialysis population for the incidence of Fabry disease [34, Internal Medicine department, AMC]. Research was conducted also into the course of the CRP level, a measure for inflammation, during a hemodialysis session and effects of an increase on the outcome of the treatment [35]. By means of frozen material research could be conducted as well into the incidence of aplastic anemia induced by erythropoietin in Dutch dialysis patients [36, cooperation with M. Daha, LUMC]. Furthermore, the significance of ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide) was investigated [37, cooperation with F. Boomsma, Erasmus Medical Center, Rotterdam]. Data from Necosad are being used in the development of a European comorbidity index.

Future possibilities

On 1 January 2003 the financing of Necosad was terminated. However, this does not mean the end of the research that may be conducted by means of the Necosad database and of the frozen material. This research will not be limited to the original Necosad study group. It will take

place in various Dutch as well as foreign research centers. For follow-up studies involving the Necosad material, subsidies will have to be applied for at various agencies. One may think of ZonMW, for instance, and the pharmaceutical industry. Besides, in the future the Dutch Kidney Foundation will also be asked to support certain projects. Thus, a joint venture with the NIVEL with regard to the social aspects and quality of life in the treatment of dialysis patients fits in neatly with the plans of the Dutch Kidney Foundation concerning the setup and steering of an effective and coherent research program into social and psychosocial aspects of renal diseases.

As far as the analysis of **factors determining the outcome of dialysis** is concerned, much may be done yet. The genotype and phenotype of the Necosad patients is being analyzed, particularly in regard to profiles that are connected with the cardiovascular mortality [38, cooperation with G.J. Navis, University Teaching Hospital Groningen]. Within this context research is also being conducted into the effects of a disturbed lipids profile. The influence of blood pressure on the outcome of the treatment is the subject of another study [39, cooperation with W.J. Bos, Antonius Hospital, Nieuwegein]. In collaboration with the Karolinska Institute in Sweden the influence of inflammation on cardiovascular diseases and the nutritional status is examined. Analyses of the influence of the calcium–phosphate metabolism on outcomes of dialysis and analyses of the course of the nutritional status are on the program. As was stated before, cooperation will be sought with the NIVEL in regard of the analysis of social factors and quality of life.

The **development of evidence-based guidelines**, as an essential component of the quality cycle for which testing will take place in the process of certification and accreditation, will be continued. As to guidelines for optimal dialysis, further analyses will be made, taking into account the clearance of small molecular substances as well as the ultrafiltration. It will be investigated whether separate guidelines are necessary for subgroups of patients, such as the elderly and patients suffering from diabetes mellitus. Not only mortality but also morbidity and quality of life will be taken into account as an outcome measure for these guidelines. In the short term research will be carried out into effects of existing guidelines for the calcium-phosphate metabolism of dialysis patients. In the area of evaluation and development of guidelines the collaboration with the quality section of the Netherlands federation for Nephrology (NfN) is important. This collaboration is fleshed out within the Hans Mak Institute that was set up at the beginning of this year by the Dutch Kidney Foundation, the kidney patient association NVN and the NfN.

Cooperation with the quality section, particularly with the visitation committee, is essential in the establishment of **benchmarks** for a treatment that meets the quality requirements.

The Necosad database was housed in the Hans Mak Institute. Formally speaking the NfN, as the successor of the DGN, which had transferred the management to the former project management of the Necosad study, is the owner of the data. Like the Renine database, the Necosad database is not freely accessible, but it may be used for various kinds of research in the field of nephritic diseases. On request aggregated data may be made available in an anonymous form. Centers do, however, have control of their own outcomes. Cooperation with other parties is sought in order to make optimal use of the Necosad database.

Publications NECOSAD

1. Merkus MP, Krediet RT. Quality of life and functional status in chronic hemo- and peritoneal dialysis. In: *Complications of dialysis – Recognition and Management*. Lameire NH, Mehta RL (eds). New York, Marcel Dekker Inc., 2000: 497-515.
2. Korevaar JC, Merkus MP, Jansen MAM, Dekker FW, Boeschoten EW, Krediet RT. Validation of the KDQOL-SF™ : a dialysis targeted health measure. *Qual Life Res* 2002; 11: 437-447.
3. Merkus MP, Jager KJ, Dekker FW, de Haan RJ, Boeschoten EW, Krediet RT for the NECOSAD Study Group. Physical symptoms and quality of life in patients on chronic dialysis: results of The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). *Nephrol Dial Transplant* 1999;14:1163-1170.
4. Manen van JG, Korevaar JC, Dekker FW, Boeschoten EW, PMM Bossuyt, Krediet RT for the NECOSAD-study group. How to adjust for comorbidity in survival studies in End-stage Renal Disease patients: a comparison of different indices. *Am J Kidney Dis* 2002;40: 82-89.
5. Manen van JG, Korevaar JC, Dekker FW, Boeschoten EW, Bossuyt PMM, Krediet RT, for The NECOSAD Study Group. Adjustment for Comorbidity in Studies on Health Status in ESRD Patients: Which Comorbidity Index to Use? *J Am Soc Nephrol* 2003; 14: 478-485.
6. Visser R, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Reliability of the 7-point subjective global assessment scale in assessing nutritional status of dialysis patients. *Adv Perit Dial* 1999; 15:222-225.
7. Korevaar JC, Jansen MAM, Dekker FW, Boeschoten EW, Krediet RT for the NECOSAD Study Group. Estimation of residual GFR and renal Kt/V-urea from creatinine clearance in End-stage renal disease patients. *Adv Perit Dial* 1999; 15:132-137.
8. Jager KJ, Merkus MP, Boeschoten EW, Dekker FW, Stevens P, Krediet RT, for the NECOSAD Study Group. Dialysis in the Netherlands: the clinical condition of new patients put into a European perspective. *Nephrol Dial Transplant* 1999; 14:2438-2444.
9. Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Quality of life in patients on chronic dialysis: self-assessment 3 months after start of treatment. *Am J Kidney Dis* 1997;29:584-592.
10. Korevaar JC, Jansen MAM, Merkus MP, Dekker FW, Boeschoten EW, Krediet RT. Quality of life in predialysis ESRD patients at the initiation of dialysis therapy. *Perit Dial Int* 2000; 20:69-75.
11. Merkus MP, Jager KJ, Dekker FW, de Haan RJ, Boeschoten EW, Krediet RT for the NECOSAD Study Group. Quality of life over time in dialysis: The Netherlands Cooperative Study on the Adequacy of Dialysis. *Kidney Int* 1999;56:720-728.
12. Merkus MP, Jager KJ, Dekker FW, de Haan RJ, Boeschoten EW, Krediet RT for the NECOSAD Study Group. Predictors of poor outcome in chronic dialysis patients: The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). *Am J Kidney Dis* 2000; 35: 69-79.
13. Jansen MAM, Korevaar JC, Dekker FW, Boeschoten EW, Stevens P, Krediet RT and the NECOSAD Study Group. Relationship between Kt/Vurea and nPNA in predialysis patients and in chronic PD patients without residual renal function. *Perit Dial Int*, 2001;21:509-515.
14. Jansen MAM, Hart AAM, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the decline rate of residual renal function in incident dialysis patients. *Kidney Int*, 2002; 62: 1046-1053.
15. Jansen MAM, Korevaar JC, Dekker FW, Boeschoten EW, Stevens P, Krediet RT and the NECOSAD Study Group. Renal function and nutritional status at the start of chronic dialysis treatment. *J Am Soc Nephrol* 2001; 12: 157-163.
16. Jager KJ, Merkus MP, Huisman RM, Boeschoten EW, Dekker FW, Korevaar JC, Tijssen JGP, Krediet RT. Nutritional status over time in hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 2001; 12:1272-1279.
17. Jager KJ, Merkus MP, Boeschoten EW, Dekker FW, Tijssen JGP, Krediet RT. What happens to patients starting dialysis in the Netherlands? *Neth J Med*, 2001;58:163-173.
18. Jager KJ, Merkus MP, Dekker FW, Boeschoten EW, Tijssen JGP, Stevens P, Bos WJW, Krediet RT, for the NECOSAD Study group. Mortality and technique failure in patients starting chronic peritoneal dialysis: results of the Netherlands Cooperative Study on the Adequacy of Dialysis. *Kidney Int* 1999; 55: 1476-1485.
19. Temorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT, for the NECOSAD Study group. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life. An analysis of the Netherlands

- Cooperative Study on the adequacy of Dialysis (NECOSAD-2). *Am J Kidney Dis* 2003;41:1295-1302.
20. Temorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT, for the NECOSAD study group. The relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis. *J Am Soc Nephrol* 2004;15:1061-1070.
 21. Manen van JG, Korevaar JC, Dekker FW, Reuselaars MC, Boeschoten EW, Krediet RT. Changes in Employment status in end-stage renal disease patients during the first year of dialysis. *Perit Dial Int*, 2001;21:595-601.
 22. Temorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT. Hemodialysis and peritoneal dialysis: a comparison of adjusted mortality rates by the duration of dialysis. An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (Necosad-2). *J Am Soc Nephrol* 2003;14: 2851-2860, 2003.
 23. Korevaar JC, Feith GW, Dekker FW, van Manen JG, Boeschoten EW, Bossuyt PMM, Krediet RT for the NECOSAD Study group. Effect of starting with hemodialysis compared with peritoneal dialysis in patients on dialysis treatment: a RCT. *Kidney Int* 2003;64:2222-2228.
 24. Korevaar JC, Jansen MAM, Dekker FW, Jager KJ, Boeschoten EW, Krediet RT, Bossuyt PMM. When to initiate dialysis - effect of proposed US guideline on survival. *The Lancet* 2001;358:1046-1051.
 25. Korevaar JC, Jansen MAM, Dekker FW, Boeschoten EW, Bossuyt PMM, Krediet RT. Early start of dialysis treatment is not associated with better health-related quality of life – Evaluation of a DOQI guideline. *Am J Kidney Dis*, 2002;39:108-115.
 26. Korevaar JC, Dekker FW, Krediet RT. Initiation of dialysis – Is the problem solved by NECOSAD? *Nephrol Dial Transplant* (2003) 18:1228-1236.
 27. Temorshuizen F, Korevaar J.C, Dekker F.W, Jager K.J, van Manen J.G, Boeschoten E.W, Krediet R.T, for The NECOSAD Study Group. Time trends in initiation and dose of dialysis in end-stage renal disease patients in the Netherlands. *Nephrol Dial Transplant* 2003;18:552-558.
 28. Korevaar JC, van Manen J.G, Boeschoten E.W, Dekker F.W, Krediet R.T, for The NECOSAD Study Group. Evaluation of Guidelines for Peritoneal Dialysis Patients: A Review from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) *Peritoneal Dial Today*. *Contrib Nephrol*. Basel, Karger, 2003, vol 140, pp 142-150.
 29. Jansen MAM, Temorshuizen F, Korevaar JC, Dekker JW, Boeschoten EW, Krediet RT. Predictors of survival in anuric peritoneal dialysis patients. Submitted
 30. Sman-de Beer F, Korevaar JC, Kharagitsingh AV, van Manen JG, Boeschoten EW, Krediet RT, Dekker FW. Adequacy of anemia management in the Netherlands. *Nephrol Dial Transplant* 2003;18 (suppl 4):687.
 31. De Wit GA, Polder JJ, Jager KJ, de Charro FTh. De maatschappelijke kosten van nierziekten in Nederland. *Tijdschrift voor Gezondheidswetenschappen* 2001;79:49-54.
 32. De Wit GA, Merkus MP, Krediet RT, de Charro F Th. A comparison of quality of life of patients on automated and continuous ambulatory peritoneal dialysis. *Perit Dial Int*, 2001; 21:306-31.
 33. Groothoff JW, Grootenhuis MA, Ofringa M, Gruppen MP, Korevaar JC, Heymans HSA. Quality of life in adults with end-stage renal disease since childhood is only partially impaired. *Nephrol Dial Transplant* 2003;18:310-317.
 34. Lindhorst GE, Hollak CEM, Korevaar JC, van Manan JG, Aerts JMFG, Boeschoten EW Alpha-galactosidase deficiency in Dutch patients on dialysis: a critical appraisal of screening for Fabry disease. *Nephrol Dial Transplant* (2003) 18:1581-1584.
 35. Korevaar JC, van Manen JG, Dekker JW, Boeschoten EW, Krediet RT. Effect of an increased CRP level during a hemodialysis session on mortality. Submitted
 36. Kharagitsingh AV, Korevaar JC, Daha M, Vandenbroucke JP, Boeschoten EW, Krediet RT, Dekker JW. Risk of rHuEPO-induced PCRA. *Nephrol Dial Transplant* 2003; 18 (suppl 4).
 37. Korevaar JC, Boomsma F, van den Meiraker AH, van Manen JG, Dekker JW, Boeschoten EW, Krediet RT. Effect of natriuretic peptides on mortality. *Abstract Ann Soc Dialysis* 2004.
 38. Verhagen C, Boorsma P, Manen van JG, Boogaard van den R, Dekker F, Boeschoten EW, Navis G, Krediet RT. ACE (I/D) polymorphism is a predictor for mortality in a dialysis population with kidney failure due to renal vascular disease. *Nephrol Dial Transplant* 2002;17 suppl 1:146.
 39. Bos WJ, van Manen J, Boeschoten E, Krediet RT, Dekker FW. Higher systolic pressure is related to better survival of incident hemodialysis patients in the Necosad study. *Abstract ASN* 2003.

A great number of researchers and institutions has been involved in the Necosad-study:

Projectgroup

Projectleaders: dr. E. W. Boeschoten, dr. F. W. Dekker, prof. Dr. R.T. Krediet

Postdocs: dr. J. C. Korevaar, dr. J. G. van Manen, dr. F. van der Sman – de Beer

Research fellows: drs. M. A. M. Jansen, drs. A. V. Kharagjitsing, dr. F. Termorshuizen, dr. C. Verhagen

Research nurses: Lucia ten Brinke, Lyda Engelsman, Yvonne Graafsma

Katja Meijs, Barbara Nijman, Helga Schrijver,

Datamanagement: Ylva Bakker–de Bruin

Administration: Jillian Aurisch

Nefrologen participating in the sounding-board

Dr. A. J. Apperloo, St. Elisabeth Ziekenhuis, Tilburg. Dr. J. N. M. Barendrecht, Gelre Ziekenhuizen, Apeldoorn. Dr. R. J. Birnie, St. Lucas Andreas, Amsterdam. Dr. M. Boekhout, Rijnland Ziekenhuis, Leiderdorp. Dr. W. H. Boer, UMC, Utrecht. Dr. E. F. H. van Bommel, Albert Schweitzer Ziekenhuis, Dordrecht. Prof. Dr. H. R. Büller, AMC, Amsterdam. Dr. F. Th. de Charro, Stichting Renine, Rotterdam. Dr. C. J. Doorenbos, Deventer Ziekenhuis, Deventer. Dr. W. T. van Dorp, Kennemer Gasthuis, Haarlem. Dr. A. van Es, Dialysecentrum 'Gooi, Hilversum. Drs. W. J. Fagel, Medisch Centrum Leeuwarden, Leeuwarden. Dr. G. W. Feith, Ziekenhuis Gelderse Vallei, Ede. Dr. C. F. M. Franssen, AZG, Groningen. Dr. L. A. M. Frenken, Atrium Medisch Centrum, Heerlen. Dr. J. A. C. A. van Geelen, Medisch Centrum Alkmaar. Dr. P. G. G. Gerlag, Maxima Medisch Centrum, Veldhoven. Drs. J. P. M. C. Gorgels, Kennemer Gasthuis, Haarlem. Dr. W. Grave, Laurentius Ziekenhuis, Roermond. Dr. R. M. Huisman, Dialyse Centrum Groningen. Dr. K. J. Jager, AMC, Amsterdam. Dr. K. Jie, Groene Hart Ziekenhuis, Gouda. Drs. W. A. H. Koning-Mulder, Medisch Spectrum Twente, Enschede. Dr. M. I. Koolen, Jeroen Bosch Ziekenhuis, Den Bosch. Dr. T. K. Kremer Hovinga, Martini Ziekenhuis, Groningen. Drs. A. T. J. Lavrijssen, Oosterschelde Ziekenhuis, Goes. Dr. A. W. Mulder, Catharina Ziekenhuis, Eindhoven. Dr. K. J. Parlevliet, Zorggroep Alysis, Arnhem. Dr. J. L. C. M. van Saase, St Clara Ziekenhuis, Rotterdam. Drs. M. J. M. Schonk, Westfries Gasthuis, Hoorn. Dr. M. M. J. Schuurmans, Canisius Wilhelmina Ziekenhuis, Nijmegen. Prof. Dr. J. G. P. Tijssen, AMC, Amsterdam. Dr. R. M. Valentijn, Rode Kruis Ziekenhuis, Den Haag. Dr GH Vastenburg, Scheper Ziekenhuis, Emmen. Dr CA Verburgh, Kennemer Gasthuis, Haarlem. Dr VMC Verstappen, Vie Curi Medisch Centrum, Venlo. Dr HH Vincent, St. Antonius Ziekenhuis, Nieuwegein. Dr. P. Vos, Dianet Utrecht.

NECOSAD nurses in the centers

Financial administration: A. A. M. van den Bremer, O. van Blokland

Co-operating researchers and institutions

Dr. F. Boomsma, Erasmus Medisch Centrum (natriuretic peptides)

Dr. W. J. Bos, Antonius Ziekenhuis, Nieuwegein (analyses blood pressure, analyses calcium – phosphate metabolism)

Prof. Dr. M. R. Daha, Leids Universitair Medisch Centrum (EPO – induced PRCA)

Prof. Dr. B. Lindholm, Karolinska Instituut, Zweden (inflammation)

Prof. Dr. G. J. Navis, Academisch Ziekenhuis Groningen (genetic polymorfisms)

Dr. A. H. M. Smelt, Leids Universitair Medisch Centrum (lipids – apoE fenotyping)

Supervisory board NECOSAD: Prof. Dr. G. K. van der Hem (voorzitter), prof. Dr. H. A. Koomans, prof. Dr. K. M. L. Leunissen, dr. R. van Leusen.