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ECONOMIC EVALUATION OF END-STAGE RENAL DISEASE TREATMENT

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Economic evaluation of end-stage renal disease treatment

Economische evaluatie van niervervangende behandelingen

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Chapter 1

Introduction

Background

One of the main functions of the human kidney is the clarification of blood from human waste products, such as ureum and creatinine. Failure of functioning of the kidneys may ultimately lead to death. When the stage of very limited kidney functioning (5 to 10% of normal) is reached, renal replacement therapy becomes essential to survive. Chronic renal replacement therapy has been available since the 1960s. At present, three major types of renal replacement therapy are available: haemodialysis, peritoneal dialysis and kidney transplantation.

With haemodialysis, the body is connected to an extracorporeal filter or dialyser, consisting of a semipermeable membrane to which blood is taken and returned. This requires a permanent artificial access to the body (a shunt, fistula or synthetic graft), that usually is created in the forearm. Dialysis fluid, resembling blood plasma, is passed in the opposite direction across the outside of the membrane. Waste products and excess water from the blood diffuse into this dialysis fluid. Several forms of haemodialysis are available in the Netherlands. Most patients receive full care centre haemodialysis which requires the patient to travel to a dialysis centre, usually 3 times a week. The patient is attached to a dialysis machine for 3-4 hours. Limited care or active centre haemodialysis is similar to full care centre haemodialysis, but the patient takes active responsibility for the treatment, implying that the majority of the (nursing) tasks involved are performed by the patient him/herself. Another modality is home haemodialysis whereby the patient has all the necessary equipment at home and takes active responsibility for the treatment; some help from a partner, family member or nursing assistant is usually necessary.

The second major form of renal replacement therapy is peritoneal dialysis, which was developed in the 1970s. With this modality, the peritoneum (abdominal membrane) is used for the removal of waste products. A sterile dialysis fluid is introduced into the peritoneal cavity through a built-in catheter and remains in place for several hours. Continuous ambulatory peritoneal dialysis is a home-based technique, requiring the patient to exchange the used dialysis fluid for fresh dialysis fluid 4 to 5 times daily. With automated peritoneal dialysis, the patient is connected each night to an automated cycler which conducts the exchange of dialysis fluids. This nightly peritoneal dialysis can be combined with one or two manual exchanges of dialysis fluid during the day (continuous cycling peritoneal dialysis).

The third major form of renal replacement therapy is renal transplantation, also available since the 1960s. Transplantation is the treatment of choice for most patients with end-stage renal disease, because with this modality more kidney functions are restored than only the removal of waste products and excess fluids from the blood. Transplantation can either be performed with a donor kidney from a relative or with a cadaver donor kidney: immunosuppressive drugs are necessary to prevent rejection of the graft. Graft survival ranges from 70 to 90% at 3-5 years. The ongoing shortage of donor organs means that there is a long waiting list for the transplantation procedure. In 2000, about 1,400 persons in the Netherlands were awaiting kidney transplantation.[1]

In the Netherlands on January 1 2001, 9,850 patients were being treated with renal replacement therapy, almost equally divided between dialysis (n=4,818) and renal trans-

plantation (n=5,032).[2] This implies a prevalence of about 600 persons per million of the population, when prevalence is defined as renal failure being treated with either dialysis or transplantation. The absolute number of patients has been growing 4-6% annually over the last 10 years. The increase in new patients with end-stage renal disease is particularly marked in the older age groups.[2] Age is a determinant of kidney failure: the prevalence of chronic kidney failure increases from 54 per million in those aged 0 to 15 years to 1,486 per million in those aged 65 to 74 years.[2] The average age at start of renal replacement therapy is currently 59 years, compared with 48 years in 1980.[2] Each year in the Netherlands 1,400 to 1,500 patients begin renal replacement therapy in one of the 53 dialysis and transplantation centres (including paediatric centres). Table 1 lists the main treatment modalities and the number of Dutch patients treated per modality as at January 1 2001.

Table 1: Number of patients per treatment modality as at 1.1.2001

Treatment modality	Sub-type (see text)	Number of patients	%
Haemodialysis (HD)	Full Care Centre HD (FCHD)	2852	29.0
	Limited Care HD (LCHD)	406	4.1
	Home HD (HHD)	84	0.9
Peritoneal Dialysis (PD)	Continuous Ambulatory PD (CAPD)	1073	10.9
	Automated PD (APD)	403	4.1
Transplantation (TX)	Post-mortem donor	4069	41.3
	Living-related donor	963	9.8
Total		9850	100.0

Source: Renal Replacement Registry of the Netherlands [2]

The incidence of renal replacement therapy is not a function of the true incidence of renal failure alone, but also of a country's healthcare budget and treatment capacity for renal failure.[3 4] Because renal replacement therapies are lifelong, complex and costly, there is continuous interest in the evaluation of costs and effects of such treatment.[5-8] This interest even precedes the period in which Health Technology Assessment (HTA) emerged. HTA can be described as a multi-disciplinary research field, investigating the societal consequences of medical technology such as drugs, medical devices and surgical procedures.[9] Its aim is to support rational medical decision making and rational healthcare policy, by providing a systematic evaluation of all relevant medical, epidemiological, economic, social and ethical issues that surround new or existing medical technologies. Within HTA research, the field of economic evaluation received increasing interest in recent years.[10] The aim of economic evaluation is to inform decision makers about the relative efficiency of alternative courses of action for a specified medical problem.[11] Limited healthcare budgets, the ageing population with concomitant pressure on healthcare provision, and advances in medical technology have stimulated further interest in this research discipline. However, efficacy or effectiveness is no longer the only criterium for a decision to reimburse a new medical technology. Information on the relation between input (costs) and output (e.g. in terms of survival and quality of life of patients) is also needed for such a decision. The work presented in this thesis has emerged against this background of health technology assessment and economic evaluation.

Outline and research questions

The main objective of the research presented here is to evaluate the costs and outcomes of end-stage renal disease treatments in the Netherlands. The study was started in 1995 as a sub-study of the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD-I), a prospective cohort study aiming at the identification of factors that determine outcome of dialysis treatment.[12 13] This sub-study, called the NECOSAD-Technology Assessment Study (NECOSAD-TAS), comprised additional data collection on costs of therapy and quality of life of patients. The results of NECOSAD-TAS are presented in this thesis.

The thesis comprises nine chapters. This chapter (chapter 1) presents a general introduction and an outline of the research questions addressed in the subsequent chapters.

Chapter 2 presents a systematic review of the literature on health-related quality of life of dialysis and transplant patients, focusing on four health profiles and two health preference methods frequently used in renal patients. The questions addressed are:

- What are the psychometric properties of health profiles and health preference methods as applied in renal patients?
- How does health-related quality of life of end-stage renal disease patients compare with that of a healthier population, such as a general population sample?
- Which medical, socio-demographic and disease-related factors determine health-related quality of life of end-stage renal disease pa-tients?
- Do health-related quality of life outcomes differ between patients treated with different therapeutic modalities?

Chapter 3 reports on health-related quality of life of haemodialysis patients and peritoneal dialysis patients. Quality of life was assessed with health profiles/health status measures (Short-Form 36 and EQ-5D$_{profile}$) and with health preference methods (Standard Gamble and Time Trade Off). The research questions are:

- Is the quality of life of both patient groups similar?
- Does the quality of life of dialysis patients differ from a general population sample of similar age?
- What is the relationship between socio-demographic, patient-related and treatment-related background variables and quality of life outcomes?
- What is the relationship between health profiles and health preference methods?

Chapter 4 presents a cross-sectional study on quality of life outcomes of two groups of peritoneal dialysis patients. This study is similar to that presented in chapter 3, but covers different patient groups. The research questions are:

- Does the quality of life of automated peritoneal dialysis patients differ from that of continuous ambulatory peritoneal dialysis patients?
- Does the quality of life of peritoneal dialysis patients differ from that of a general population sample of similar age?
- What is the relationship between quality of life outcomes and socio-demographic, patient-related and treatment-related background variables?

Chapter 5 addresses economic aspects of renal replacement therapy. An overview of economic evaluations of renal replacement therapies, published between 1985 and 2000, is presented. The main research questions are:

- What is the current knowledge on the costs and effects of renal replacement therapies?
- What is the quality of economic evaluation studies performed in the field of renal replacement therapies?

Chapter 6 reports on the cost of illness and the public health burden of end-stage renal disease in the Netherlands. Four research questions are addressed:

- What are the costs of the different renal replacement therapies?
- What are the societal costs of end-stage renal disease in 1994?
- What are the expected societal costs in the period 1999-2003, taking into account demographic and epidemiological developments?
- How many Disability Adjusted Life Years are associated with end-stage renal disease in the Dutch population?

Chapter 7 combines the quality of life information and economic data presented in the previous chapters in an economic evaluation of six renal replacement therapies (five dialysis modalities and renal transplantation). The main questions are:

- What is the cost-effectiveness and cost-utility of the six renal replacement therapies?
- What is the overall cost-effectiveness and cost-utility of the Dutch end-stage renal disease treatment program?
- What is the expected influence of policies to transfer patients from more expensive to less expensive treatment modalities on the overall cost-effectiveness of the Dutch end-stage renal disease treatment program?

Chapter 8 offers a reflection on the use of health preferences in economic evaluation studies. This chapter is rooted in an observation made while performing the quality of life studies in dialysis patients. Although no differences in health preferences were found between the patient groups, the general population samples seemed to have different health preferences for health states of different patient groups. This triggered interest in the influence of experience with disease on the valuation of health status. Thus, the following questions are addressed:

- Is there any evidence that experience with illness influences the valuation of health?
- Is there any difference between valuations of students and dialysis patients regarding hypothetical health states?
- Do the valuations of the actual health status of dialysis patients differ from valuations of the general population for similar health states?

Finally, chapter 9 presents the main conclusions of this work, together with some methodological and theoretical reflections. Furthermore, implications for future research are discussed. A summary in English and Dutch concludes the thesis. Because chapters 2 to 8 of this thesis were written as independent papers, there is some overlap concerning study design and methodology; however, this means that each chapter can be read as an independent study.

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Chapter 2

The use of health profiles and health preference methods in end stage renal disease patients: a systematic review of the literature

De Wit GA, de Charro FTh. The use of health profiles and health preference methods in end-stage renal disease patients: a systematic review of the literature. Submitted.

Abstract

This paper reports on a systematic review of the literature on Health Related Quality of Life (HRQOL) of end-stage renal disease patients, as measured with four well-known health profiles (Short-Form-36, Nottingham Health Profile, Sickness Impact Profile and Quality of Life Index) and two health preference methods (Time Trade Off and Standard Gamble). In a MedLine search, 815 articles regarding HRQOL of end-stage renal disease patients were found. Of these, 109 had applied one of the six HRQOL questionnaires listed above. Five more of such papers were identified with an additional search in EMBASE and PsycINFO databases. Of the 114 publications initially selected, 57 remained after further selection based on study quality criteria. Findings are discussed along the four main research questions that were covered in the selected papers:

1 What are the psychometric properties of health profiles and health preference methods as applied in renal patients?

2 How does HRQOL of end-stage renal disease patients compare with that of a healthier population, such as a general population sample?

3 Which medical, socio-demographic and disease-related factors determine HRQOL of end-stage renal disease patients?

4 Do HRQOL outcomes differ between patients treated with different therapeutic modalities?

The main conclusions are:

1 the methodological soundness of Short Form 36 and Sickness Impact Profile is best documented,

2 HRQOL of end-stage renal disease patients is worse than HRQOL of the general population,

3 a higher age and the presence of comorbid diseases are strong determinants of lower HRQOL,

4 HRQOL of transplanted patients is better than HRQOL of dialysis patients, but no major HRQOL differences exist between patients treated with different dialysis modalities.

Introduction

Dialysis and transplantation, treatment options for patients with end-stage renal disease (ESRD), have been among the first fields of medicine where the "quality of life concept" was introduced.[1] Dialysis became available in the 1960s and was the first treatment for patients who would otherwise have died. It soon became clear that the quality of this extension of life was considerably affected. Patients were hampered in many domains of everyday life and dialysis was not providing the return to normal health that was initially hoped for. New therapeutic possibilities such as renal transplantation, the rising prevalence of renal failure, the high cost of therapy, and improvements in existing therapies have inspired sustained interest in quality of life aspects of renal replacement therapies. Historical reviews on quality of life research in ESRD patients were performed by Gokal,[2-3] Parsons and Harris,[4] and Kaplan De-Nour and Brickmann.[5] Over the last 30 years, the definition of quality of life and thus the character of quality of life research has changed dramatically, reflecting the maturation of the scientific discipline itself.[6] In the early years of dialysis, research was mainly directed at vocational rehabilitation and the presence of stress and psychiatric disturbances in patients.[7-8] The 1980s constituted a research period with large studies comparing different treatments, using batteries of questionnaires, each directed at separate dimensions of quality of life (uni-dimensional questionnaires).[9] The availability of more sophisticated, multi-dimensional questionnaires to describe and value quality of life in the 1990s is reflected in increasing use of such questionnaires in ESRD patients.[10-11] Also, disease specific questionnaires,[12] and health preference methods or utility instruments have been applied more often in recent years.[13]

Despite the maturation of the discipline of quality of life measurement, consistency in the definition and measurement of quality of life is still lacking.[14] Psychologists, economists and clinicians all seem to have their own ideas on quality of life. Different "schools" do agree on the fact that quality of life is a multi-dimensional and subjective phenomenon. Besides, the limitation of (measurement of) quality of life to health-related quality of life is increasingly common. One workable definition of health-related quality of life (HRQOL) is: "those health-related aspects of life which are capable of being modified by the provision of healthcare".[15] A modern taxonomy of approaches to the measurement of HRQOL is described by Guyatt et al.[16] They distinguish between generic and disease-specific instruments to assess HRQOL. Generic instruments may be used in any population, regardless of the underlying condition, while disease-specific instruments are only applicable in specific patient-groups. Two types of generic instruments exist: (1) health profiles and (2) health preference methods or utility measures. Health profiles cover a range of dimensions of HRQOL, including physical, psychological and social functioning. Depending on the specific health profile, scores on individual dimensions may be combined into summary scores for physical, mental or psychosocial functioning, or into one overall score. Health preference methods or utility measures are rooted in economic and medical decision making theory. These measures are aimed at eliciting the value a person attaches to a health state, relative to perfect health and death. HRQOL is summarised as a single number, usually between 0 and 1. Health preference scores elicited from patients reflect both the health status of the patient and the value of that health status to the patient. In recent years, the emphasis in HRQOL research in ESRD patients has been on the use of these health pro-

files and health preference methods. Uni-dimensional questionnaires, widely used in the 1980s, seem to be used less often nowadays. The aim of this article is to present a review of the literature on the application of health profiles and health preference methods in ESRD patients. Besides a part of the literature that is entirely descriptive in nature, the literature in this field aims generally at answering one or more of the following questions:

1 What are the psychometric properties of health profiles and health preference methods as applied in renal patients?

2 How does HRQOL of ESRD patients compare with that of a healthier population, such as a general population sample?

3 Which medical, socio-demographic and disease-related factors determine HRQOL of ESRD patients?

4 Do HRQOL outcomes differ between patients treated with different therapeutic modalities?

We will discuss our findings along these four questions.

Methods

Several sources were used to identify published papers on HRQOL of ESRD patients (including pre-dialysis patients entering ESRD treatment). Firstly, a MEDLINE search (1966 through 1999) was performed. The search strategy is outlined in Appendix I. Other sources of information were two general quality of life bibliographies [1 17] and other published reviews [2-5 18]. Further, we carefully tracked all the references of selected publications. Finally, we searched the EMBASE and PsycINFO databases for additional references not found using the strategy described above.

We have used the following selection criteria for our search, to ensure that only the relatively well designed and well-reported studies were incorporated in our review:

- studies must report self-assessed HRQOL data of ESRD patients,
- no interim reports were selected if a final report was available,
- double publications of the same study data were only included if different research questions were addressed,
- data must be reported in a way that allows for verification (for instance, conclusions drawn should be supported by reported data),
- in cross-sectional studies aiming at the comparison of HRQOL of patients treated with different modalities, multivariate control for case-mix differences must have been applied,

- studies aiming at the comparison of ESRD patients' HRQOL and HRQOL of the general population must have used age-matched control samples from the general population, or control for age in a multivariate analysis.

Furthermore, the following types of studies were excluded from the review:

- studies with a main focus on HRQOL of diabetes mellitus patients or combined kidney-pancreas transplant,
- studies that report only staff-assessment of HRQOL of ESRD patients,
- studies that applied generic instruments only to test construct validity of disease-specific or uni-dimensional HRQOL instruments,
- studies describing samples of less than 20 patients, and
- cross-sectional studies that describe HRQOL outcomes without any further analysis.

Results

HRQOL instruments used in ESRD patients

Because our current review was aimed only at the use of health profiles and health preference methods in ESRD patients, we *a priori* limited the list of instruments relevant to our review. However, some further limitations in the list of viable instruments were made on the basis of the following reflections. Some authors regard rating scales (Visual Analog Scales) also as health preference methods.[19] However, many different operationalisations of rating scales were found in the literature, with different anchor points, instructions and scaling. These differences in operationalisation hamper unambiguous interpretation of scores. We therefore choose not to include the rating scale approach in our review. Another category of HRQOL instruments combines patient-derived information on health status with community-derived valuations for these health states. These instruments are primarily suitable for use in economic evaluation studies since they allow for the calculation of *Quality Adjusted Life Years* (QALYs). Examples of such instruments are the EuroQol (EQ-5D) Instrument,[20] the Rosser and Kind Scale,[21] and the Quality of Well Being Scale.[22] Such instruments have scarcely found application in ESRD patients and have therefore not been included in our review. Also, not all available health profiles have been applied in ESRD patients. As a consequence, well-known profiles, such as the COOP charts and the Duke Health Profile, could not be selected for our review. Ultimately, the following six HRQOL instruments were selected for the review: Medical Outcomes Study Short-Form Health Survey, Sickness Impact Profile, Nottingham Health Profile and the Quality of Life Index (representing the health profiles), and Time Trade Off and Standard Gamble (representing the health preference methods). In the following, the six selected instruments are described briefly.

The *Medical Outcomes Study Short-Form Health Survey* is available in different lengths, the 36-item short-form health survey (SF-36) being by far the most frequently used. The SF-36 generates a profile of scores on 8 multi-item scales, reflecting 8 dimensions of HRQOL.[23] These dimensions are (1) physical functioning, (2) role limitations due to physical problems, (3) bodily pain, (4) general health perceptions, (5) vitality, (6) social functioning, (7) role limitations caused by emotional problems and (8) mental health. Raw scores are transformed to scale scores between 0 and 100, where a higher score indicates better health. Two summary scores may be computed from the scores of the 8 sub-scales of the SF-36, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[24] Norm-scores for (sub-groups of) the general population are available.

The *Sickness Impact Profile* (SIP) is a behaviourally based measure to assess the impact of disease and treatment on functional status.[25] The instrument contains 136 statements, covering 12 different domains: (1) sleep and rest, (2) eating, (3) work, (4) home management, (5) recreation and pastime, (6) ambulation, (7) mobility, (8) body care and movement, (9) social interaction, (10) alertness behaviour, (11) emotional behaviour, and (12) communication. Respondents either agree or disagree with the statement. Results may be presented as a 12-dimensional profile score, or by means of sub-scores: a "physical" score based on 3 scales, a "psychosocial" score based on 4 scales, and a total score. Scores represent a percentage of the total possible score and range from 0 to 100, where 0 represents optimal health.

The *Nottingham Health Profile* (NHP-1) contains 38 dichotomous questions about health status, which may be summarised in 6 sub-scales: (1) physical mobility, (2) energy, (3) pain, (4) sleep, (5) social isolation, and (6) emotional reaction.[26] Scales range from 0 to 100, with higher scores indicating more limitations. The NHP does not summarise individual scale scores in an overall score.

The *Quality of Life Index* (or *Spitzer's Quality of Life Index* - QLI) was originally designed to measure the general well-being of terminally ill cancer patients, but has been used broadly for chronically ill patients populations.[27] The QLI consists of five domains of HRQOL ((1) activity level (including occupation), (2) activities of daily living, (3) feelings of healthiness, (4) quality of social support and (5) psychological outlook), each with three levels of functioning. Scores of 0, 1 and 2 for each level reflect increasing well-being and may be summed to a total score ranging from 0 to 10.

The *Time Trade Off (TTO)* is an interview technique that is aimed at eliciting the value a person attaches to his current health state.[28] It is based on the principle that the less preferable the current health state is, the higher the proportion of remaining life-time a person is willing to trade off to gain normal health will be. The respondent is asked whether he is prepared to give up some remaining time of life, in order to improve the current health state to normal health. The quotient of the chosen number of years in a normal health state over statistical life expectancy yields the TTO score, a score between 0 and 1, where a higher score represents a better health state.

Finally, the *Standard Gamble* (SG) is an interview technique, that is based on the principle that a respondent will be more willing to accept a risk in order to gain normal health, if the current health state is regarded as less desirable.[19] The respondent is presented with two

hypothetical alternatives and asked to choose the one preferred most. The first alternative offers the certainty of staying in the current health state for the remainder of the respondent's life. The second alternative is a gamble with specified probabilities for both the positive outcome of the gamble (a normal health state for the remainder of the time) and the negative outcome (death). As with TTO, a score between 0 and 1 is derived, where higher scores represent better health states.

Results of the literature search

The MEDLINE search generated 815 references that were all checked for the type of HRQOL instrument that was used. Out of these 815 papers, a total number of 109 papers was initially selected because one of more of the six selected HRQOL instruments was applied. Five more papers were identified with a control search in EMBASE and PsycINFO. After reading those 114 papers, a further selection was made on the basis of criteria discussed in the methods section. Finally, 57 papers were selected for this review. Most studies that were not selected were (older) descriptive cross-sectional studies that suffered from a lack of adjustment for differences in case-mix between different treatment groups. Appendix 2 shows a comprehensive overview of all selected studies with the following key features: first author, year of publication, study design, aim of study, number and treatment modality of patients, HRQOL instrument used and main outcomes. In addition, appendix 3 provides six tables that show published scores for each of the six selected HRQOL instruments. These tables may be used as a quick reference for clinicians and researchers who apply those instruments in ESRD populations. In the remainder of the results section, we will discuss the findings of selected studies, centred around the four research questions that were formulated in the introduction section.

Research question 1: What are the psychometric properties of health profiles and health preference methods as applied in renal patients?

Because the six selected HRQOL instruments are well tested and validated generic instruments, they should be useful for application in both healthy and diseased populations. Therefore, psychometric testing for specific patient groups, i.e. dialysis patients, is in general not considered as a necessity. Indeed, many authors refer to the fact that these generic instruments have been tested for psychometric properties in other populations and in general were found to have adequate test properties.[11 29-37] However, extensive methodological work on feasibility, reliability, validity and responsiveness of these HRQOL instruments in ESRD populations was found in our review. Also, because all instruments aim to measure HRQOL, some authors have studied the relationship of health profiles scores to health preference scores.

Feasibility. The administration of TTO and SG requires an interview situation. The SIP is often presented in an interview situation as well, although self-assessment is also possible. Both NHP and SF-36 are generally self-administered. The TTO and SG require a certain level of cognitive functioning from the respondent.[38] Several publications mention that some respondents were unable to answer SG and TTO because of cognitive failures, or stipulate that patients refused to answer because of other reasons, e.g. religion.[38-41]

Percentages of non-response to these instruments as high as 19 % have been reported.[38] Other authors did not encounter specific problems when administering SG and/or TTO.[42] The SF-36, SIP and NHP are generally well accepted by patients and can be self-administered.[43-47] In a study comparing the feasibility of NHP and SIP, Essink-Bot et al. found the NHP to be more feasible than the SIP, i.e. shorter and less difficult.[44] No information on feasibility of QLI was found.

Validity. Evidence for discriminant validity, in a sense that the instrument is able to discriminate between HRQOL of patients on different treatment modalities or with different underlying diseases in a way that is predicted a priori, is presented for the TTO,[40 48] and for the SF-36.[43 49] In one study, evidence for construct validity of TTO (the level of agreement with other measures that aim to measure the same underlying construct) was obtained through a comparison of the independent rating of the quality of life of a patient by his nephrologist and the patient himself.[39] The rank correlation between the mean scores of nephrologists and patients was 0.51. Another study also provided with evidence for construct validity by means of a comparison of patient TTO scores and nephrologists', nurses' and relatives' assessment of patients HRQOL.[40] The correlations between patients' TTO scores and external raters' scores were positive and statistically significant, but relatively low (r from 0.27 to 0.40). Essink-Bot et al. studied the construct validity of NHP and SIP in dialysis patients, comparing the pattern of Intra Class Correlation (ICC) coefficients between conceptually similar scales of NHP and SIP, and between scales of NHP/SIP and related domain-specific HRQOL measures with proven validity.[44] The association patterns observed between the NHP and the SIP, and other instruments were largely as expected, supporting the construct validity of these two instruments. No information on validity of SG and QLI was found.

Reliability (reproducibility or test-retest reliability) refers to the degree to which results obtained by a measurement can be reproduced. The study of reliability of HRQOL scores in ESRD patients might be troubled by the occurrence of real changes in health status between two moments of measurement, for instance when assessed before and after a dialysis session. One study reported test-retest reliability of the TTO to be 0.85, when the tests were administered 6 weeks apart.[48] One large study reassessed the TTO in 171 ESRD patients 4 weeks after the first interview and found the intra-class correlation coefficients (ICC) to be 0.81.[40] A pilot study from the same research group reported a test-retest correlation coefficient of 0.628, 6 weeks after the initial interview.[39] One study on the reliability of the NHP found Spearman correlation coefficients of 0.69 to 0.85 between first and second administration of this questionnaire.[50] Another study used ICC's for the test-retest reliability of the NHP, and found these to be between 0.55 and 0.80.[44] Because the NHP was administered just before and one day after dialysis in that study, the authors preclude that the relatively low ICC's might be attributed to real differences in patients' health status before and after dialysis.[44] Laupacis et al found ICC's exceeding 0.80 when the reproducibility of the SIP was studied two months after the initial interview in 40 patients who received a placebo to erythropoietin, a drug used for anaemia.[51] Test-retest reliability of SG and QLI has not been studied in ESRD populations.

Reliability (homogeneity or internal consistency) estimates the extent to which different sub-parts of an instrument measure the critical attribute. Evaluating the internal consistency of SF-36, adequate Cronbach's alphas for group comparisons (> 0.7) were reported by several authors.[45-47 49] The internal consistency of NHP, as studied by Badia et al.,[50] was very good for the entire instrument (Cronbach's alpha 0.91), and somewhat less for individual sub-scales (ranging from 0.58 (social isolation) to 0.86 (pain). One other study compared internal consistency of NHP and SIP, and found that the NHP (Cronbach's alphas 0.39-0.80) yielded somewhat higher internal consistency estimates than the SIP (0.14 to 0.95).[44]

Responsiveness to change. Another important feature of a HRQOL instrument should be sensitivity, or responsiveness to clinically meaningful changes. This is especially relevant in studies evaluating the effectiveness of interventions. One study evaluated the responsiveness to change of TTO in a prospective study that attempted to reach an adequate dialysis dose (defined as total weekly clearance of waste products $Kt/V_{urea} > 1.0$) in underdialysed patients ($Kt/V_{urea} < 0.8$, n=26).[52] The TTO was found not to be responsive: no significant correlation between change in Kt/V_{urea} values from initial to second evaluation and the change in TTO values could be demonstrated (r = 0.07). The authors' explanation for this finding is that, because the TTO allows patients to apply internal weights to the effect of ESRD and its treatment on HRQOL, the patient does not weight such improvements in therapy heavily. Several other studies reported on TTO's responsiveness to change in prospective studies evaluating the effect of the drug erythropoietin.[13 53-54] Two studies found that TTO scores remained stable over time, although health profiles showed increases in some domains of HRQOL, such as fatigue and physical functioning.[13 53] One smaller study (n=28) by Harris showed higher TTO scores after introduction of erythropoietin.[54] Larger improvements in HRQOL, such as found when prospectively comparing pre- and post-transplant HRQOL, were reflected ($P<0.005$) in higher TTO scores in several studies.[55-57] Responsiveness may in general be hampered by floor- or ceiling effects, indicating that the majority of the patients show scores around the upper or lower bound of the range of possible scores. One study found such effects using the NHP.[58] In a group of limited care haemodialysis patients, the median score in 2 out of 6 scales was 0 (best possible score), while median scores in the other 4 scales also did not allow for further differentiation between sub-groups of patients. A comparative study between NHP and SIP found the distribution of scores of the SIP to be even more skewed in the direction of good functioning than those of NHP.[44] Appropriate use of the whole range of possible scores was reported for the SF-36 sub-scales, [12 45-47] except for the two role functioning scales.[45-47] No information was found on responsiveness of SG and QLI instruments.

Relationship of health profiles and health preference scores. Although all instruments selected aim to measure HRQOL, reported correlations between the respective outcome measures were low to moderate. A correlation of 0.43 was found between QLI and TTO.[40] Correlations between the global, physical and psycho-social SIP scores and TTO were -0.23, -0.15 and -0.17, respectively, as reported in the Canadian Erythropoietin Study.[51] Similar correlations between SIP and TTO (r = 0.19) and SIP and SG (r = 0.31) were found in a study by Hornberger et al.[42] The two health preference instruments that were used in that study (SG and TTO), showed only a moderate correlation (r = 0.31), despite the conceptual similari-

ty of both instruments. Hornberger et al. found that agreements between measures were especially poor at the individual level, with patients reporting low HRQOL according to one method and a high HRQOL according to the other. Most patients had discrepancies of greater than 50 percent between the highest and lowest scores on the different instruments used. This study showed that the method chosen to evaluate HRQOL may produce substantially different impressions of HRQOL of patients. Revicki used (sub-scales of) SIP, SF-36 and SG in a group of 73 pre-dialysis patients and found correlations between SIP and SG and SF-36 and SG not to be higher than 0.19, with one exception of 0.30, for the correlation between the SIP sub-scale home management and SG.[38] Although the selected instruments all aim at measuring HRQOL, different instruments may lead to different conclusions on HRQOL of a patient population. Health profiles and health preference methods are at best moderately correlated.

Research question 2: How does HRQOL of ESRD patients compare with that of a healthier population, such as a general population sample?

Because it is known that HRQOL scores are negatively related with age, only those studies that compared HRQOL of ESRD patients with age-matched samples of the general population are reviewed here. Thirteen studies provide with such information.[11 29 46-47 59-67] Except three studies that were performed in transplanted patients,[61 64 66] all studies reported that ESRD patients rated their HRQOL on average lower than the normal population, irrespective of the type of HRQOL instrument that was used. However, differences between ESRD patients and the general population were more obvious in the physical domains of HRQOL than in the mental domains.[11 60-63 65] Five studies that focused on HRQOL differences between transplanted patients and the general population draw different conclusions.[61 63-64 66-67] The studies by Benedetti et al.[61] and Rebollo et al.[64] found little differences in SF-36 scores and a study by Niechzial et al.[66] found equal or better NHP scores for transplant recipients, compared with the general population. The study by Shield et al.[67] found that transplanted patients were not significantly different from the general population in SF-36 dimensions of bodily pain, vitality and mental health. Finally, a study by Matas et al.[63] described that up to 40% of non-diabetic and up to 65% of diabetic transplant recipients had SF-36 scores below the 95% confidence interval for age-matched controls of the general population. This was especially true in the physical domains of the SF-36. Three studies stratified the ESRD populations into age-groups and found that differences between ESRD patients and general population samples are smaller in the higher age-group(s).[60-62] One of the two studies that found little HRQOL differences between ESRD patients and the general population was also performed in a group of patients older than 65 years.[64]

Research question 3: Which medical, socio-demographic and disease-related factors determine HRQOL of ESRD patients?

HRQOL of dialysis patients may be determined by socio-demographic, treatment related and disease related variables, as well as psychological and social factors. Many studies have linked HRQOL outcomes to such variables, but only those studies that report these analyses in a multivariate way are reviewed here. Of the selected studies, sixteen reported on

important determinants of HRQOL.[10-11 29 32 34-36 47 49 65 68-73] All studies that analyzed the influence of the presence of co-morbid conditions on HRQOL outcomes reported similar findings: concurrent diseases have a negative influence on HRQOL.[10 29 34-36 47 49 68 70-71 73] Especially diabetes mellitus [10 35-36 68 71 73] and cardiovascular disease [10 34-35 73] were identified as diseases that influence the physical domains of HRQOL. A higher age was found to be negatively associated with NHP scales of pain and mobility,[65] SF-36 scales physical functioning,[29 47 49 68] vitality [47 49] and role limitations due to physical functioning,[29 49] physical SIP score,[10 35-36 69] psychological SIP score,[10 69] total SIP score,[10 35 69] QLI score [71] and positively with SF-36 scale social functioning.[68] More years of education was found to be positively associated with overall HRQOL outcomes,[10 35 69 71] physical [10 35] and psychological/mental HRQOL outcomes.[10 35 65 69] Some socio-demographic factors that were found to be negatively associated with HRQOL were female sex [10 47] black race [36] and Hispanic race,[49] while being married,[72] a higher socio-economic status,[10] and being employed [29 69 71] were positively associated with HRQOL. No agreement was found on the relationship between time on dialysis / total time with end-stage renal disease and HRQOL outcomes. A large study by Niechzial et al.[65] found that patients who were on dialysis for a longer time had more severe problems with NHP scales pain, emotional reactions, sleep and mobility. Wight et al. described a similar negative influence of treatment duration on physical functioning.[47] In contrast, Morton and colleagues [73] described that length of time on dialysis was positively associated with good outcomes on physical and social functioning. Others [71] found no influence of length of time on dialysis on HRQOL scores. Higher haemoglobin levels were described to have a positive influence on total SIP score,[10] physical SIP score,[10] SF-36 domains of social functioning, role limitations caused by emotional problems and vitality,[29] and physical functioning and vitality.[47] Some studies have analysed the associations between HRQOL outcomes and renal function parameters. Higher hematocrit levels were found to positively affect total SIP score [10] and changes in hematocrit levels were associated with positive changes in overall health.[11] Serum albumin was found to be positively related to 7 out of 8 SF-36 scales,[68] QLI score [71] and total SIP score.[34] One study that linked HRQOL outcomes to residual renal function found that this was positively associated with SF-36 scales social functioning, role limitations due to physical problems, role limitations caused by emotional problems, mental health and vitality.[29] A later report on the same study population showed that physical HRQOL in haemodialysis and peritoneal dialysis and mental HRQOL in haemodialysis patients was to a larger extent explained by a greater physical symptom burden (occurrence and frequency of itching, cramps, fatigue etc.) than by any other determinant.[70] Morbidity, defined as the number of hospital admissions in the past six months, was negatively related with total SIP score and physical and psychosocial SIP scores,[69] with some SF-36 scales [49] and with the TTO score.[72] One striking finding is that five studies that aimed to explain HRQOL outcomes from dialysis adequacy data, all found that adequate dialysis was not an important factor.[10 29 47 68 73]

Ten studies focused on the effects that erythropoietin treatment of ESRD-related anaemia had on HRQOL.[11 13 53-54 74-79] Of these studies, only two were designed as randomised controlled trials.[13 74] The study by the Canadian Erythropoietin Study Group showed that the global and physical scores on the SIP improved in patients treated with erythropoietin compared with those given placebo.[13] Significant improvements were noted in

the response of patients to questions on body care and movement, home maintenance, ambulation, communication and work among those treated with erythropoietin. Despite these improvements, patients' TTO scores remained stable.[13] The second randomised controlled trial was performed in predialysis patients.[74] This study showed that there were significant differences between patients using erythropoietin and the placebo group on changes in SF-36 sub-scales of energy (vitality) and physical functioning. Other published studies were all observational studies, with patients serving as their own controls in a pre- and post-erythropoietin use situation. The largest of these observational studies involved 1004 patients, divided over patients who were not using erythropoietin before (new-to-erythropoietin) and patients who were already using erythropoietin (old-to-erythropoietin).[11] Significant improvements in SF-36 sub-scales of physical functioning, vitality, social functioning and mental health, and in the Mental Component Summary Score were described for new-to-erythropoietin patients. Patients already using erythropoietin did not experience changes in HRQOL during the study period. At follow-up, a comparison of the old-to-erythropoietin patients with the new-to-erythropoietin patients revealed that SF-36 scores for the latter group achieved the same levels as the former group. Three studies used the SIP to evaluate changes in HRQOL after start of erythropoietin use.[53 77 79] These studies all described improvements in the psychosocial dimension of SIP and the global SIP scores, and two studies also described improvements in the physical dimension of SIP.[53 79] Three studies evaluated HRQOL changes after start of erythropoietin use with the NHP instrument.[75-76 78] A large study by Evans et al. found significant improvements in the energy, emotional wellbeing and social isolation domains of the NHP.[78] The positive effect of erythropoietin on energy and emotional wellbeing was confirmed in two smaller studies.[75-76] Only two studies have attempted to identify factors that were independently related to HRQOL improvement after erythropoietin treatment.[11 79] It was found that most substantial improvements in HRQOL were experienced by patients with poor baseline HRQOL.[79] Furthermore, erythropoietin induced changes in haematocrit level were positively associated with HRQOL outcomes in SF-36 scales of general health, vitality and social functioning,[11] and with the global score of SIP.[79]

Research question 4: Do HRQOL outcomes differ between patients treated with different therapeutic modalities?

Many studies comparing the HRQOL of different treatment modalities have been published. A major drawback of all studies is the lack of randomisation of patients over different modalities. As a consequence, selected patients are being treated with selected modalities. To overcome this objection at least partially, cross-sectional studies were only selected for this review if differences in case-mix had been corrected with multivariate analyses techniques. The NHP was used in one study in 1027 haemodialysis and peritoneal dialysis patients.[65] For each of the 6 sub-scales of NHP, it was concluded that peritoneal dialysis patients did not differ significantly from haemodialysis patients. From this cohort of dialysis patients, 138 patients were transplanted,[66] which markedly affected their functioning in the energy, sleep and emotional reactions domains of HRQOL. The TTO was used in six studies comparing modalities.[40 55-57 72 80] One small study compared HRQOL effects of high-flux and conventional haemodialysis techniques in a cross-over trial.[80] The 22 patients who completed both phases of the trial did not experience differences with respect to

HRQOL. Five studies concluded that transplanted patients had a better HRQOL as measured with TTO than dialysis patients.[40 55-57 72] Three of those studies were prospective studies that followed unselected samples of patients from dialysis through transplantation.[55-57] Six to thirty months after transplantation, patients valued their HRQOL on average with a TTO score that was 0.17-0.33 ($P<0.001$) higher than their pre-transplantation score. Two of these prospective studies also included the SIP instrument.[55-56] Both the physical ($P<0.001$) and psychosocial sub-scores ($P<0.01$), and the total SIP score improved significantly ($P<0.001$) after transplantation. A study by Julius et al. using the SIP found that CAPD patients had the highest scores on the physical functioning scale (indicating more physical dysfunctioning), followed by centre haemodialysis patients, cadaver transplant and related transplant patients.[36] Differences were not statistically significant, except between CAPD and related transplant patients. The SIP instrument was also used in a Spanish study involving 1013 dialysis patients, who received either conventional haemodialysis, haemodiafiltration or peritoneal dialysis.[10] After adjusting the HRQOL outcomes for case-mix differences, no significant differences were found in relation to dialysis modality. Of this sample of 1013 Spanish dialysis patients, 88 patients were successfully transplanted. Their changes in HRQOL were described by Jofré et al.[81] Improvements were reported in the physical, psychosocial and global domains of SIP, but were most marked in the psychosocial domain. For unclear reasons, women benefited less from a transplant than men. Also, older age and greater prior co-morbidity diminished the beneficial effects of transplantation.[81] The widely cited study by Hart and Evans used the SIP in a study comparing HRQOL of home-haemodialysis, centre haemodialysis, CAPD and transplanted patients.[35] This study clearly demonstrated for the first time that many of the intermodality differences observed in other studies may have resulted from variations in case-mix. After such adjustments, only transplanted patients showed significantly better SIP scores. The three dialysis modalities were comparable with regard to adjusted SIP scores. Finally, four studies used the SF-36 and one study the SF-20 for comparison of ESRD treatment modalities.[20 31 43 47 73] A study by Khan et al showed that CAPD and haemodialysis patients showed significantly worse ($P<0.01$) scores than transplanted patients on 6 out of 8 sub-scales of SF-36.[43] The differences between dialysis and transplant patients were most pronounced in the physically oriented scales of the SF-36. Only emotional role functioning and mental health of dialysis patients were similar to those of transplanted patients. A prospective study by Meers et al. compared a cohort of patients that was trained for self-care haemodialysis with an age- and co-morbidity-matched cohort of full-care haemodialysis patients.[31] It was concluded that self-care dialysis patients performed better than full-care dialysis patients on SF-36 scales role limitations caused by emotional problems, social functioning, mental health and vitality. Merkus et al. reported on HRQOL of patients three months after the start of dialysis treatment.[29] Peritoneal dialysis and haemodialysis patients in this study showed comparable levels of HRQOL, except for the mental health sub-scale, where haemodialysis patients appeared more impaired than peritoneal dialysis patients. This patient sample was followed until 18 months after start of dialysis.[82] It was shown that haemodialysis had a consistently favourable effect on physical HRQOL over time compared with peritoneal dialysis. Mental HRQOL remained stable over time. The study by Wight et al. showed a HRQOL advantage of transplanted patients and similar HRQOL of patients on all dialysis modalities, except for an independent negative effect of hospital haemodialysis on mental

health.[47] Finally, one study that compared HRQOL of CAPD and APD patients found no influence of treatment on HRQOL of patients.[73] In conclusion, there is convincing evidence that HRQOL of transplant patients is better than that of dialysis patients. Most studies that have compared HRQOL of patients on different dialysis modalities have found no or few differences between the modalities.

Discussion

The use of one or more of the six selected HRQOL scales, four of them health profiles and two of them health preference methods, has been described more than 100 times. Especially the health profiles SIP and SF-36 have found widespread application in ESRD populations. Of the health preference methods, TTO was used more often than SG. Out of all publications, we have selected 57 relatively well designed and conducted studies for the current review. Four main research questions could be distinguished in the selected papers. We will discuss our main findings along these research questions.

With respect to the methodological and psychometric aspects of the use of these generic instruments in ESRD patients, most studies found that test properties were acceptable to satisfying. However, some concerns about the TTO instrument remained. Application of the TTO was hampered by relatively high non-response.[38-40] Also, the TTO was found not to be responsive to clinical changes.[13 52-53] Elsewhere, we have postulated that TTO might be less suitable for use in chronically ill patient populations, because patients adapt to their illness and tend to use only the upper parts of the scale.[83] The same remarks may be valid for a HRQOL instrument familiar to TTO, the SG, but less evidence on the use of SG in ESRD populations was available. The correlations between scores derived with the health preference methods and the health profiles scores were poor to moderate. This finding is in accordance with results of previous research in other seriously ill patient groups.[84-85] The low correlation coefficients found in the studies imply that the variance in SG and TTO scores can hardly be explained by the individual HRQOL dimensions covered in the health profiles. The implication is that both types of questionnaires truly reflect different and possibly complementary aspects of the HRQOL concept. The health status measures mainly assess patients' functioning on different domains of quality of life, whereas the health preference methods elicit individual judgements on the value of the current health status, relative to full health and death. The preference scores may be influenced by factors not covered by the health status questionnaires: beliefs about health, previous experiences and knowledge, a person's attitude towards risk and time and non-health related factors, such as financial status and the availability of social support.[86]

The second research question focused on comparisons with age-matched samples of the general population. It was shown convincingly that dialysis patients' HRQOL is worse than HRQOL of age-matched samples from the general population. However, differences were less marked for older patient groups and for transplanted patients. In general, differences were more profound in the physical than in the mental and social domains of HRQOL.

Concerning the third research question, the determinants of HRQOL of ESRD patients, extensive research was found in our review. The number and type of co-morbid conditions

(especially diabetes mellitus), age and educational level were often found to be associated with HRQOL outcomes. The positive influence of use of erythropoietin on HRQOL of ESRD patients is undoubted. Positive changes after the introduction of erythropoietin use have been reported in the physical, mental and social domains of HRQOL. Furthermore, it was found that the physical and overall domains of HRQOL are far better explained than the psychosocial domains of HRQOL, both in terms of number of determinants known to be associated with HRQOL and total amount of variation explained. Limitations of most studies are that only a few of the many possible determinants were included in the analyses. Therefore, the total explained variation of HRQOL by the selected background characteristics was low to moderate, in general. This implies that factors so far not known or not analysed contribute to HRQOL levels of ESRD patients. Even studies that attempted to include demographic, treatment related, biomedical as well as renal disease related factors found R^2 to be only 10 to 37 %.[10 29 34-36 47 73] Efforts to identify additional factors that influence HRQOL of ESRD patients have not been particularly successful so far. Besides, not all determinants known can be modified by healthcare interventions. One interesting study found that large HRQOL differences existed between patients treated in different dialysis centres, even after adjustment for differences in case-mix.[71] This study draws the attention to a less well studied area: the relationship between the process of care and HRQOL outcomes. Why do patients in one dialysis centre show better HRQOL than in another centre? Can differences in the process of care be identified and quantified? These questions remain to be answered by future research.

The fourth research question, the comparison of HRQOL of patients treated with different modalities resulted in the conclusion that there is convincing evidence that HRQOL of transplanted patients is better than HRQOL of dialysis patients. However, results of this review of the literature do not justify the choice of one dialysis modality over the other because of perceived HRQOL benefits. Most studies concluded, when differences in case-mix between patient groups were statistically controlled for, that treatment modality is not a determinant of HRQOL. The quality of life of patients who are being treated with two more recently developed dialysis techniques, namely APD and daily home haemodialysis, is less well studied so far. Two of the selected studies included APD patients,[32 73] but only one small study explicitly compared HRQOL of APD patients with CAPD patients.[73] No differences were found. Larger studies should certify this finding.

Summarising, 57 well-designed and well-performed HRQOL measurements using health profiles or health preference methods were found in the literature. Especially the Short-Form-36 and Sickness Impact Profile have found widespread application in ESRD patients. In some dialysis centres, SF-36 is even used for regular monitoring of patients, to identify (changes in) problem areas and to modify these problems where possible.[46] Also, for SF-36 and SIP, most evidence on the psychometric soundness of application in ESRD patients is available. The health preference methods Time Trade Off and Standard Gamble have been used less often, and more doubts about their application remain after studying the literature. One striking finding is that TTO and SG scores do not correlate with health profiles scores. When using TTO and SG, it would be advisable to also apply one of the health profiles. Convincing evidence is available on the fact that HRQOL of dialysis patients is worse, especially in the more physically oriented domains of HRQOL, than HRQOL of the gen-

eral population, and on the fact that HRQOL of transplanted patients is better than HRQOL of dialysis patients. No major differences in HRQOL of patients on different dialysis modalities were found. Regarding the four research questions identified, the question on determinants of HRQOL in ESRD patients seems to leave most room for further research.

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Wim ten Have (Library of the National Institute of Public Health and the Environment) provided access to bibliographic databases.

Appendix I

The following search strategy was used for the MEDLINE literature search (period covered 1966 through 1999). The MESH terms "Quality-of-life", "Quality-Adjusted-Life-Years", "Health Surveys" and "Health Status Indicators" were each combined with all of the following ESRD specific MESH terms: "Haemodialysis", "Peritoneal Dialysis", "Kidney Transplantation", "Dialysis", "Kidney Failure", "Kidney Failure, Chronic" and "Renal Failure". All subheadings were included with each MESH term. The selection was a priori limited to publications in the English, French, German and Dutch languages and to adult populations. A similar search strategy was used for an additional search in EMBASE (1974 through 1999) and PsycINFO (1967 through 1999) databases, supplemented with the requirement that one of the six selected HRQOL instruments (either full name or abbreviated name) was found in either title, abstract or control (= MESH) terms.

Appendix II: Systematic overview of all selected studies

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Research question 1: What are the psychometric properties of health profiles and health preference methods as applied in renal patients?					
Churchill et al., 1984 [39]	Prospective, observational	Testing TTO instrument	n=73: 42 FCHD, 17 CAPD, 14 TX	TTO	Use of the TTO instrument was considered feasible in ESRD patients. Test-retest reliability was high (correlation coefficient 0.8). Construct validity of TTO was supported by test-results (rank correlation between different raters 0.51).
Churchill et al., 1987 [40]	Prospective, observational	- Psychometric testing of TTO instrument - To study the relationship between LCHD QLI and TTO	N=194: 28 HHD, 42 FCHD, 79 TX, 31 CAPD, 14	TTO, QLI	- Evidence for discriminant validity was found. Test-retest reliability was high (Intra-Class-Correlation coefficient 0.81). - QLI and TTO were moderately correlated: the correlation coefficient was 0.43.
Churchill et al., 1991 [52]	Prospective, observational	Testing responsiveness of TTO	n=47: 47 FCHD + LCHD (n.s.)	TTO	TTO not responsive to changes in adequacy of dialysis.
Laupacis et al., 1991 [51]	Prospective, intervention (rct)	- Testing reliability and responsiveness of TTO - To study the relationship between SIP and TTO	n=118: 118 FCHD	TTO, SIP	- TTO not responsive to changes in hemoglobin caused by use of erythropoietin. Test-retest reliability was good: Intra-Class-Correlation coefficient > 0.80. - SIP and TTO were weakly correlated: Pearson's correlation coefficients between –0.15 and –0.23.
Schrama et al., 1991 [58]	Cross-sectional, observational	Testing feasibility of NHP	n=60: 60 LCHD	NHP	Administration feasible. Ceiling effects were found: more than 40 % of patients had highest possible scores in NHP scales.
Hornberger et al., 1992 [42]	Prospective, observational	Relationship between TTO, SG and SIP	n=58: 58 FCHD	TTO, SG, SIP	Moderate correlation between SG and SIP (Spearman rank-correlation coefficient 0.31). Weak correlation between TTO and SIP (correlation coefficient 0.18). SG and TTO were moderately correlated (0.31).
Kurtin et al., 1992 [45]	Prospective, observational	Testing feasibility and reliability of SF-36	n=37: 37 FCHD	SF-36	Administration feasible. Floor- and ceiling-effects were found in two role functioning scales. Reliability estimates adequate for group comparisons (Cronbach's α from 0.62 to 0.90).
Revicki, 1992 [38]	Cross-sectional, observational	- Relationship between SG and SIP - Testing feasibility of SG	n=73: 73 pre-dialysis	SG, SIP [b], SF-36 [b]	- Correlations were weak to moderate: Pearson's correlations between SG and individual SIP scales between –0.07 and –0.30. Correlations between SG and individual SF-36 scales between 0.09 and 0.12. - 19 % of patients were unable to complete the SG or provided inconsistent responses.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Badia et al., 1994 [50]	Prospective, observational	Testing test-retest reliability and internal consistency of NHP	n=170: 170 FCHD	NHP	Spearman-correlation coefficients > 0.6 for all NHP scales. NHP was considered sufficiently reliable. Overall NHP showed satisfactory internal consistency (Cronbach's α 0.91), but not all sub-scales equally satisfactory.
Meyer et al., 1994 [46]	Cross-sectional, observational	Testing feasibility and reliability of SF-36	n=112: 112 dialysis (n.s.)	SF-36	Reliability (Cronbach's α) > 0.77 for all scales. SF-36 was considered sufficiently reliable. Administration to dialysis patients on a regular basis in a busy clinic was considered feasible.
Khan et al., 1995 [43]	Cross-sectional, observational	Testing feasibility and validity of SF-36	n=185: 102 TX, 43 FCHD, 27 CAPD	SF-36	Administration of SF-36 was feasbile. Evidence for discriminant validity of SF-36 was found.
Meers et al., 1995 [33]	Cross-sectional, observational	Inter-rater agreement on patients' HRQOL	n=30: 30 FCHD	SF-36	Caregivers' (nurses and nephrologists) scores were lower than patients' scores.
Essink-Bot et al., 1996 [44]	Cross-sectional, observational	Psychometric testing of SIP and NHP	n=63: 63 FCHD	SIP, NHP	Weak correlations between NHP and SIP. NHP performed better than SIP in terms of feasibility and internal consistency.
Lenert, 1996 [41]	Prospective, observational	Testing feasibility of SG and TTO with computer and interview based administration	N=25: 25 FCHD	SG, TTO	Both interviews and computer based-administration were feasible. Computer-assisted administration derived higher scores. One patient did not understand the concept of probability with SG.
Molzahn et al., 1996 [48]	Prospective, observational	Psychometric testing of TTO	n=215: 52 FCHD, 37 HHD, 30 CAPD, 96 TX	TTO	Test-retest reliability was good (0.85). Evidence for discriminant validity was found.
Molzahn et al., 1997 [72]	Prospective, observational	Inter-rater agreement on patients' HRQOL	n=215: 52 FCHD, 37 HHD, 30 CAPD, 96 TX	TTO	Significant differences in ratings among rater groups: nurses' ratings were lower than patients', physicians' ratings were higher than patients' ratings. Correlations among ratings ranged between 0.19 and 0.49.
Ozminkowski, 1997 [49]	Cross-sectional, observational	Testing validity and reliability of SF-36	N=515: 212 TX, 304 dialysis (n.s.)	SF-36	Evidence for discriminant and construct validity is presented. Internal consistency was good (Cronbach's α > 0.85 for all scales).
Wight et al., 1998 [47]	Cross-sectional, observational	Psychometric testing of SF-36	N=520: 100 FCHD, 42 HHD, 41 LCHD, 228 TX, 109 CAPD	SF-36	Self-administration is feasible. Internal consistency was satisfactory (Cronbach's α > 0.72 for all scales). Floor- and ceiling effects were found for the role functioning scales.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Research question 2: How does HRQOL of ESRD patients compare with that of a healthier population, such as a general population sample?					
Björvell et al., 1989 [59]	Cross-sectional, observational	Comparison dialysis and general population	n=53: 53 FCHD	SIP	Dialysis patients showed more dysfunction than did age-matched controls from the general population.
Benedetti et al., 1994 [61]	Cross-sectional, observational	Comparison dialysis and general population	n= not mentioned (all TX patients)	SF-36	Authors claim that differences between transplanted patients > 60 years and the general population were not significant. Because the number of patients is not given in the paper, this might be caused by insufficient power of the study.
Meyer et al., 1994 [46]	Cross-sectional, observational	Comparison dialysis and general population	n=112: 112 dialysis (n.s.)	SF-36	Dialysis patients' HRQOL was worse than HRQOL of the general population, in all eight sub-scales of the SF-36.
Beusterien et al., 1996 [11]	Prospective, intervention	Comparison dialysis and general population	n=484: 411 FCHD, 53 CAPD, 20 n.s.	SF-36 [b]	Dialysis patients' HRQOL was worse than HRQOL of the general population.
DeOreo, 1997 [62]	Cross-sectional, observational	Comparison dialysis and general population	n=1000: 1000 FCHD	SF-36	Patients' physical functioning worse than general population scores, except in the oldest age groups. In mental functioning, less difference was observed.
Merkus et al., 1997 [29]	Cross-sectional, observational	Comparison dialysis and general population	n=226: 120 FCHD, 106 CAPD	SF-36	Dialysis patients' HRQOL scores were lower than general population scores, with the exception of bodily pain in peritoneal dialysis patients.
Niechzial et al., 1997 [65]	Cross-sectional, observational	Comparing dialysis and general population	n=1027: 1027 FCHD + CAPD (n.s.)	NHP	Patients showed worse HRQOL than the general population in all NHP sub-scales, except pain.
Shield et al., 1997 [67]	Cross-sectional, observational	Comparing TX and general population	n=303: 303 TX	SF-36	At hospital discharge after transplantation, patients' scores were lower than general population norms. One year later, patients were similar to general population in three scales (bodily pain, vitality and mental health) and worse in the other five scales of SF-36.
Matas et al., 1998 [63]	Prospective, intervention	Comparison ESRD patients and general population	n=1138: 1138 TX	SF-36	Up to 65 % of transplanted patients showed HRQOL scores that were below the 95 % confidence interval of general population norms, especially in the physical HRQOL domains.
Mingardi et al., 1998 [60]	Cross-sectional, observational	Comparison dialysis and general population	n=240: 240 dialysis (n.s.)	SF-36	Dialysis patients showed worse HRQOL than the general population, except in the mental health field. Differences were less marked in older patients.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Rebollo et al., 1998 [64]	Cross-sectional, observational	Comparison ESRD patients > 65 years and general population	n=124: 100 FCHD, 24 TX	SIP, SF-36	HRQOL of transplanted patients was similar to HRQOL of the general population. Dialysis patients scored worse in the physical functioning and general health domains.
Wight et al., 1998 [47]	Cross-sectional, observational	Comparison ESRD patients and general population	N=520: 100 FCHD, 42 HHD, 41 LCHD, 228 TX, 109 CAPD	SF-36	HRQOL of all patients was worse than HRQOL of the general population.
Niechzial et al., 1999 [66]	Cross-sectional, observational	Comparing TX and general population	n=104: 104 TX	NHP	Three months after transplantation, transplanted patients were similar to general population in five out of six NHP scales and showed fewer problems than the general population in the sleep dimension.
Research question 3: Which medical, socio-demographic and disease-related factors determine HRQOL of ESRD patients?					
Hart et al., 1987 [35]	Cross-sectional, observational	Identify determinants of HRQOL	n=859: 347 FCHD, 287 HHD, 81 CAPD, 144 TX	SIP	Strongest independent associations with SIP scores had: diabetes mellitus, educational level, respiratory conditions, neurological problems, cardiovascular problems, transplantation, musculoskeletal disorders, gastrointestinal problems.
Julius et al., 1989 [36]	Cross-sectional, observational	Identify determinants of HRQOL	n=459: 171 FCHD, 125 CAPD, 163 TX	SIP	Strongest independent associations with SIP scores had: age, diabetes mellitus, number of co-morbidities, black race, CAPD (as opposed to transplantation).
Auer et al., 1990 [76]	Prospective, intervention	Comparing HRQOL pre-post start EPO use	n=24: 24 FCHD	NHP	HRQOL improvements after start of EPO use in energy, physical mobility and emotional wellbeing sub-scales of NHP.
Canadian EPO Study Group, 1990 [13]	Prospective, intervention (rct)	Study influence of EPO on HRQOL	n=118: 118 FCHD	TTO, SIP	Patients using EPO improved in the global and physical scales of SIP, but no changes in HRQOL as measured with TTO could be demonstrated.
Deniston et al., 1990 [77]	Cross-sectional, observational	Compare patients with and without EPO	n=187: 187 FCHD	SIP	Patients using EPO had better HRQOL as measured with global SIP and psychosocial SIP scales.
Evans et al., 1990 [78]	Prospective, intervention	Comparing HRQOL pre-post start EPO use	n=333: 333 FCHD	NHP	HRQOL improvements after start of EPO use in energy, emotional reactions and social functioning sub-scales of NHP.
Harris et al., 1991 [54]	Prospective, intervention	Comparing HRQOL pre-post start EPO use	n=28: 28 FCHD	TTO	TTO scores improved after the introduction of EPO.
Auer et al., 1992 [75]	Prospective, intervention	Comparing HRQOL pre-post start EPO use	n=22: 22 CAPD	NHP	HRQOL improvements after start of EPO use in energy and emotional reactions sub-scales of NHP.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Harris et al., 1993 [34]	Cross-sectional, observational	Identify determinants of HRQOL	n=360: 360 pre-dialysis	SIP	Strongest independent associations with SIP scores were found for stroke, coronary artery disease, serum albumin level, educational level, income.
Muirhead et al., 1994 [53]	Prospective, intervention	Comparing HRQOL pre-post start EPO use	n=40: 40 TX	TTO, SIP	HRQOL improvements after start of EPO use in global, physical and psychosocial domains of SIP, but no improvement of TTO score.
Hilbrands et al., 1995 [87]	Prospective, intervention (rct)	Compare two immunosuppressive therapies	n=120: 120 TX	SIP	Patients who were treated with cyclosporine showed better psychosocial functioning than patients treated with a combination of azathioprine and prednison.
Revicki et al., 1995 [74]	Prospective, intervention (rct)	Study influence of EPO on HRQOL	n=83: 83 pre-dialysis patients	SIP [b], SF-36 [b]	Patients using EPO improved in the physical function and vitality sub-scales of SF-36. No changes were shown in three SIP sub-scales that were used.
Beusterien et al., 1996 [11]	Prospective, intervention	- Identify determinants of HRQOL - Comparing HRQOL of new-to-EPO and old-to- EPO users	- n=484: 411 FCHD, 53 CAPD, 20 n.s. - n=1004: 884 FCHD, 89 CAPD, 31 n.s.	SF-36 [b]	- Positive changes in HRQOL were associated with erythropoietin use and changes in hematocrit level. - New EPO users reported improvements in physical functioning, vitality, social functioning, mental health and the Mental Component Summary Score. No improvements were shown in old-to-EPO group.
Moreno et al., 1996 [10]	Cross-sectional, observational	Identify determinants of HRQOL	n=1013: 891 FCHD, 7 HHD, 40 CAPD, 70 haemodiafiltration	SIP	Strongest independent associations with SIP scores were found for age, co-morbidity, diabetes mellitus, female sex, educational level, socio-economic level, hemoglobin and hematocrit.
Moreno et al, 1996 [79]	Prospective, intervention	Compare patients with and without EPO use	n=86: 86 FCHD	SIP	Patients using EPO improved in global, physical and psychosocial domains of SIP. Patients with lower HRQOL at baseline experienced a more substantial improvement than patients with higher baseline HRQOL scores.
Morton et al., 1996 [32]	Cross-sectional, observational	Is adequate dialysis associated with HRQOL?	n=115: 55 FCHD, 27 CAPD, 33 APD	SF-36	Adequate dialysis was not a predictor of any of the HRQOL outcomes.
Morton et al., 1996 [73]	Cross-sectional, observational	Identify determinants of HRQOL	n=60: 44 CAPD, 16 APD	SF-20	Strongest independent associations with HRQOL outcomes were found for time on dialysis, diabetes mellitus, peripheral vascular disease, heart disease, creatine-, protein-, calcium-, phosphate- and glucose levels.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Molzahn et al., 1997 [72]	Cross-sectional, observational	Identify determinants of HRQOL	n=215: 52 FCHD, 37 HHD, 30 CAPD, 96 TX	TTO	The TTO score was associated with transplantation, the number of hospitalizations, marital status and outlook (future expectations).
Merkus et al., 1997 [29]	Cross-sectional, observational	Identify determinants of HRQOL	n=226: 120 FCHD, 106 CAPD	SF-36	Strongest independent associations with SF-36 outcomes were found for number of co-morbid conditions, residual renal function, hemoglobin level, age, employment, protein intake, CAPD, renal vascular disease.
Mozes et al., 1997 [71]	Cross-sectional, observational	Identify determinants of HRQOL	n=680: 525 FCHD, 155 CAPD	QLI	The following attributes were found to be independently associated with HRQOL: age, education, employment, diabetes, stroke. Furthermore, differences in adjusted HRQOL scores between dialysis centres were found.
Niechzial et al., 1997 [65]	Cross-sectional, observational	Identify determinants of HRQOL	n=1027: 1027 all dialysis (n.s.)	NHP	Strongest independent associations with NHP outcomes were found for time on dialysis, age, educational level, primary renal disease, previous transplant.
Ozminkowski, 1997 [49]	Cross-sectional, observational	Identify determinants of HRQOL	N=515: 212 TX, 304 dialysis (n.s.)	SF-36	Strongest independent associations with SF-36 outcomes were found for age, risk group (type of co-morbid conditions), household income, race.
Shield et al., 1997 [67]	Cross-sectional, observational	Compare two immunosuppressive therapies	n=303: 303 TX	SF-36	Patients treated with tacrolimus had similar SF-36 outcomes as patients treated with cyclosporine.
Hathaway et al., 1998 [69]	Prospective, observational	Identify determinants of post-transplant HRQOL	n=91: 91 TX	SIP	Strongest predictors of post-transplant HRQOL were employment, the number of hospital admissions in first six months, age, social support and education.
Johnson et al., 1998 [88]	Prospective, observational	Are race and gender associated with post-transplant HRQOL?	n=90: 90 TX	SIP	Although baseline HRQOL was not different between Caucasian-Americans and African-Americans, African-Americans showed less positive changes in HRQOL after renal transplantation than Caucasian-Americans.
Sloan et al., 1998 [68]	Cross-sectional, observational	Identify determinants of HRQOL	n=95: 95 FCHD	SF-36	Strongest independent associations with SF-36 outcomes were found for serum albumin concentration, age and presence of diabetes mellitus.
Wight et al., 1998 [47]	Cross-sectional, observational	Identify determinants of HRQOL	N=520: 100 FCHD, 42 HHD, 41 LCHD, 228 TX, 109 CAPD	SF-36	Strongest independent associations with SF-36 outcomes were described for age, presence of comorbidity, presence of social and emotional support and female sex.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Merkus et al., 1999 [70]	Cross-sectional, observational	Identify determinants of HRQOL	n=226: 120 FCHD, 106 CAPD	SF-36	Strongest independent associations with SF-36 outcomes were found for physical symptom burden, medium and high comorbidity-age index, lower residual renal function, lower hemoglobin and lower protein intake.
Research question 4: Do HRQOL outcomes differ between patients treated with different therapeutic modalities?					
Churchill et al., 1987 [40]	Cross-sectional, observational	Comparing treatment modalities	N=194: 28 HHD, 42 FCHD, 79 TX, 31 CAPD, 14 LCHD	TTO	Transplantation patients showed better HRQOL than all dialysis patients. No differences in HRQOL between dialysis modalities.
Hart et al., 1987 [35]	Cross-sectional, observational	Comparing treatment modalities	n=859: 347 FCHD, 287 HHD, 81 CAPD, 144 TX	SIP	Transplantation patients showed better HRQOL than all dialysis patients. No differences in HRQOL between dialysis modalities.
Julius et al., 1989 [36]	Cross-sectional, observational	Comparing treatment modalities	n=459: 171 FCHD, 125 CAPD, TX 163	SIP	CAPD patients showed worse physical functioning than transplanted patients.
Churchill et al., 1992 [80]	Prospective, intervention (rct)	Comparing high-flux and conventional FCHD	n=22: 22 FCHD	TTO, SIP	HRQOL of patients on both treatments was similar.
Russell et al., 1992 [57]	Prospective, intervention	Comparing HRQOL pre- and post TX	n=27: 9 HHD, 10 FCHD, 8 CAPD	TTO	HRQOL improved after transplantation.
Laupacis et al., 1993 [55]	Prospective, intervention	Comparing HRQOL pre- and post TX	n=73: 73 FCHD	TTO, SIP [b]	HRQOL improved after transplantation, as measured with TTO and SIP.
Khan et al., 1995 [43]	Cross-sectional, observational	Comparing treatment modalities	n=172: 102 TX, 43 FCHD, 27 CAPD	SF-36	Transplanted patients showed better HRQOL than all dialysis patients.
Laupacis et al., 1996 [56]	Prospective, intervention	Comparing HRQOL pre- and post TX	n=167: 167 FCHD	TTO, SIP	HRQOL improved after transplantation, as measured with TTO and SIP.
Meers et al., 1996 [31]	Prospective, observational	Comparing treatment modalities	n=34: 17 FCHD, 17 LCHD	SF-36	Self-care haemodialysis patients showed better HRQOL in SF- 36 domains of social functioning, mental health, role functioning emotional and vitality.
Moreno et al., 1996 [10]	Cross-sectional, observational	Comparing treatment modalities	n=1013: 891 FCHD, 10 HHD, 41 CAPD, 71 haemodiafiltration	SIP	No differences were found in HRQOL between dialysis modalities.

(Appendix II continued)

Study, year	Design	Aim [a]	N patients / Treatment [a]	HRQOL instrument	Main Outcomes
Morton et al., 1996 [73]	Cross-sectional, observational	Comparing treatment modalities	n=60: 44 CAPD, 16 APD	SF-20	HRQOL of patients treated with APD and CAPD was found to be similar.
Klang et al., 1997 [30]	Prospective, intervention	Comparing HRQOL pre-post start dialysis	n=28: 28 pre-dialysis patients	SIP	After start with dialysis, overall SIP scores and scores in the physical and psychosocial domains did not change.
Merkus et al., 1997 [29]	Cross-sectional, observational	Comparing treatment modalities	n=226: 120 FCHD, 106 CAPD	SF-36	FCHD patients showed lower levels of mental health, in comparison with CAPD patients.
Molzahn et al., 1997 [72]	Cross-sectional, observational	Comparing treatment modalities	n=215: 52 FCHD, 37 HHD, 30 CAPD, 96 TX	TTO	HRQOL of transplanted patients was better than HRQOL of all dialysis patients.
Niechzial et al., 1997 [65]	Cross-sectional, observational	Comparing treatment modalities	n=1027: 1027 FCHD + CAPD (n.s.)	NHP	HRQOL of patients treated with FCHD and CAPD was found to be similar.
Jofré et al., 1998 [81]	Prospective, intervention	Comparing HRQOL pre- and post TX	n=93: 93 dialysis (n.s.)	SIP	HRQOL improved after transplantation.
Wight et al., 1998 [47]	Cross-sectional, observational	Comparison treatment modalities	N=520: 100 FCHD, 42 HHD, 41 LCHD, 228 TX, 109 CAPD	SF-36	HRQOL of transplanted patients was better than HRQOL of all dialysis patients. No HRQOL differences were described within the dialysis modalities, except a mental health disadvantage for FCHD patients.
Merkus et al., 1999 [82]	Prospective, observational	Comparing HRQOL over time in dialysis patients	N=139: 84 FCHD, 55 CAPD	SF-36	After adjustment for initial HRQOL and comorbidity, a consistently favorable effect of haemodialysis on physical HRQOL over time was found compared with peritoneal dialysis, whereas mental HRQOL values remained similar.
Niechzial et al., 1999 [66]	Prospective, intervention	Comparing HRQOL pre- and post TX	n=138: 138 FCHD + CAPD (n.s.)	NHP	HRQOL improved in the energy, emotional reactions and sleep domains.

a abbreviations: EPO = erythropoietin, FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, HHD = home haemodialysis, CAPD = continuous ambulatory peritoneal dialysis, APD = automated peritoneal dialysis, TX = renal transplantation, n.s. = non-specified

b only selected sub-scales of the instruments were used

Appendix 3: Reference tables with reported values of six selected HRQOL instruments

Table 3A: Reported values of Time Trade Off (TTO) instrument [a], by treatment modality

First author/year	FCHD [b]	HHD [b]	LCHD [b]	CAPD [b]	TX b	Non-specified dialysis
Churchill, 1984 [39]	0.57			0.57	0.80	
Churchill, 1987 [40]	0.43	0.49	0.49	0.56	0.84	
Canadian EPO Study, 1990 [13] & Laupacis, 1991 [51]	0.42 - 0.58					
Churchill, 1991 [52]	0.44 - 0.50		0.44 - 0.50			
Harris, 1991 [54]	0.49 - 0.72					
Russell, 1992 [57]					0.74	0.41
Hornberger, 1992 [42]	0.72 - 0.81					
Churchill, 1992 [80]	0.58 - 0.64					
Laupacis, 1993 [55]					0.79	0.58
Muirhead, 1994 [53]					0.60 - 0.61	
Laupacis, 1996 [56]	0.57				0.68 - 0.75	
Lenert, 1996 [41]	0.71 – 0.84					
Molzahn, 1996 [48] & Molzahn, 1997 [72]	0.39	0.61		0.53	0.76	

a values relative to 0 (death) and 1 (full health)
b abbreviations of treatment modalities: FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, HHD = home haemodialysis, CAPD = continuous ambulatory peritoneal dialysis, APD = automated peritoneal dialysis, TX = renal transplantation, n.s. = non-specified

Table 3B: Reported values of Standard Gamble (SG) instrument [a], by treatment modality

First author/year	FCHD [b]	HHD [b]	LCHD [b]	CAPD [b]	TX [b]	Pre-dialysis patients
Hornberger, 1992 [42]	0.62 - 0.72					
Revicki, 1992 [38]						0.63
Lenert, 1996 [41]	0.66 – 0.72					

a values relative to 0 (death) and 1 (full health)
b abbreviations of treatment modalities: see table 3A

Table 3C: Reported scores on Sickness Impact Profile (SIP), by treatment modality

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Global SIP score [b]							
Hart, 1987 [35]	13.9	9.5		13.7		5.5	
Björvell, 1989 [59]	13.0						
Canadian EPO Study, 1990 [13] & Laupacis, 1991 [51]	4.4 – 12.2						
Deniston, 1990 [77]	13.0 – 18.0						
Churchill, 1992 [80]	18.3 – 20.3						
Harris, 1993 [34]							24.5
Muirhead, 1994 [53]						8.8 – 12.9	
Hilbrands, 1995 [87]						3.5 – 9.1	
Moreno, 1996 [10]					15.0		
Moreno, 1996 [79]	13.5 – 19.8						
Essink, 1996 [44]	12.2						
Laupacis, 1996 [56]	13.1					5.3	
Klang, 1997 [30]	6.0						4.0
Rebollo, 1998 [64]	20.0					9.3	
Hathaway, 1998 [69]					17.4	5.4 – 6.3	
Jofré, 1998 [81]	9.7					5.9	
Johnson, 1998 [88]					16.4 – 19.1	3.6 – 9.0	
Physical SIP score [b]							
Hart, 1987 [35]	10.3	6.1		11.7		3.3	
Björvell, 1989 [59]	12.0						
Canadian EPO Study, 1990 [13] & Laupacis, 1991 [51]	2.4 – 6.4						
Deniston, 1990 [77]	11.0 – 13.0						
Churchill, 1992 [80]	11.9 – 10.4						
Harris, 1993 [34]							21.3
Laupacis, 1993 [55]					6.4	2.6	
Muirhead, 1994 [53]						6.4 – 8.4	
Hilbrands, 1995 [87]						0.8 – 5.7	
Moreno, 1996 [10]					12.0		
Moreno, 1996 [79]	15.4 – 19.6						
Essink, 1996 [44]	9.8						
Laupacis, 1996 [56]	6.4					3.3	
Klang, 1997 [30]	3.6						3.1
Rebollo, 1998 [64]	15.5					4.6	
Hathaway, 1998 [69]					11.0	2.5 – 3.2	
Jofré, 1998 [81]	5.5					3.6	
Johnson, 1998 [88]					10.4 – 12.0	1.7 – 6.3	
Psychosocial SIP score [b]							
Hart, 1987 [35]	9.7	6.4		8.2		4.1	
Björvell, 1989 [59]	9.5						
Canadian EPO Study, 1990 [13] & Laupacis, 1991 [51]	3.0 – 11.8						
Deniston, 1990 [77]	10.0 – 16.0						

(Table 3C continued)

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Psychosocial SIP score [b]							
Churchill, 1992 [80]	15.8 – 18.8						
Harris, 1993 [34]							21.4
Laupacis, 1993 [55]					12.0	4.3	
Muirhead, 1994 [53]						6.7 – 11.0	
Hilbrands, 1995 [87]						1.3 – 4.5	
Moreno, 1996 [10]					14.0		
Moreno, 1996 [79]	10.8 – 19.0						
Essink, 1996 [44]	8.6						
Laupacis, 1996 [56]	12.4					4.7	
Klang, 1997 [30]	4.3						2.3
Rebollo, 1998 [64]	20.1					7.6	
Hathaway, 1998 [69]					17.2	5.4 – 6.3	
Jofré, 1998 [81]	10.1					5.6	
Johnson, 1998 [88]					16.1 – 18.8	3.8 – 10.2	

a abbreviations of treatment modalities: see table 3A
b lower scores indicate a better quality of life

Table 3D: Reported scores on Short-Form 36 (SF-36), by treatment modality

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Physical Component Summary score (PCS) [b]							
Beusterien, 1996 [11]	35-37						
De Oreo, 1997 [62]	35						
Merkus, 1999 [82]	41-43			38-41			
Mental Component Summary score (MCS) [b]							
Beusterien, 1996 [11]	43-47						
De Oreo, 1997 [62]	48						
Merkus, 1999 [82]	44-45			43-46			
Physical functioning sub-scale (PF) [b]							
Kurtin, 1992 [45]	48 – 60						
Revicki, 1992 [38]							45 – 54
Benedetti, 1994 [61]						61	
Meyer, 1994 [46]					49		
Khan, 1995 [43]	46			39		68	
Meers, 1995 [33]	49						
Revicki, 1995 [37]							44 – 52
Beusterien, 1996 [11]	44 – 48						
Meers, 1996 [31]	37		61				
Morton, 1996 [32]	43			46 c			
De Oreo, 1997 [62]	44						
Merkus, 1997 [29]	51			61			
Shield, 1997 [67]						57 – 69	

(Table 3D continued)

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Physical functioning sub-scale (PF) [b]							
Mingardi, 1998 [60]					52		
Matas, 1998 [63]						55 – 79	
Ozminkowski, 1998 [49]					53	70	
Rebollo, 1998 [64]	48					75	
Sloan, 1998 [68]	43						
Wight, 1998 [47]	34	47	28	41		62	
Merkus, 1999 [70 82]	53 - 59			49-56			
Role limitations due to physical problems - sub-scale [b]							
Kurtin, 1992 [45]	28-35						
Benedetti, 1994 [61]						58	
Meyer, 1994 [46]					33		
Khan, 1995 [43]	51			30		63	
Meers, 1995 [33]	41						
Meers, 1996 [31]	37		63				
Morton, 1996 [32]	34			20 c			
De Oreo, 1997 [62]	40						
Merkus, 1997 [29]	29			32			
Shield, 1997 [67]						29-38	
Mingardi, 1998 [60]					38		
Matas, 1998 [63]						46-78	
Ozminkowski, 1998 [49]					39	60	
Rebollo, 1998 [64]	64					81	
Sloan, 1998 [68]	62						
Wight, 1998 [47]	24	41	17	20		54	
Merkus, 1999 [70 82]	38-39			28-34			
Bodily pain sub-scale [b]							
Kurtin, 1992 [45]	50-63						
Benedetti, 1994 [61]						68	
Meyer, 1994 [46]					60		
Khan, 1995 [43]	71			59		78	
Meers, 1995 [33]	70						
Beusterien, 1996 [11]	62-64						
Meers, 1996 [31]	66		68				
Morton, 1996 [32]	67			61 c			
De Oreo, 1997 [62]	60						
Merkus, 1997 [29]	64			74			
Shield, 1997 [67]						60-75	
Mingardi, 1998 [60]					60		
Matas, 1998 [63]						64 – 79	
Ozminkowski, 1998 [49]					59	76	
Rebollo, 1998 [64]	67					79	
Sloan, 1998 [68]	55						
Wight, 1998 [47]	49	55	55	59		70	
Merkus, 1999 [70 82]	70-72			59-66			

(Table 3D continued)

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
General health sub-scale [b]							
Kurtin, 1992 [45]	38-41						
Benedetti, 1994 [61]						64	
Meyer, 1994 [46]					44		
Khan, 1995 [43]	42			40		64	
Meers, 1995 [33]	49						
Beusterien, 1996 [11]	43-45						
Meers, 1996 [31]	45		55				
Morton, 1996 [32]	37			43 c			
De Oreo, 1997 [62]	50						
Merkus, 1997 [29]	43			46			
Shield, 1997 [67]						37-65	
Mingardi, 1998 [60]					36		
Matas, 1998 [63]						45-69	
Ozminkowski, 1998 [49]					44	58	
Rebollo, 1998 [64]	36					69	
Sloan, 1998 [68]	39						
Wight, 1998 [47]	32	38	32	35		54	
Merkus, 1999 [70 82]	44-46			39-48			
Vitality sub-scale [b]							
Kurtin, 1992 [45]	35-43						
Revicki, 1992 [38]							38
Benedetti, 1994 [61]						58	
Meyer, 1994 [46]					45		
Khan, 1995 [43]	41			38		63	
Meers, 1995 [33]	48						
Revicki, 1995 [37]							37-43
Beusterien, 1996 [11]	39-49						
Meers, 1996 [31]	39		64				
Morton, 1996 [32]	39			39 c			
De Oreo, 1997 [62]	47						
Merkus, 1997 [29]	49			52			
Shield, 1997 [67]						38-62	
Mingardi, 1998 [60]					44		
Matas, 1998 [63]						49-62	
Ozminkowski, 1998 [49]					42	58	
Rebollo, 1998 [64]	50					67	
Sloan, 1998 [68]	41						
Wight, 1998 [47]	35	42	32	36		53	
Merkus, 1999 [70 82]	49-52			45-50			
Social functioning sub-scale [b]							
Kurtin, 1992 [45]	55-56						
Benedetti, 1994 [61]						80	
Meyer, 1994 [46]					65		
Khan, 1995 [43]	54			50		80	

(Table 3D continued)

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Social functioning sub-scale [b]							
Meers, 1995 [33]	74						
Beusterien, 1996 [11]	53-61						
Meers, 1996 [31]	63		81				
Morton, 1996 [32]	60			61 c			
De Oreo, 1997 [62]	66						
Merkus, 1997 [29]	63			69			
Shield, 1997 [67]						53-79	
Mingardi, 1998 [60]					63		
Matas, 1998 [63]						73-87	
Ozminkowski, 1998 [49]					66	82	
Rebollo, 1998 [64]	80					93	
Sloan, 1998 [68]	63						
Wight, 1998 [47]	42	63	49	50		75	
Merkus, 1999 [70 82]	68-72			61-69			
Role limitations caused by emotional problems – sub-scale [b]							
Kurtin, 1992 [45]	35-54						
Benedetti, 1994 [61]						73	
Meyer, 1994 [46]					55		
Khan, 1995 [43]	75			67		80	
Meers, 1995 [33]	69						
Meers, 1996 [31]	47		90				
Morton, 1996 [32]	61			45 c			
De Oreo, 1997 [62]	58						
Merkus, 1997 [29]	53			64			
Shield, 1997 [67]						48-79	
Mingardi, 1998 [60]					56		
Matas, 1998 [63]						74-90	
Ozminkowski, 1998 [49]					72	79	
Rebollo, 1998 [64]	74					93	
Sloan, 1998 [68]	47						
Wight, 1998 [47]	31	65	30	56		69	
Merkus, 1999 [70 82]	57-57			57-62			
Mental health sub-scale [b]							
Kurtin, 1992 [45]	62-70						
Benedetti, 1994 [61]						78	
Meyer, 1994 [46]					70		
Khan, 1995 [43]	66			73		79	
Meers, 1995 [33]	80						
Beusterien, 1996 [11]	66-70						
Meers, 1996 [31]	71		84				
Morton, 1996 [32]	70			70 c			
De Oreo, 1997 [62]	70						
Merkus, 1997 [29]	63			72			
Shield, 1997 [67]						63-75	

(Table 3D continued)

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Mental health sub-scale [b]							
Mingardi, 1998 [60]					69		
Matas, 1998 [63]						74-79	
Ozminkowski, 1998 [49]					72	77	
Rebollo, 1998 [64]	76					84	
Sloan, 1998 [68]	65						
Wight, 1998 [47]	60	69	67	66		73	
Merkus, 1999 [70 82]	68-70			66-70			

a abbreviations of treatment modalities: see Table 3A
b lower scores indicate a worse quality of life
c includes APD patients' scores

Table 3E: Reported scores on Nothingham Health Profile (NHP), by treatment modality

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Energy dimension [b]							
Auer, 1990 [76]	62-11						
Evans, 1990 [78]	50-23						
Schrama, 1991 [58]			24 [c]				
Auer, 1992 [75]				76-24			
Badia, 1994 [50]	31-36						
Essink, 1996 [44]	33						
Niechzial, 1997 [65]	39						
Niechzial, 1999 [66]						12-18	
Pain dimension [b]							
Auer, 1990 [76]	12-7						
Evans, 1990 [78]	15-16						
Schrama, 1991 [58]			0 [c]				
Auer, 1992 [75]				15-11			
Badia, 1994 [50]	20-21						
Essink, 1996 [44]	13						
Niechzial, 1997 [65]	39						
Niechzial, 1999 [66]						8-13	
Emotional Reactions dimension [b]							
Auer, 1990 [76]	22-9						
Evans, 1990 [78]	20-13						
Schrama, 1991 [58]			9 [c]				
Auer, 1992 [75]				30-14			
Badia, 1994 [50]	27						
Essink, 1996 [44]	18						
Niechzial, 1997 [65]	18						
Niechzial, 1999 [66]						5-9	

(Table 3E continued)

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Sleep dimension [b]							
Auer, 1990 [76]	32-24						
Evans, 1990 [78]	34-28						
Schrama, 1991 [58]			23 [c]				
Auer, 1992 [75]				42-29			
Badia, 1994 [50]	35-37						
Essink, 1996 [44]	39						
Niechzial, 1997 [65]	32						
Niechzial, 1999 [66]						9-12	
Social isolation dimension [b]							
Auer, 1990 [76]	19-10						
Evans, 1990 [78]	19-14						
Schrama, 1991 [58]			0 [c]				
Auer, 1992 [75]				24-12			
Badia, 1994 [50]	14-15						
Essink, 1996 [44]	13						
Niechzial, 1997 [65]	10						
Niechzial, 1999 [66]						2-4	
Mobility dimension [b]							
Auer, 1990 [76]	32-10						
Evans, 1990 [78]	21-19						
Schrama, 1991 [58]			11 [c]				
Auer, 1992 [75]				33-22			
Badia, 1994 [50]	26-27						
Essink, 1996 [44]	26						
Niechzial, 1997 [65]	18						
Niechzial, 1999 [66]						11-17	

a abbreviations of treatment modalities: see Table 3A
b lower scores indicate a better quality of life
c reported scores are median scores

Table 3F: Reported scores on (Spitzer's) Quality of Life Index (QLI), by treatment modality

First author/year	FCHD [a]	HHD [a]	LCHD [a]	CAPD [a]	Non-specified dialysis	TX [a]	Pre-dialysis
Churchill, 1987 40	77	75	75	79		86	
Mozes, 1997 71	58-67			57-78			

a abbreviations of treatment modalities: see Table 3A
b lower scores indicate a worse quality of life

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Chapter 3

Health profiles and health preferences of dialysis patients

De Wit GA, Merkus MP, Krediet RT, de Charro FTh. Health profiles and health preferences of dialysis patients. Nephrol Dial Transplant 2002; 17: 86-92.

Abstract

Background. Health-related quality of life (HRQOL) of haemodialysis (HD) and peritoneal dialysis (PD) patients has been assessed with health profiles and health preferences methods. Few studies have used both types of HRQOL instruments. The main objective of this study was to assess the relationship between information from the two types of HRQOL instruments in dialysis patients.

Methods. We interviewed 135 patients, using two health profiles (Short Form 36 and EuroQol/EQ-5D) and two health preferences methods (Standard Gamble and Time Trade Off). Socio-demographic, clinical and treatment related background data were collected from patient charts and during the interview. Relationships between the outcome measures were assessed with Pearson correlation coefficients. Multiple regression models were used to study the relationship of HRQOL outcomes to background variables.

Results. HRQOL of dialysis patients as measured with health profiles was severely impaired. The health preferences scores were higher (0.82 to 0.88) than scores previously reported in the literature. Correlations between health profiles and health preferences were poor to modest. HRQOL outcomes were poorly explained by background characteristics. Differences between HD and PD groups could not be demonstrated.

Conclusions. Health profiles and health preferences represent different aspects of HRQOL. An impaired health status may not be reflected in the preference scores. Coping strategies and other attitudes towards health may affect the preference scores more than they do influence health profile outcomes. The added value of health preferences methods in clinical research is limited.

Introduction

Many different questionnaires and interview techniques, either generic or disease-specific, have been used for the assessment of health-related quality of life (HRQOL) in end-stage renal disease (ESRD) patients.[1-2] Generic HRQOL measures cover all important aspects of health and are intended to be applicable in a wide variety of conditions, patients and demographic groups. Therefore, they can be used to compare a patient group suffering from a certain disease with other patient groups and with general population samples. Within the group of generic measures, a distinction can be made between health profiles and preference or utility based measures.[3] Health profiles describe the health status of a person on a number of domains, such as physical, psychological and social function. Preference based measures aim to express HRQOL in a single indicator, often a number between 0 and 1, where 0 represents death and 1 represents full health.

The experience with preference measurements in dialysis patients is relatively limited. A MedLine literature search identified 16 studies using preference measurements in dialysis and renal transplant patients.[4-19] Most studies that applied preference measurements have assessed small patient groups and focused on renal transplantation and haemodialysis (HD). Peritoneal dialysis (PD) was only covered in two Canadian studies from the 1980s,[4 7] and in one more recent publication that included 30 PD patients.[14] Only two studies reported on the relationship between health profiles and health preferences in ESRD patients.[10 18] Both studies found low to moderate correlations between the two types of instruments (correlation coefficients between 0.15 and 0.31). The purpose of the present cross-sectional study was to compare health preference methods with health profiles in HD and PD patients. Two health preferences methods (Standard Gamble and Time Trade Off) and two health profiles (Short-Form 36 and EuroQol/EQ-5D) were used to study HRQOL.

Subjects and methods

Study design and patients

A total number of 135 dialysis patients participated in this study. These patients participated in a prospective cohort study on the adequacy of dialysis, the NECOSAD-1 study.[20] The 135 patients interviewed were treated in 13 of the 49 dialysis centres in the Netherlands. The study was approved by the ethical committees of all participating centres. In the period October 1993 - March 1995, all new patients in these 13 centres were asked to participate in NECOSAD. All patients who had not been withdrawn from NECOSAD by the time we started the present HRQOL study and who had received the same dialysis treatment for at least three months were considered for inclusion. Further inclusion criteria were written informed consent, age above 18 years, adequate eyesight to enable the administration of questionnaires and an adequate understanding of the Dutch language. Interviews were conducted at patients' homes by one of three trial nurses, who received a training to administer the HRQOL questionnaires. For HD patients, interviews were carried out on non-dialysis days.

Background variables

At the interview, data were collected on sex, age, marital and employment status and educational level. Data on primary diagnosis, dialysis adequacy, current treatment, treatment history, length of time on dialysis and presence of comorbid diseases at the start of dialysis were obtained from the NECOSAD study and the patient's nephrologist. Primary diagnosis of renal failure was classified according to the EDTA-ERA classification. Adequacy of dialysis was expressed as weekly total Kt/V_{urea} in HD and PD patients. Hemodialysis Kt/V_{urea} was estimated using a second generation Daugirdas formula.[21] The weekly Kt/V_{urea} in PD patients was calculated as the peritoneal Kt/V_{urea} per 24 hours multiplied by 7.

Questionnaires used to assess health-related quality of life

HRQOL was assessed with the Short Form 36 Health Survey, EuroQol/EQ-5D, Standard Gamble and Time Trade Off. The four questionnaires were always administered in this sequence. The first two questionnaires were self-completed. The interviewer then continued with the administration of the Standard Gamble and Time Trade Off.

The *Short-Form 36 Health Survey* (SF-36) generates a profile of scores on 8 dimensions of quality of life.[22] These dimensions are (1) Physical Functioning, (2) Role Functioning - Physical, (3) Bodily Pain, (4) General Health perception, (5) Vitality, (6) Social Functioning, (7) Role Functioning - Emotional, (8) Mental Health. Raw scores on the eight scales are transformed to calculate a score between zero and hundred, where a higher score indicates better health. The physical and mental components of the eight scales are combined into a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The two summary measures are standardized to have a mean of 50 and a standard deviation of 10 in the general population and therefore allow for easy comparison of patient scores with general population scores. SF-36 scores of persons of similar age (55-64 years) were derived from a validation study in the Dutch population.[23]

The *EQ-5D* or *EuroQol* (EQ-5D) is a generic questionnaire, consisting of a classification system ($EQ\text{-}5D_{profile}$) and a visual analog scale (EQ_{VAS}).[24] The $EQ\text{-}5D_{profile}$ covers 5 domains of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with three levels of functioning: (level 1: no problems; level 2: some problems; level 3: severe problems). The EQ_{VAS} is a graduated, vertical line, anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). The patient is asked to mark a point on the EQ_{VAS} that best reflects his/her actual health state.

The *Standard Gamble* (SG) is a method to measure preferences for health states.[25] The respondent is presented with two alternatives and asked to choose the one most preferred. The first alternative offers the certainty of staying in the current health state for the remainder of the respondent's life. The second alternative is a gamble with specified probabilities for both the positive outcome of the gamble (a normal health state for the remainder of time) and the negative outcome (immediate death). These probabilities are varied until the respondent is indifferent between the gamble and living in his/her current health state. The SG score, a score between zero and one, is calculated as one minus the risk percentage at the point of indifference, divided by hundred. An SG-score of 0.80 implies that a person

is prepared to take a gamble with 20 percent risk of dying immediately and 80 percent chance to improve his current health to normal health. The SG score reflects the value a person assigns to his own health state. In our study, the concept of the SG was practiced with a visual aid, using imaginary health states. Afterwards, the patient was asked to value his own current health state.

The *Time Trade Off method* (TTO) is also a preference-based method.[4,7] Patients are asked whether they are prepared to give up some remaining time of their lives, in order to improve their current health state to normal health. The time perspective that is presented to the patient corresponds with statistical life expectancy of people of the same age and sex. The quotient of the chosen number of years in a normal health state over statistical life expectancy yields the TTO score. A TTO score of 0.80 implies that a person is indifferent between living 8 years in excellent health versus 10 years in his current health state. We practiced the TTO concept with imaginary health states, before the patient was asked to value his/her own current health state.

Statistical analysis

Differences between HD and PD treatment groups were tested by means of Student's t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using the Pearson Chi-square test. Mann-Whitney U test was used for non-response analysis. In order to be able to control for case-mix differences, the association between background variables (see above) and main quality of life outcomes was studied with multiple regression models. A forward stepwise selection strategy was chosen, using the F-statistic with P=0.05 as the criterion level for selection. To search for violations of necessary assumptions in multiple regression, normal plots of the residuals of the regression models were produced. The relationship between health profiles and health preference measures was assessed with Pearson correlation coefficients. Analyses reported here are based on treatment at the time of the interview. A two-sided P-value of 0.05 was chosen as cut off for statistical significance.

Results

Patient characteristics

In April 1995, 193 patients still participated in the NECOSAD study. Eight patients (4 %) could not be interviewed because they were medically unstable or had language problems. A group of 24 patients (13 %) was withdrawn from follow-up in the NECOSAD study before an interview could be scheduled, either because of transplantation, death or transfer to a non-participating dialysis centre. Finally, 26 patients (14 %) refused to participate in the present study. This resulted in 135 patients (70 %) who were interviewed. Table 1 lists the main demographic, clinical and treatment characteristics of the 135 patients interviewed, according to treatment modality. Sixty-nine patients were treated with HD and 66 with PD (59 CAPD and 7 APD). The HD and PD groups differed significantly with respect to age and educational level. On average, PD patients were 5 years younger and better educated than HD patients. No other demographic and clinical differences were found between the groups.

Table 1: Patient characteristics according to treatment modality (mean, SD, range or %)

	HD (n=69)	PD (n=66)
Age [a]	60 (15) 21-87	55 (13) 25-79
Male	52 %	66 %
Married/living together	75 %	86 %
Employed	19 %	30 %
Educational level [a]		
- low	32 %	20 %
- intermediate	64 %	73 %
- high	4 %	12 %
Primary kidney disease:		
- glomerulonephritis	10 %	13 %
- renal vascular disease [b]	25 %	23 %
- nephritis	16 %	11 %
- cystic kidney disease	10 %	11 %
- diabetes mellitus	7 %	15 %
- others and unknown	32 %	27 %
Number of comorbid conditions	1.75 (1.40) 0-6	1.80 (1.29) 0-7
Type of comorbid condition:		
- cardio-vascular	62 %	77 %
- diabetes mellitus	12 %	18 %
- malignancy	9 %	3 %
Weekly Kt/V_{urea} (total)	3.7 (0.89) 2.0-5.8	2.0 (0.43) 1.3-2.9
Therapy change in past 6 months	12 %	8 %
Months on dialysis	15 (3) 7-23	15 (4) 7-22
Months on this modality	12 (5) 3-23	13 (5) 3-21

a $P<0.05$, HD versus PD

b including hypertensive nephrosclerosis

Table 2: Mean (SD and range) scores on health-status and health-preference questionnaires

Outcome parameter	HD (n=69)	PD (n=66)
Health profiles		
SF-36 PCS [a b]	37.6 (10.6) 15-58	38.3 (10.7) 16-56
SF-36 MCS [a]	47.9 (12.3) 14-66	48.4 (11.0) 23-65
Visual Analog Scale		
EQ_{VAS} (scale 0-100)	60.3 (17.7) 5-100	62.4 (20.3) 10-95
Health preferences		
SG (scale 0-1)	0.86 (0.19) 0.2-1.0	0.82 (0.23) 0.0-1.0
TTO (scale 0-1)	0.89 (0.17) 0.15-1.0	0.87 (0.21) 0.0-1.0

a standardised to general population mean (mean 50, SD 10)

b $P<0.001$, compared to a similar age-group from the general population [23]

Results of SF-36

The upper part of Table 2 contains the two SF-36 summary scores for physical (PCS) and mental (MCS) HRQOL. HD and PD patient groups did not differ with regard to PCS and MCS scores. The mean PCS score of this sample of dialysis patients was 1.2 standard deviations ($P<0.001$) below the mean score for a general population sample of the same age. The mean MCS score of both groups of dialysis patients was not different from the reference group.

Results of EQ-5D

As shown in Table 2, self-rated health status on the EQ_{VAS} was similar for both patient groups, with scores of 60 and 62 on a scale from 0 to 100. Table 3 shows the proportion of HD and PD patients that indicated to have some or severe problems on the 5 dimensions of the $EQ\text{-}5D_{profile}$. None of the differences between HD and PD patients were significant. Patients turned-out to have problems on all 5 dimensions. Most problems were present with 'daily activities': 61 percent of the patients could not perform their daily activities normally. Approximately half of the patients reported some or severe difficulties with 'mobility' and 'pain'. Fourteen percent of the patients had difficulties with self-care, such as bathing and dressing independently. In this patient sample, 24 percent of responders felt anxious and/or depressed.

Table 3: Proportion of HD and PD patients showing none (level 1), some (level 2) or severe (level 3) problems on $EQ\text{-}5D_{profile}$

EQ-5D dimension a	HD			PD		
	level 1	level 2	level 3	level 1	level 2	level 3
mobility	46.4	53.6	0.0	57.6	39.4	3.0
self-care	82.6	14.5	2.9	89.4	9.1	1.5
daily activities	40.6	39.1	20.3	37.9	50.0	12.1
anxiety/depression	78.3	20.3	1.4	74.2	22.7	3.0
pain	59.4	36.2	4.3	53.0	42.4	4.5

a differences between modalities not significant ($P>0.05$)

Results of Standard Gamble and Time Trade Off

Answers to SG could not be obtained in 5 patients (3.7 %) and answers to TTO could not be obtained in 14 (10.4 %) patients. This non-response was caused by patient refusal to answer and/or cognitive problems in understanding the SG and TTO concepts. The reasons for refusal were diffuse and included religious reasons, familial circumstances and patient fatigue. Responders and non-responders to SG and/or TTO were compared with respect to age, number of comorbid conditions, time on dialysis and HRQOL as measured with health profiles. Results of the non-response analysis are shown in Table 4. Compared to responders, non-responders were older and had a worse self-rated health as assessed with the EQ_{VAS}. The lower part of Table 2 shows the mean SG and TTO scores of both patient groups. HD and PD patients groups valued their health status equally high ($P>0.05$), with scores between 0.82 and 0.89.

Table 4: Analysis of non-response to Standard Gamble (n=5) and/or Time Trade Off (n=14)

Feature	Non-responders mean (SD)	Responders mean (SD)
Age [a]	67 (11)	56 (14)
No. of comorbid conditions	1.9 (1.6)	1.8 (1.3)
Time on dialysis (months)	14 (2.4)	15 (3.9)
SF-36 PCS score [b]	34 (12)	38 (10)
SF-36 MCS score [b]	44 (16)	49 (11)
EQ_{VAS} score [a]	48 (16)	63 (19)

a $P<0.01$, responders versus non-responders
b standardised to the general population mean (mean 50, SD 10)

Association between background variables and health-related quality of life outcomes

The results of the multiple regression analyses to explain the independent associations between demographic, clinical and treatment variables on the one hand and outcome variables on the other hand are shown in Table 5. The number of comorbid conditions was negatively associated with all HRQOL outcomes, except MCS. Age was negatively associated with PCS and with the EQ_{VAS} score. Employed patients had better PCS and EQ_{VAS} scores. The number of months on dialysis was negatively associated with MCS and EQ_{VAS} scores. Treatment modality was not associated with any of the HRQOL outcomes. The models constructed showed that HRQOL was poorly explained by the background variables under study (total Adjusted R^2 from 1.9 % to 18.2 %).

Table 5: Multiple regression analysis to study the association between demographic, clinical and treatment related variables and outcome variables, expressed as standardised regression coefficient β, partial R^2 and total R^2 [b]

	SF-36 PCS	SF-36 MCS	EQ_{VAS}	SG	TTO
Age	-0.14 (2.0 %)		-0.19 (2.6 %)		
Employment status	0.18 (3.3 %)		0.16 (7.0 %)		
No. of comorbid conditions	-0.28 (8.9 %)		-0.20 (3.7 %)	-0.19 (3.0 %)	-0.14 (1.9 %)
No. of months on dialysis		-0.17 (3.3 %)	-0.24 (4.9 %)		
Total R^2	15.1 %	3.3 %	18.2 %	3.0 %	1.9 %

a No violations of necessary assumptions in multiple regression analyses were detected.
b Associations shown in the table were the only significant associations found. The number in each cell refers to the standardised regression coefficient β, indicating the relative importance of the independent variable: the higher the β coefficient the higher the contribution of the independent variable in the regression equation. The bracketed number in each cell symbolises R^2, the explained variance of the dependent variable accounted for by the single independent variable. Total R^2 is the percentage of variation of the dependent variable score that is accounted for by the independent variables together.

Relationships between health profiles and health preferences

The correlations between health profiles outcomes and health preference measurements are shown in Table 6. Correlations between the two types of questionnaires were poor to modest (r = 0.03 to 0.31). With regard to the TTO, the highest correlations were found with SF-36 scales Social Functioning (r =0.29), Bodily Pain (r =0.23) and Vitality (r =0.21). The SF-36 domains that correlated best with the SG score were Vitality (r =0.31), Mental Health (r =0.29) and Social Functioning (r =0.24).

Table 6: Correlations (Pearson's r) between descriptive instruments and preference measurements

		Time Trade Off	Standard Gamble
Short-Form 36 [a]	PF	0.18	0.16
	RP	0.15	0.23 [c]
	BP	0.23 [b]	0.23 [c]
	GH	0.14	0.16
	VT	0.21 [b]	0.31 [c]
	SF	0.29 [c]	0.24 [c]
	RE	0.11	0.07
	MH	0.15	0.29 [c]
	PCS	0.21 [b]	0.21 [b]
	MCS	0.19 [b]	0.23 [c]
$EQ\text{-}5D_{profile}$	Mobility	- 0.15	- 0.18 [b]
	Selfcare	0.03	- 0.07
	Daily activities	- 0.19 [b]	- 0.20 [b]
	Pain	- 0.16	- 0.13
	Anxiety/depression	- 0.18 [b]	- 0.20 [b]

a abbreviations: PF = Physical Functioning, RP = Role Functioning Physical, BP = Bodily Pain, GH = General Health Perceptions, VT = Vitality, SF = Social Functioning, RE = Role Functioning Emotional, MH = Mental Health, PCS = Physical Component Score, MCS = Mental Component Score
b $P<0.05$
c $P<0.01$

Discussion

The present cross-sectional study using four different HRQOL measures showed a similar impairment of quality of life in HD and PD patients. Compared to a general population sample of similar age, impairments were most obvious in the physical components of health profiles, but much less for the mental components. The preference based measures yielded relatively high scores for dialysis patients. Multiple regression analysis showed that background variables, such as the presence of comorbid diseases, explained 15 % of physical HRQOL and 18 % of the Visual Analog Scale. Correlations between the different HRQOL tests were poor to modest. These findings will be discussed in the following sections.

The severely reduced physical HRQOL of dialysis patients in comparison with the general population has been reported in many other studies. [reviewed in [26]] The equivalence of HRQOL in HD and PD patients found in the present study is in accordance with the results of other recently published investigations,[27-28] but could also be related to inadequate power to detect differences between groups. Given the number of patients included in our study, the power was adequate ($\beta > 80$ %) to detect differences of 5.3 (PCS) to 5.7 (MCS) units in the scale scores between PD and HD patient groups. Our study adds to the existing nephrologic HRQOL literature because we have not only applied health status measures but also health preference measurements. Preference based instruments have been used less often than health status measures and only three studies have reported on health preferences of PD patients.[4 7 14] The present study has shown that health preferences of HD and PD patients were similar. A remarkable finding of the present study were the high scores (0.82 to 0.89) obtained using the preference measurements. These values indicate that patients on average valued their current health state as 82 to 89 % of normal health. The average TTO value found in the present study (0.88), was similar to the value found after renal transplantation (0.87) in a study from the 1980s.[4] Typical values of prevalent dialysis patients are in the 0.40 - 0.70 range, with two exceptions of patients reporting values above 0.80.[10 19] Highest scores were found in patients with a renal transplant,[4 16] in patients using erythropoietin,[9] and in more recently published studies.[6 10 12 19]

Why do our scores differ from scores previously found? We excluded patients with language or vision problems from our study, but, due to the nature of preference measurement, such positive patient selection must also have been present in other series. Besides, the SF-36 outcomes in our patients are similar to other published SF-36 scores of dialysis patients,[29-30] making it less likely that our higher preference scores are caused by selection bias. Our patients were recruited from a clinical study on adequacy of dialysis. Consequently, patients were monitored intensively by highly motivated staff members. This may have had a positive influence on perceived HRQOL. Further, wide-spread use of EPO among study patients (85 %) may have played a role. Most of the previous work on preferences of dialysis patients stems from the pre-EPO period. Of the three studies that have reported on the contribution of EPO to health preference scores, one small study (n=28) showed higher TTO scores after introduction of EPO.[9] However, a large (n=118) placebo-controlled randomised trial [5] and an observational study in 40 patients [17] showed stable TTO scores after the introduction of EPO, despite improvements in the physical and fatigue domains of HRQOL. Given the fact that the best evidence is provided by the randomised trial, we consider EPO use not as an important factor to explain our relatively high preference scores.

The influence of non-responders on the high average preference scores has at best been limited. The patients in our sample that did not respond to SG and/or TTO (12 %) were older and had a worse self-rated health than responders. In the unlikely event that all non-responders to the TTO had valued their current health state at 0, the average TTO score still would have been 0.79. Finally, it has to be considered that preference-based methods are less-reliable than suggested,[4 7 31] at least in a cross-cultural context, because cultural differences present between countries or continents might have a strong influence on the valuation of health. In the present study, some patients refused to answer SG and TTO for

religious reasons. It is possible that this religious factor resulted in unwillingness of patients to trade-off quality and quantity of life or to accept a gamble with a negative outcome, resulting in higher scores than in non- or less religious populations. Also, cultural differences in the attitude towards risk may exist. Our finding of high preference values in Dutch dialysis patients is in accordance with data from other international comparative research,[32] which showed that the Netherlands, among 48 countries, scored highest on several well-being scales. A positive general attitude to life in the Netherlands might therefore have influenced preference scores in our study. We suggest that health preference scores of similar patient populations may not easily be compared if elicited in different countries or continents. The influence of cultural differences on health preferences and the transferability of study results to other countries remains a subject for future study.

Correlations between health preferences methods and health profiles were absent to moderate (maximal Pearson's r 0.31). This finding is in accordance with results of previous research in ESRD patients,[10 18] pre-dialysis patients,[33] and other seriously ill patients,[34-35], but could also be contributed to insufficient variance in the data or insufficient statistical power to detect correlations. Correlation as a measure of association depends on the variance of values found. Because patients' preference scores in the present study concentrated at the upper end of the scale, high correlations are unlikely. The sample size used was large enough to detect correlations as low as 0.25 with adequate statistical power, but most correlation coefficients were below that threshold. Two studies which have used multiple regression analyses to study the independent associations between health profiles and health preferences found R^2 of 19 % and 0 %.[33-34] We have not reported such multivariate analyses because it is instantly clear from the low Pearson correlation coefficients (Table 6) that health preferences scores cannot be explained by health profile outcomes. The implication of this finding is that both types of questionnaires truly reflect different aspects of the HRQOL concept. The health profiles assess patients' functioning on different domains of quality of life, whereas the health preferences methods elicit individual judgements of the value of the current health status, relative to full health and death. The implication is that the two types of questionnaires may lead to different conclusions on HRQOL of dialysis patients. The descriptive questionnaires SF-36 and EQ-5D indicated that quality of life of dialysis patients in this study was severely impaired. Despite these impairments, patients valued their health status as high as 82 to 89 percent of normal health. The discrepancy between the results of the descriptive questionnaires and the preference measurements might be explained by the fact that the coping mechanism, through which patients gradually learn to adapt to their new situation and to accept the fact that it will remain unchanged, is more reflected in the preference based methods than in the descriptive questionnaires. The reality for many ESRD patients seems to be that, despite the severe physical limitations experienced in everyday life, they subjectively experience a relatively high quality of life.

The multivariate regression analyses (Table 5) failed to show obvious relationships between social-demographic, clinical and treatment related variables and health preferences scores. Previous research showed that health preferences were also not correlated with clinical variables, such as hematocrit, hemoglobin and glomerular filtration rate.[33] If health preferences scores are poorly explained by both health status (Table 6) and social-demographic, clinical and treatment related variables (Table 5), what else constitutes a person's

preference score? Besides by coping behaviour of patients, the preference scores may be influenced by beliefs about health, previous experiences and knowledge, a person's attitude towards risk and time and non-health related factors, such as financial status, family circumstances and social support.[31] These confounders hamper the strict interpretation of the preference scores as the valuation of health status only and, consequently, the use of health preference methods in clinical HRQOL studies, especially in populations of chronic patients. In such populations, the coping process may prevent patients from using the whole range of possible scores.[36] Two of the three prospective EPO studies that used the TTO instrument reported no difference in health values after treatment with EPO had been started.[5 17] Also, a study in survivors of myocardial infarction concluded that health values are stable over time, despite changes in health status.[37] This further reduces the usefulness of health preference methods, especially in prospective studies. Other disadvantages of health preferences methods include the necessity of an interviewer situation, the relatively high non-response and the unknown influence of cross-cultural factors on health values of patients. Until these issues are resolved, the use of health preferences methods should be limited to a research context.

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Chapter 4

A comparison of quality of life of patients on automated and continuous ambulatory peritoneal dialysis

De Wit GA, Merkus MP, Krediet RT, de Charro FTh. A comparison of quality of life of patients on automated and continuous ambulatory peritoneal dialysis. Perit Dial Int 2001; 21: 306-312

Abstract

Objective. Data on health-related quality of life (HRQOL) of Automated Peritoneal Dialysis (APD) patients are scarce. The objectives of this study were (1) to explore HRQOL of APD patients, to compare it with HRQOL of CAPD patients and a general population sample and (2) to study the relationship between HRQOL outcomes and background variables.

Design. Home interviews of APD and CAPD patients. HRQOL, social-demographic, clinical and treatment related background data were collected at the interview and from patient charts. Multiple regression analysis and logistic regression analysis were used to study the relationship of HRQOL outcomes towith background variables.

Setting. Sixteen Dutch dialysis centres.

Patients. Convenience sample of 37 APD patients and 59 CAPD patients matched for total time on dialysis.

Main outcome measures. Four HRQOL instruments: Short Form 36, EuroQol/EQ-5D, Standard Gamble and Time Trade Off.

Main results. Physical functioning of both APD and CAPD patients was impaired in comparison with the general population, while mental functioning was not different. In multivariate analyses, mental health of APD patients was found to be better than that of CAPD patients. In addition, APD patients were less anxious and depressed than CAPD patients. Regarding physical aspects of HRQOL and role-functioning, no differences were observed between APD and CAPD patients. Other variables to explain HRQOL outcomes were age, the number of comorbid diseases and primary kidney disease.

Conclusions. HRQOL of APD patients is at least equal to HRQOL of CAPD patients.

Introduction

The concept of Automated Peritoneal Dialysis (APD) was first described in 1981, five years after the introduction of continuous ambulatory peritoneal dialysis(CAPD).[1] APD has been used by relatively few patients in the almost two decades of its existence. From the United States Renal Data Registry, it appears that 4.4% of all American dialysis patients was using APD in 1997.[2] In the Netherlands, 6.2% of all dialysis patients were treated with APD in 1997, mostly with Continuous Cycling Peritoneal Dialysis (CCPD).[3] Although many papers on health-related quality of life (HRQOL) of dialysis patients have been published,[4] it is surprising that quality of life of APD has hardly been studied yet. A MedLine literature search identified four earlier studies that had incorporated APD patients.[5-8] Two of those studies [6 7] only reported data on the aggregate level, making it impossible to draw conclusions on the relative performance of APD patients. One study focused on the impact of different types of APD equipment on quality of life.[5] Only one study was aimed at a formal assessment of HRQOL of APD patients.[8] This was a small randomised trial (n=25), comparing APD and CAPD with regard to quality of life. Using a standardised and validated questionnaire, no differences between both groups were found.

Health-related quality of life is an important outcome of patient care.[9] The term includes different concepts as functional status, health status, well being, patient satisfaction and patient preferences. Over the past 30 years, many different questionnaires and interview techniques have been developed to measure HRQOL.[9] Generic questionnaires allow for comparisons with other patient groups and with general population samples. They may be distinguished in health profiles and in preference based measures, also called utility measures.[10] Health profiles aim to describe various dimensions of quality of life, including physical, psychological and social functioning. Health preference measurements explicitly seek to value the quality of life in a single indicator, a number between zero and one, where zero represents death and one represents full health.

The purpose of the present study was to explore the HRQOL of a sample of APD patients and to compare it with HRQOL of CAPD patients and a general population sample of similar age. Both health profiles and health preference methods were used to assess the HRQOL of patients. Results were analyzed with regard to social-demographic, clinical and treatment related variables.

Subjects and methods

Data collection

We recruited APD patients from three Dutch dialysis centres that were known to treat relatively much APD patients. We compared HRQOL of these APD patients with HRQOL of CAPD patients who were recruited from 13 dialysis centres that participated in a Dutch prospective cohort study on the adequacy of dialysis, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD-I Study).[11] APD and CAPD patients were matched for total time on dialysis, all of them had started dialysis after October 1st 1993.

All patients in these 16 centres who had been treated with their current modality for at least three months, were above 18 years, and had adequate eyesight and understanding of the Dutch language to enable the administration of questionnaires were asked to participate in this study. Interviews were conducted at patients' homes by one of three trial nurses with experience in end-stage renal disease treatment. The nurses received a training to administer the various HRQOL measures. The ethical committees of all dialysis centres approved the study and all patients consented before study entry. The funding organisation neither had interference with data collection, data analysis and writing the manuscript, nor did it have the right to approve or disapprove the manuscript.

Background variables

Data on background variables were collected atduring the interview and included age, sex, marital status, employment status, educational level, number of hospitalisations in last six months, and number and type of comorbid conditions. Comorbidity at the time of the interview was evaluated using a validated list of chronic conditions from the annual Dutch National Health Survey.[12] Major diseases such as diabetes mellitus, myocardial infarction, stroke and malignancy are included in this list. Respondents were asked to indicate for each condition whether they suffered from the condition at present or in the year preceding the interview. Data on primary diagnosis, treatment history, length of time on dialysis and current treatment, and dose of dialysis in terms of dialysis related urea clearance were obtained from the patient's nephrologist. Primary diagnosis was classified according to the EDTA-ERA classification.[13] The weekly Kt/V_{urea} was calculated as the peritoneal Kt/V_{urea} per 24 hours multiplied by 7.

Questionnaires used to assess HRQOL

The interview consisted of the administration of four generic questionnaires, including two health profiles (Short-Form 36 Health Survey and EuroQol/EQ-5D) and two health preferences methods (Standard Gamble and Time Trade Off). The four questionnaires were always administered in this sequence. The first two questionnaires were self-administered. After completion, the interviewer continued with the administration of the Standard Gamble and Time Trade Off.

The *Short-Form 36 Health Survey* (SF-36) generates a profile of scores on eight dimensions of quality of life.[14] These dimensions are: (1) physical functioning, (2) role limitations due to physical functioning, (3) bodily pain, (4) general health perceptions, (5) vitality, (6) social functioning, (7) role limitations due to emotional functioning, and (8) mental health. Raw scores on the eight scales are transformed to calculate a score between zero and hundred, where a higher score indicates better health. The physical and mental components of the eight scales are combined into a physical and a mental summary score.[15] The two summary measures are standardized to have a mean of 50 and a standard deviation of 10 in the general population and therefore allow for easy comparison of patient scores with general population scores. SF-36 scores of persons of similar age (55-64 years) were derived from a validation-study in the Dutch population.[16]

The *EQ-5D* or *EuroQol* (EQ-5D) is a validated generic questionnaire that includes a classification system ($EQ\text{-}5D_{profile}$) and a visual analogue scale (EQ_{VAS})[17 18] The $EQ\text{-}5D_{profile}$ records the level of self-assessed problems on 5 domains of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with three levels of functioning: (level 1: no problems; level 2: some problems; level 3: unable to perform/extreme problems). The EQ_{VAS} records the respondents rating of his/her overall health status on a graduated, vertical visual analogue scale. The EQ_{VAS} is anchored at 0 (worst imaginable health state) and 100 (best imaginable health state).

The *Standard Gamble* (SG) is a method to measure preferences for health states.[19] The respondent is presented with two alternatives and asked to choose the one most preferred. The first alternative offers the certainty of staying in the current health state for the remainder of the respondent's life. The second alternative is a gamble with specified probabilities for both the positive outcome of the gamble (a normal health state for the remainder of time) and the negative outcome (immediate death). These probabilities are varied until the respondent is indifferent between the gamble and living in his/her current health state. The SG score, a score between zero and one, is calculated as one minus the risk percentage at the point of indifference, divided by hundred. An SG score of 0.80 implies that a person is prepared to take a gamble with 20 percent risk of dying immediately and 80 percent chance to improve his current health to normal health. The SG score reflects the value a person assigns to his own health state. In our study, a visual aid was used to explain the concept of the SG. Before the patient was asked to value his own current health state, the concept was explained and practised using imaginary health states.

The *Time Trade Off* (TTO) is also a preference-based method.[20] Patients are asked whether they are prepared to give up some remaining time of their lives, in order to improve their current health state to normal health. The time perspective that is presented to the patient corresponds with the statistical life expectancy of people of the same age and sex. The quotient of the chosen number of years in a normal health state over statistical life expectancy yields the TTO score. A TTO score of 0.80 implies that a person is indifferent between living 8 years in excellent health versus 10 years in his current health state. We practised the TTO concept with imaginary health states, before the patient was asked to value his/her own current health state.

Statistical analysis

Differences between treatment groups were tested by means of the Student's t-test in case of continuous variables. Where the distribution of scores deviated from normality, non-parametric methods were used (Mann-Whitney U Test). Categorical variables were compared using the Pearson Chi-square test. In order to be able to control for case-mix differences, the association between continuous HRQOL outcomes (SF-36, SG, TTO, EQ_{VAS}) and background variables was studied with multiple regression models. Logistic regression analysis was used to study the relationship between background variables and categorical HRQOL outcomes ($EQ\text{-}5D_{profile}$). These $EQ\text{-}5D_{profile}$ outcomes were dichotomised into the presence of problems, either at level 2 (some problems) or level 3 (severe problems), and the absence of problems. A forward stepwise selection strategy with $P=0.05$ as the criterion level for selection was chosen for all regression analyses. Analyses reported here are

based on treatment at the time of the interview. A two-sided P-value of 0.05 was chosen as cut-off for statistical significance.

Results

Patient characteristics

A total number of 96 patients were interviewed (37 APD, 59 CAPD). Table 1 lists the main demographic and clinical characteristics of patients. The proportion of males in the CAPD group was significantly higher than in the APD group. APD patients more often had glomerulonephritis as primary disease, while there was a trend towards more renal vascular diseases and diabetes mellitus in the CAPD group. The total number of months on dialysis was the same in both treatment groups (15 months), but CAPD patients had on average been treated longer with their current treatment modality (13 months) than APD patients (10 months). No other demographic and clinical differences were present between the groups.

Table 1: Patient characteristics according to treatment modality (mean, SD, range or %)

	CAPD (n=56)	APD (n=37)
Age	56 (13) 25-80	55 (13) 28-76
Male [a]	69%	49%
Married/living together	86%	81%
Employed	25%	29%
Educational level		
- low	17%	24%
- intermediate	73%	68%
- high	10%	8%
EDTA-ERA primary disease		
- glomerulonephritis [a]	12%	29%
- renal vascular diseases [b]	25%	11%
- interstitial nephritis	7%	14%
- cystic kidney disease	12%	11%
- diabetes mellitus	17%	5%
- others and unknown	27%	30%
Number of comorbid conditions	2.6 (1.9) 0-9	2.3 (1.6) 0-6
Number of hospitalizations in last six months	0.6 (1.0) 0-5	0.6 (0.8) 0-3
Months on dialysis	15 (4) 7-21	15 (8) 3-31
Months on this modality [a]	13 (4) 7-21	10 (7) 3-29
Dialysis Kt/V_{urea}	2.0 (0.4) 1.3-2.9	1.9 (0.5) 1.3-3.6

a $P<0.05$

b including hypertensive nephrosclerosis

Results of SF-36

Table 2 presents patients' and reference group scores on the eight SF-36 sub-scales and the two SF-36 summary scores for physical and mental functioning. Comparison with scores of a general population sample showed that the mean SF-36 physical summary score of both patient groups was 1.0 to 1.2 standard deviations lower than the mean score of the general population (P<0.001). The SF-36 mental summary score of both patient groups was not different from the general population. Analysis of the differences in SF-36 scores between CAPD and APD patients showed that APD patients scored equal to or slightly better than CAPD patients on all SF-36 sub-scales, but that only the difference in Social Functioning was significant (P=0.03).

Table 2: Mean (SD) scores on eight SF-36 sub-scales and two SF-36 summary scores, by treatment modality, and for a general population sample of similar age (55-64)

	CAPD (n=59)	APD (n=37)	General population (n=140)
Physical functioning	61 (28) [a]	66 (28)	73 (24)
Role functioning – physical	37 (43) [a]	52 (43) [a]	77 (38)
Bodily pain	66 (30) [a]	75 (26)	75 (25)
General health	42 (21) [a]	42 (21) [a]	64 (22)
Vitality	51 (22) [a]	57 (20) [a]	67 (21)
Social Functioning (SF) [b]	65 (33) [a]	79 (29)	87 (21)
Social functioning	65 (33) [a]	79 (29) [b]	87 (21)
Role functioning – emotional	77 (37) [a]	86 (34)	90 (25)
Mental health	74 (18)	78 (16)	77 (19)
SF-36 physical summary score	38 (11) [a]	40 (11) [a]	50 (10)
SF-36 mental summary score	48 (11)	51 (9)	50 (10)

a P<0.05, vs. general population
b P<0.05, APD vs. CAPD

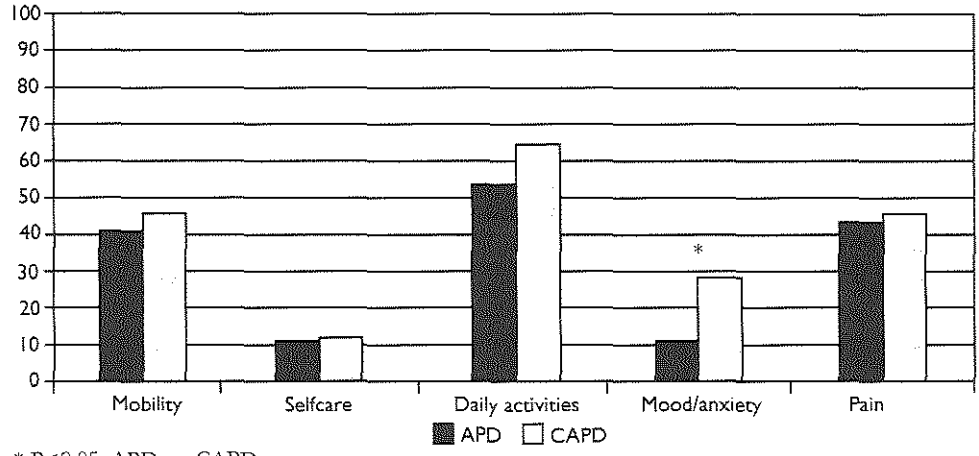
Results of EQ-5D

Figure 1 shows the proportion of CAPD and APD patients that indicated to have some or severe problems on the five dimensions of the $EQ\text{-}5D_{profile}$. Compared to CAPD patients, APD patients showed somewhat fewer problems with mobility, daily activities and pain, but the differences were not significant. CAPD patients were more anxious and/or depressed than APD patients (P<0.05). With a score of 61 (SD 0.20), self-rated health status on the EQ_{VAS} was similar for both patient groups.

Results of Standard Gamble (SG) and Time Trade Off (TTO)

The mean SG score of CAPD patients was 0.81 (SD 0.24), the mean SG score of APD patients was 0.74 (SD 0.24). The TTO scores of patients were somewhat higher than SG scores: 0.86 (SD 0.23) for CAPD and 0.93 (SD 0.14) for APD patients. The differences between CAPD and APD patients were not significant.

Figure 1: Percentage of patients reporting some or severe problems in 5 domains of EQ-$5D_{profile}$, by treatment modality



* P<0.05, APD vs. CAPD

Associations between background variables and HRQOL outcomes

Independent explaining variables of HRQOL are shown in Table 3. Regarding the SF-36 physical summary score, a higher number of comorbid conditions was associated with impaired HRQOL, while glomerulonephritis as primary kidney disease was associated with better HRQOL. The SF-36 mental summary score was also negatively associated with the number of comorbid conditions, while diabetes mellitus as primary kidney disease and APD treatment were positively associated with mental QL of patients. A higher number of comorbid diseases and a longer time on dialysis were negatively associated with self-rated health status (EQ_{VAS}). Regarding health preferences, the TTO score of patients was nega-

Table 3: Regression models to explain quality of life outcomes in peritoneal dialysis patients (standardized regression coefficient ß, (partial R^2) and total R^2)[a]

	SF-36 physical summary	SF-36 mental summary	EQ-$5D_{VAS}$	Time Trade Off	Standard Gamble
		Standardized regression coefficient (partial R^2)			
No. of comorbidities	-.59 (35.2%)	-.36 (9.9%)	-.48 (27.0%)	-.27 (7.3%)	-.39 (12.9%)
Diabetes mellitus [b]		.26 (4.5%)			
Glomerulonephritis [b]	.22 (4.8%)				-.31 (7.7%)
Cystic kidney disease [b]					-.21 (4.1%)
APD		.22 (4.9%)			
Time on dialysis			-.28 (7.7%)		
Total R^2	40.0%	19.3%	34.7%	7.3%	24.7%

a ß denotes the relative importance of the explaining variable: the higher the ß coefficient, the higher the contribution of that variable in the regression equation. Partial R^2 symbolizes the explained variance of the dependent variable accounted for by the variable. Total R^2 is the percentage of the total variation of the quality of life score that is explained by the independent variables together

b as primary kidney disease

tively associated with the number of comorbid diseases. The SG score of the patient could be explained by the number of comorbid conditions and by primary kidney disease: patients with glomerulonephritis and cystic kidney disease as primary disease showed lower SG scores. The models constructed had a low to moderate capacity to explain the variation in scores on the HRQOL outcomes (Total Adjusted R^2 from 7.3% to 40.0%).

Logistic regression analysis (Table 4) showed that more comorbid diseases were associated with an increasing likeliness to indicate problems on the $EQ\text{-}5D_{profile}$ dimension "mobility". Employed patients and patients with glomerulonephritis as primary kidney disease were less likely to have problems with "daily activities" than unemployed patients and patients with other primary kidney diseases. Again, a higher number of comorbid diseases was associated with a higher risk of not being able to performing daily activities without

Table 4: Logistic regression models to explain the association between $EQ\text{-}5D_{profile}$ scores (absence/ presence of problems) and background variables (odds ratios with 95% C.I.[a])

	mobility	selfcare [b]	daily activities	anxiety/depression	pain
		Odds ratios with 95% Confidence Intervals			
Age				1.06 (1.01-1.11)	
No. of comorbidities	1.85 (1.33-2.58)	1.56 (1.02-2.40)	1.78 (1.22-2.58)	1.37 (1.01-1.86)	1.30 (1.01-1.68)
Employed			0.33 (0.11-0.96)		
Diabetes mellitus [c]		10.58 (1.80-61.95)			
Glomerulonephritis [c]			0.13 (0.04-0.58)		
Renal vascular disease [c]					0.21 (0.05-0.83)
APD				0.10 (0.01-0.79)	

a The odds ratio indicates how much more likely (or unlikely) the presence of problems is in patients with the characteristic than in patients without that characteristic or, for continuous variables, the relative increase in likelihood to have problems associated with one extra unit of the continuous variable
b results given for reasons of completeness; however, results unreliable because few subjects showed problems with selfcare
c as primary kidney disease

problems. Elderly people and patients with more comorbidities were more likely to be anxious and depressed, while APD patients were less likely to be anxious and depressed than CAPD patients. A higher number of comorbid diseases was associated with a higher likelihood to experience pain. Renal vascular disease as primary kidney disease was associated with less pain.

Discussion

This paper presents an explicit assessment of HRQOL of APD patients, in comparison with CAPD patients. A general conclusion drawn from the four HRQOL instruments used is that HRQOL of APD patients is equal to HRQOL of CAPD patients, and slightly better in a few HRQOL domains. The differences in health preference scores (SG and TTO)

of both patient groups were not significant, indicating that on average CAPD and APD patients valued their current health status equally.

After adjustment for case-mix variables, APD treatment appeared an independent indicator of better mental health (measured with SF-36 mental health summary score) and of the absence of problems of anxiousness and depression (measured with $EQ\text{-}5D_{profile}$). Inspection of the SF-36 sub-scales that compose the mental health summary score showed that especially social functioning of APD patients was better, compared with CAPD patients. The better social functioning of APD patients might be related to the fact that daytime in these patients is free from treatment, thus facilitating a normal social life. An explanation for the factour finding that APD patients were less anxious and depressed than CAPD patients is more difficult to find. Possibly, treatment selection may have played a role. Patients with higher anxiety levels may not have chosen the APD technique, because they find it scary to be attached to a machine while sleeping. Because our study was of cross-sectional nature, it remains difficult to differentiate between a real treatment effect and treatment selection. A longitudinal study also controlling for possible base-line differences in social functioning and anxiety/depression levels would be preferential to determine the independent influence of treatment modality on these HRQOL outcomes.

Four earlier HRQOL studies that had incorporated APD patients were identified.[5-8] Two of those studies[6 7] only reported data on the aggregate level, making it impossible to draw conclusions on the relative performance of APD patients. Of the two studies that provided with data of APD patients, one study reported SF-36 scores that were similar to scores of our patients,[8] the other study found slightly lower SF-36 scores.[5] However, patients in that study had more comorbid diseases than patients in our study. The health preference scores elicited in our study are relatively high in comparison with previously published scores of dialysis patients, which fell in the 0.42 [21] to 0.81 [22] range. The general implication of the health preference scores as found in our study is that peritoneal dialysis patients valued their current health status as 74 to 92% of a normal health state. Most previous studies on health preferences of dialysis patients have been performed in the United States and Canada. An explanation for our higher scores may be that health values are not comparable cross-nationally and cross-continentally. A similar phenomenon was described by Veenhoven et al, who found that the perception of happiness and wellbeing was very different between countries and continents.[23] Their study comprised 50 countries, and identified the Netherlands as one of the countries with highest levels of wellbeing. Besides to this more general cultural phenomenon, the relatively high values of patients for their own health status might be attributable to successful coping strategies of patients or may as well reflect the high quality of healthcare for Dutch dialysis patients. The variance in all HRQOL outcomes was only poorly to moderately explained by the clinical, socio-demographic and treatment-related variables that were included in our study, as was found by others.[6 24] This implicates that HRQOL outcomes may be determined by other factors than the ones we have explored. Although the health preference instruments explicitly ask respondents to value their current health state only, financial circumstances, attitudes to risk, religion and family support may also influence its outcomes.[19] Furthermore, the health preference outcomes depend on cognitive processes such as remembering past experiences and integrating beliefs and biases about health.[25] We found that patients with glomeru-

lonephritis as primary kidney disease had lower SG scores, while at the same time showing a higher SF-36 physical summary score and less problems with daily activities than patients with other primary diseases. This could as well be an incidental finding as an indication of the fact that health preference scores reflect more than health status alone.

In comparison with a general population sample of the same age, both CAPD and APD patients showed worse SF-36 physical summary scores. However, the SF-36 mental summary scores of patients were similar to those of the general population. The differences between the general population and PD patients were especially large ($P<0.001$) on the subscales physical role functioning, general health perceptions, vitality and social functioning (CAPD patients only). Two recent publications reported also that physical functioning of dialysis patients is impaired in comparison with the general population, but that mental functioning is not essentially different from mental functioning of the general population.[26 27] The SF-36 physical and mental summary scores in both studies were similar to scores of our PD patients.

Since APD is more expensive than CAPD,[28] HRQOL information should be involved in the assessment of the relative merits of alternative PD treatment modalities.[29] Our study suggests a slightly higher mental QOL of APD patients, compared to CAPD patients. If this finding is confirmed by other studies, the higher costs of APD might be justified. Such future studies should be of a longitudinal nature, facilitating better control for possible differences in base-line characteristics of patient groups.

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Chapter 5

Economic evaluation of renal replacement therapy: a literature review

De Wit GA, Jager JC, de Charro FTh. Economic evaluation of renal replacement therapy: a literature review. Submitted.

Abstract

This paper reports on a systematic review of the literature on economic evaluation of end-stage renal disease treatments. The purpose of this study was twofold: (1) to review and compare current knowledge about the costs and effects of renal replacement therapies, and (2) to assess the methodological quality of the economic evaluations. Six bibliographic databases (MEDLINE, EMBASE, HEED, NHS-EED, INAHTA Database, ECONLIT) were searched to identify original studies published between 1988 and 2000. Inclusion criteria were (1) full economic evaluation; (2) publication in English, French, German or Dutch; (3) sufficient methodological quality (assessed with a standardised rating system). Of the 127 publications initially selected, 11 remained after further selection based on study quality criteria. The main conclusions of this literature review are that few good quality economic evaluations have been published; that studies appeared especially week in the costing parts, including lack of discounting; and that full care haemodialysis was consistently found to be less efficient than renal transplantation and continuous ambulatory peritoneal dialysis. Future studies should concentrate on cost-effectiveness of treatments for subgroups of patients with similar age and comorbid status.

Introduction

Renal replacement therapies (RRT) have first come into clinical use in the 1960s. The most commonly used techniques are haemodialysis (HD), peritoneal dialysis (PD) and renal transplantation (TX). With haemodialysis, the blood is cleaned from waste products through an extracorporeal artificial kidney. Haemodialysis can either be performed by the patient at home (home haemodialysis - HHD), or in a dialysis centre or hospital, with more (limited care haemodialysis - LCHD) or less active (full care centre haemodialysis - FCHD) input of the patient in the treatment. With peritoneal dialysis, waste products are removed through a cleaning fluid in the abdominal cavity. PD has two main treatment varieties, either with manual exchange of dialysis fluid (continuous ambulatory peritoneal dialysis - CAPD) or with automated exchange of dialysis fluid at night (automated peritoneal dialysis - APD). Kidney transplantation eliminates the necessity of dialysis as long as the recipient does not irreversibly reject the graft.

The treatments currently available are lifelong, complex, and costly, and have always been so. Therefore, from the early beginning there has been an interest in the evaluation of costs and effects of RRT.[1-4] Such economic evaluations aim to inform policy makers on the relative efficiency of several competitors for healthcare money, in order to allocate scarce resources as rational as possible.[5] In recent years, the research discipline of economic evaluation of healthcare interventions has matured, both in the number of analyses performed [6], and in the definition of the methodological characteristics that are a prerequisite for good quality studies.[5-9] However, reviews of economic evaluation in several areas of medicine and healthcare have shown the paucity of much of the published research.[10-15] No earlier systematic review of the quality and outcomes of economic evaluation studies in the field of RRT has been found in the literature. However, one review that concentrated on the analysis and interpretation of cost data in dialysis was published recently.[16] It was concluded that costing information in this field was often handled inconsistently and unsatisfactorily, and that the analysis and reporting of costs needs improvement.

The purpose of this study was twofold: (1) to review and compare current knowledge about the costs and effects of renal replacement therapies, and (2) to assess the methodological quality of the economic evaluations. We limited our search to studies published between 1988 and 2000, to be sure that major therapeutic improvements such as the introduction of cyclosporin as an immunosuppressant for transplanted patients and the introduction of erythropoietin for the treatment of renal anaemia were incorporated in the outcomes of studies. Also, PD did not come into widespread use before the second half of the 1980s. Furthermore, it was anticipated that older studies would not adhere to current methodological standards for economic evaluations.[11]

Methods

Inclusion of studies

Inclusion criteria were (1) full economic evaluation (to be explained later in this section) considering two or more RRT; (2) publication in English, French, German or Dutch languages; (3) the fulfilment of minimal quality standards for full economic evaluation studies (see separate paragraph).

Studies were identified by searches in the following databases:

- MEDLINE (from 1988 until December 1999). MEDLINE is maintained by the United States National Library of Medicine. MEDLINE was accessed with WINSPIRS software.
- EMBASE (from 1988 until December 1999). EMBASE is a database primarily oriented at European biomedical literature, maintained by Elsevier Science. EMBASE was accessed with DIALOG software.
- HEED (Health Economic Evaluation Database). This database is maintained by the Office of Health Economics of the Department of Health and Social Security (London) and is accessible through CD-ROM.
- INAHTA Database. The International Network of Agencies of Health Technology Assessment (INAHTA) maintains a database of publications by its member organisations. This database is accessible through CD-ROM (via Cochrane Collaboration) and Internet (http://www.york.ac.uk/inst/crd/).
- NHS-EED (NHS ECONOMIC EVALUATION DATABASE). This database is maintained by the National Health Service Centre for Reviews and Dissemination, University of York, and is accessible through CD-ROM (via Cochrane Collaboration) and Internet (http://www.york.ac.uk/inst/crd/). The database includes standardised descriptions of published economic evaluation studies.
- ECONLIT. This database is maintained by the American Economic Association and contains economic literature. The database was accessed using DIALOG software.

The search strategy that was used for the Medline search is specified in Appendix 1. Basically, similar worded strategies have been used for searches in other databases, but each search was adapted to the requirements of the specific database. The Medline search was used as the "reference search", in a sense that results from searches in the other five databases were compared against these Medline results. The references of all articles that were assessed and the references of a published bibliography of economic evaluations [6] were also checked for relevant articles. Furthermore, some unpublished studies we knew of, such as PhD theses and other "grey" literature were considered for inclusion as well.

A full economic evaluation is a study describing all necessary input and all relevant outcomes of healthcare interventions.[5] One basic principle of economic evaluation is that at least one intervention is compared to another: either a status quo intervention or doing nothing. Four basic types of full economic evaluations may be distinguished: cost-minimisation-analysis (CMA), cost-benefit-analysis (CBA), cost-effectiveness-analysis (CEA), and cost-utility-analysis (CUA).[5] In a CMA, equal effectiveness of the healthcare interventions under study is assumed. Only relevant costs are compared, and the cheapest intervention is assumed to be the most efficient. With a CBA, interventions for which the consequences are not identical and clinical success is measured in very different units may be compared. Both input and output of healthcare interventions are valued in monetary terms. Because of the inherent problems of valuing all relevant outcomes in monetary terms, especially the intangible ones, this type of economic evaluation is relatively rare in medicine. CEA is the evaluation technique used most frequently. In a CEA, the outcome measure can be any naturally occurring unit relevant for the intervention under study, such as infections averted, hospitalisations avoided, or units of blood pressure reduced. However, the number of life-years gained is an outcome measure used relatively frequently in CEA. One special form of CEA is CUA, where outcomes are measured in healthy years gained. Life-years gained have to be adjusted for the quality of life in those years, using a utility-index for the different health states a person can be in. A utility of 1 corresponds to perfect health, while a utility of 0 corresponds to death. The outcome unit in a CUA usually is the QALY (Quality Adjusted Life Year) or Healthy Years Equivalent (HYE).

Exclusion criteria

The following studies were not considered in our systematic review: (1) studies evaluating interventions relevant to patients receiving RRT, but not RRT itself, such as the comparison of erythropoietin use and blood transfusion for anaemia[17], the cost-effectiveness of screening to prevent renal failure in insulin dependent diabetic patients[18], evaluation of parenteral iron administration in haemodialysis patients[19], or the comparison of two immunosuppressive agents for transplanted patients[20], (2) multiple publications on one study, (3) editorials, reviews and letters, (4) studies concentrating on cost of therapy alone (partial economic analyses[5]), (5) cost of illness studies, and (6) studies that presented insufficient data to assess the merits of the study, such as short reports and abstracts.

Quality rating

For each paper under review, a quality rating was completed, according to Bradley et al.[21] and Sacristan et al.[22] This checklist consists of 13 items and is based on widely accepted standards of economic evaluation methodology[5], but has the additional advantage of composing a numerical score for the quality of the paper. Studies with an average quality rating ≥ 2.5 per applicable item (out of a maximum score of 4 per item) were selected for the current review. The quality rating form is included in Appendix 2.

Results

The results of the searches in the six databases that were mentioned in the methods section are shown in Table 1. Often, it was immediately clear from either the language of the paper, content of the abstract, or publication type, that the paper was not suitable for further assessment. Table 1 shows the number of papers retrieved, the number of papers that were initially removed from the selection because either inclusion criteria did not apply or exclusion criteria did apply, and the remaining number of papers that were considered for inclusion.

Table 1: Results of literature searches in 6 databases

Database	# of hits	# removed	# assessed
Medline	1,186	1,124	62
Embase	514 (unique non-Medline)	467	47
HEED	77 (17 unique non-Medline, non-Embase)	74	3
INAHTA	26	19	7
NHS-EED	178 (13 not found before)	165	5
Econlit	324 (316 duplicate Medline)	324	0

As appears from Table 1, 1,764 unique documents were found with the various literature searches. Of these, 1,640 were removed initially because exclusion criteria applied. Besides the 124 papers reported on in Table 1, three additional unpublished reports have been assessed for this review. After reading those 127 papers and reports, a further selection was made on the basis of criteria discussed in the methods section. Finally, 11 papers were selected for this review. Most studies that were not selected appeared to be partial economic evaluations, although they were labelled as full economic evaluation studies in either title or abstract. Also, studies often appeared to be cost studies only. Other studies were not selected because they lacked quality. There were for instance many clinical studies that included an undiscounted and otherwise inadequate cost calculation, while at the same time not reporting on a sensitivity analysis and lacking the integration of costs and outcomes in a sensible measure.

Table 2 shows a comprehensive overview of all 11 selected studies with the following key features: first author and year of publication, interventions compared, study design, number of patients, economic study design, viewpoint of study, type of costs included, valuation of costs, year of study, time span of study, discounting of costs and effects with discount rate, (type of) sensitivity analysis, and main outcomes. In the remainder of the results section, we will discuss some of the findings of selected studies.

Table 2: Summary of main characteristics of studies selected for review

First author /year of publication	RRT assessed [a] / type of patients	Design [a]	Economic designa	View-point	Costs included[b]	Valuation of costs [c]	Main effects [a]	Source effec-tive-ness	Year and country of study	Time-span of study	Dis-counting	Incremental analysis	Sensitivity analysis	Main outcomes [a]
Croxson, 1990 [23]	FCHD, HHD, CAPD, TX for all ESRD	Markov-chain-like model	CEA	Health-care system	1	1,2	LYG	Data from literature and 2 hospitals	New Zea land, 1988	5 yrs	10 % costs 10 % ef fects	No	Yes, one-way	Average cost per LYG for FCHD $35,270, TX $18,463, CAPD $25,395 –26,390, HHD $28,175.
De Charro, 1988 [24]	FCHD, HHD, LCHD, TX, CAPD for all ESRD	Markov-chain model	CEA	Health-care system	1,3	1,2	LYG	Dutch and European patient cohorts	The Neth erlands, 1984-1985	5 yrs	10 % costs 10 % ef fects	No	Yes, one-way	Cost per LYG all ESRD treatment = NLG 58,000, no separate analysis for different treatment modalities.
De Wit, 1998 [25]	FCHD, LCHD, CAPD, APD, HHD, TX, for all ESRD	Markov-chain model + cohort study	CEA, CUA	Health-care system-	1,3,5	1,2	LYG, utilities (patients), utilities (population)	N=165 patients, national registry data	The Neth erlands, 1996	5 yrs	5 % costs 5 % effects	Yes, also	Yes, one-way	Cost per LYG all ESRD treatment = NLG 78,700, cost per QALY = NLG 98,300. Cost per LYG all dialysis = NLG 133,100, cost per LYG TX = NLG 25,000.
Douzdjian, 1999 [26]	TX + PAK, SPK for type 1 diabetics	Decision-analytic model	CUA	Health-care system	1	2	LYG, utilities (patients)	Literature	US, 1996	5 yrs	No	No	Yes, one + two way	SPK was more cost-effective than TX + PAK: Cost per QALY were $110,828 and $153,911, respectively.
Douzdjian, 1998 [27]	FCHD, TX-CAD, TX-LD, SPK for type 1 diabetics	Decision-analytic model	CUA	Health-care system	1	2	LYG, utilities (patients)	N=17 patients, literature	US, 1996	5 yrs	No	Yes, also	Yes, one-way	Average cost per QALY for dialysis $317,746, TX-CAD $156,042, TX-LD $123,923, SPK $102,422. Incremental analysis shows TX-LD to be most cost-effective.
Greiner, 1999 [28]	TX versus FCHD for all ESRD	Cohort study	CUA	Health-care system	2,4	1,2	Utilities (population)	N=1023 (waiting list), n=172 (TX)	Germany, 1993	10-20 yrs	5 % costs 5 % effects	Yes	Yes, one-way	TX was dominant (more QALY's, less cost) strategy. Average cost per QALY for FCHD DM 147,000, versus DM 38,000 for TX.
Hamel, 1997 [29]	Initiating FCHD for acute renal failure in very ill patients	Cohort study	CUA	Health-care system	2,5	2	LYG, utilities (patients)	N=491 patients	US, 1994	Max. 4.4 yrs	3 % costs 3 % effects	Yes	Yes, one-way	Incremental cost per QALY for initiating dialysis compared to withholding dialysis $128,200. Cost per QALY for best prognostic group $61,900, for worst prognostic group $274,100.

(Table 2 continued)

First author /year of publication	RRT assessed [a] / type of patients	Design [a]	Economic design[a]	View-point	Costs included[b]	Valuation of costs [c]	Main effects [a]	Source effec-tive-ness	Year and country of study	Time-span of study	Dis-counting	Incremental analysis	Sensitivity analysis	Main outcomes [a]
Horn-berger, 1993 [30]	High-flux FCHD versus conventional FCHD	Retro-spective cohort study	CEA	Health care system	1	2	LYG	N=253 patients	US, 1990	Un clear	5 % costs 5 % effects	Yes	Yes, one-way	Incremental cost per LYG of high-flux dialysis compared to conventional dialysis, was $28,188 – $29,743, de-pending on model.
Horn-berger, 1997 [31]	Repeated TX for patients with graft failure	Decision-analytic model	CUA	Health care system	1,3	2	LYG, utilities (patients)	N=878 patients, literature	US, 1995	Life-time	5 % costs 5 % effects	Yes	Yes, one-way	Incremental cost per QALY of a re-transplantation policy compared to no re-transplantation policy was $9,659.
Laupacis, 1996 [32]	TX versus dialysis (n.s.) for patients on waiting list	Prospec-tive co-hort study	CUA	Soci ety	1,3,4	1,2	LYG, utilities (patients)	N=269 patients	Canada, 1994	2 yrs	No	Yes	No	Transplantation was dominant strategy (more effective, less costly) for all subgroups of patients examined.
Sesso, 1990 [33]	FCHD, TX-CAD, TX-LD, CAPD for non-diabetic ESRD	Retro-spective cohort study	CEA	Health care system	1	2	LYG	N=121 patients	Brazil, 1985	2 yrs	No	Yes, also	Yes, one-way	Average cost per LYG for FCHD $10,065, TX-CAD $ 6,978, TX-LD $3,022, CAPD $ 12,134. Incremental analysis shows TX-LD to be most cost-effective.

a RRT = Renal Replacement Therapy, ESRD = end-stage renal disease patients, HD = haemodialysis, PD = peritoneal dialysis , FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, HHD = home haemodialysis, CAPD = continuous ambulatory peritoneal dialysis, APD = automated peritoneal dialysis, TX = kidney transplantation, n.s. = non-specified, CMA = Cost Minimisation Analysis, CBA = Cost Benefit Analysis, CEA = Cost Effectiveness Analysis, CUA = Cost Utility Analysis, LYG = Life Years Gained, QALY = Quality Adjusted Life Year Gained, PAK = Pancreas after Kidney Transplantation, SPK = simultaneous pancreas and kidney transplantation, TX-CAD = kidney transplantation with cadaver donor organ, TX-LD = kidney transplantation with living-related donor

b 1 = direct healthcare costs (complete), 2 = direct healthcare costs (partially), 3 = direct non-healthcare costs, 4 = indirect non-healthcare costs (productivity costs), 5 = indirect healthcare costs

c 1 = real (opportunity) costs, 2 = charges/tariffs, 3 = unclear, not stated

RRT assessed / type of patients

Not surprisingly, most selected studies concerned the FCHD technique (9/11) and/or renal transplantation (9/11). Four studies included the CAPD technique, while APD was covered in only one study.[25] The majority of studies (8/11) were targeted at all end-stage renal disease patients. Two studies from the same research group were exclusively evaluating available transplantation techniques for diabetic patients.[26 27] One study focused on initiating FCHD for acute renal failure in very ill hospitalised patients.[29]

Study design

Five economic evaluations were conducted alongside a clinical study. These studies were either retrospective[30 33] or prospective[28 29 32] cohort studies. Randomised controlled trials could not be selected for this review, inherent to the fact that to date randomised studies have never been conducted in the field of renal replacement therapies. Six selected studies were model-based economic evaluations, combining data from patient cohorts, literature, national and international patient registries.[23-27 31] Four selected studies applied the CEA format,[23 24 30 33] six studies used the CUA approach,[26-29 31 32] while one study combined the two economic study designs.[25]

Viewpoint

Almost all studies took a healthcare system perspective. Only one study chose a societal perspective[32], although some other authors claimed this perspective too.[24 25 30 31]

Costs incurred and valuation method used for costing

All studies incorporated direct healthcare costs, although not all of them reported on all relevant direct healthcare costs. For instance, only one study reported on healthcare use outside the hospital, such as general practitioners visits and use of community nursing.[25] Some papers lacked own costing studies, but quoted cost data (i.e. charges) from the literature.[26 27 29 30 31 33] None of the studies succeeded in applying the opportunity cost principle for the entire cost study. At best, studies combined the use of charges for some cost categories (i.e. drugs) with the use of a more realistic costing concept for other cost categories, such as dialysis unit staff costs and hospitalisations.[25 32] Indirect non-healthcare costs (productivity costs) were included in only one study, the same study that took a societal perspective.[32] Two studies included indirect healthcare costs, the costs of non-renal medical care in future life years.[25 29]

Valuation of quality of life within CUA approach

Five of the seven CUA studies used patient utilities to calculated Quality Adjusted Life Years.[26 27 29 31 32] Two studies applied utilities from the general population[25 28], and one of these also applied patient utilities in sensitivity analysis.[25]

Discounting

Discounting of costs and benefits was applied in most studies with a time-span longer than one year. However, four studies omitted to discount costs and benefits.[26 27 32 33] In two of these studies, this may have been related to the short time horizon of two years[32 33], but in the other two studies discounting was simply ignored.[26 27] The discount rates applied varied between 3 and 10 percent, but this may be related to differences in timing of the eleven selected studies and cross-country differences in appropriate discount rates.

Incremental analysis

Economic analyses should include an incremental analysis: the additional costs of one programme over another should be related to the additional benefits of that programme. Of the 11 studies selected, 8 have reported such incremental analyses. In general, transplantation programmes were found to be dominant over dialysis programmes, because they provide more effects at less cost. Three studies have only reported average cost-effectiveness figures.

Discussion

Because RRT are expensive, the economic aspects of RRT have received attention from the early beginning in the 1960s[1-4]. This paper points out that few good quality studies have been published. We reviewed 127 studies published in 1988 or later that dealt with economic aspects of renal replacement therapies. Many studies appeared of insufficient methodological quality and were therefore rejected for this review. Only eleven studies of sufficient quality could be identified. To identify these eleven studies, we had to stretch quality criteria in comparison with an earlier review that was prepared by one of the authors[11], dealing with healthcare programmes directed at the prevention of infection with the hepatitis B virus. In this earlier review, studies with an average quality rating ≥ 3 per applicable item (out of a maximum score of 4 per item) were selected, while the current review used a threshold of 2.5 per applicable item. Should the criterion of 3 out of 4 points per applicable item have been used, even less than eleven studies would have been selected. None of the eleven selected studies reached the maximum score in every applicable item, implying that each of the studies selected showed at least one major drawback in the application of standard methodology.

In general, studies appeared especially weak in the costing parts, including lack of discounting and not applying the opportunity cost principle. Many of the studies that were not selected for the review were in fact clinically oriented studies, were some but insufficient economic data were gathered or were some unfounded economic conclusions were drawn. The lack of quality of costing studies in the RRT field was identified recently by other authors16. In other fields of medicine, the paucity of economic research and the scarcity of full economic evaluation studies have also been reported[10-15]. As such, the review's findings in the RRT field fit into a broader picture. However, a general improvement of study methodology in more recently published studies was identified. The majority of studies selected for the current review was published in the last four years. More widespread knowl-

edge on economic evaluation methodology and the introduction of quality standards by journal editors [34] may account for further improvement of economic studies in the near future. As an example, a large number of recent good quality economic evaluations in the field of prevention of progression of end-stage renal disease in diabetes mellitus patients were found. They were excluded for this review but would merit a separate review of these studies.

Although the "main conclusions / main outcomes" column (Table 2) is presented in a league table like format, the ratio's presented in this column can not be compared directly. The ratio's mentioned in this table are compiled directly from the selected studies, but refer to different points in time, different study designs, different sizes of programmes being compared and different healthcare systems in different countries. However, one conclusion that may be drawn is that FCHD was consistently found to be less efficient than CAPD and renal transplantation. Would it therefore be appropriate to conclude that healthcare money could be spend better in the CAPD field than in the FCHD field? It is difficult to arrive at such a conclusion because not all therapies are available for all patients. For instance, renal transplantation is hampered by long waiting lists, and many patients will never receive a transplant at all. Furthermore, the case-mix of each RRT may be entirely different, making it difficult to compare effects of therapy directly over the different RRT. For instance, it is well established that patients who receive a transplant are relatively healthy. Also, patients may have medical or social contra-indications to the use of the more efficient CAPD technique. Besides, the status quo in RRT is that clinicians tend to consider all patients, regardless of age or comorbidity, for the initiation of the less efficient FCHD technique. However, as Hamel and colleagues showed, initiation of dialysis in the frailest elderly, with cost per QALY as high as $ 274,000 is relatively inefficient in comparison with other healthcare provisions.[35] None of the other studies reported cost-effectiveness at the level of subgroups of patients with similar age and comorbid status. Future studies should concentrate on such subgroup analysis, because this adds to the existing knowledge on the relative cost-effectiveness of different RRT.

A further limitation to the interpretation of the cost-effectiveness and cost-utility ratios as shown in Table 2 is that, despite the limited time span of the current review, treatment options in older studies may be incomparable to the same treatment options in more recent studies. Especially on the cost side, older studies may underestimate the cost of therapy, because the techniques of both haemodialysis and peritoneal dialysis have been subject to change over the last 10 years. For instance, new dialysis membranes in haemodialysis and non-dextrose based dialysate solutions in peritoneal dialysis have been introduced. Some of the selected studies were cohort studies published around 1990. The data that were used in these publications often are from the 1980s. The effects of changes in technology or improvements in the management of patients during recent years may not be fully measured by these analyses. For example, the peritonitis rates have dropped following the introduction of the Y-set connection technique for CAPD patients.[36] As a result, hospitalisation rates have dropped, with subsequent consequences for the relative cost-effectiveness of the CAPD technique, compared with other dialysis techniques. In order to eliminate these time effects, we could have limited our review to an even smaller time period, but then the number of good quality studies selected would have been even more limited.

We conclude that the methodological quality of the published economic evaluations is disappointing in general. The quality of future studies to be conducted should be improved by applying basic principles that are widely acknowledged to be standard methodology in this research field[5 7]. Otherwise, the ambition of economic evaluation to serve as a reliable aid in healthcare policy and decision making can not be fulfilled. To guarantee the highest possible level of conduction of health economic studies, skilled health economist should be consulted in an early phase of the design of clinical studies and form part of the research team during the entire study.

Acknowledgement

Wim ten have (Library of the National Institute of Public Health and the Environment) provided access to bibliographic databases.

Appendix 1: Medline search strategy

No.	Records	Request
1	26612	(explode "Hemodialysis"/ all subheadings) in mjme
2	9714	(explode "Peritoneal-Dialysis"/ all subheadings) in mjme
3	1058	(explode "Dialysis"/ all subheadings) in mjme
4	223309	explode "Kidney-Diseases"/ all subheadings
5	22	#3 and #4
6	34230	("Kidney-Transplantation"/ all subheadings) in mjme
7	69306	(explode "Renal-Replacement-Therapy"/ all subheadings) in mjme
8	39565	(explode "Kidney-Failure"/ all subheadings) in mjme
9	952	("Nephrology"/ all subheadings) in mjme
10	97938	#1 or #2 or #5 or #6 or #7 or #8 or #9
11	43803	((renal near transplant*) or (kidney near transplant*) or renal disease* or renal therapy or renal replacement or renal failure or kidney failure) in ti
12	32765	(haemodialysis or hemodialysis or dialysis or (allocation near kidney*) or capd or apd or esrd) in ti
13	73470	#11 or #12
14	64798	explode "Costs-and-Cost-Analysis"/ all subheadings
15	10436	explode "Health-Care-Costs"/ all subheadings
16	37041	(cost* or econom*) in ti
17	80182	#14 or #15 or #16
18	1001	(#10 or #13) and #17
19	1186	#10 or #18

Appendix 2: Checklist to evaluate economic studies

Nr	Items	4	3	2	1	0	N/A [a]
1	Definition of study aim:						
	Does a well-defined question exist?						
	Are the perspective and alternatives compared clearly specified?						
2	Sample selection:						
	Are the types of patients chosen suitable and are they specified?						
	Are the diagnostic criteria adequately specified?						
3	Analysis of alternatives:						
	Are all the relevant alternatives analysed?						
	Is / are the comparison alternative(s) suitable?						
	Is this the most commonly used treatment, or one that will be replaced by the new drug?						
	Is the indication the most relevant one?						
	Are adequate doses used?						
	Are the treatment reproducible (e.g. doses, interval, duration)?						
	Is the "do nothing" option analyzed or should it be analyzed?						
	Is a decision analysis applied?						
4	Analysis of perspective:						
	Is it clearly specified (e.g. society, patient, hospital)?						
	Is it justified for the question asked?						
5	Measurement of benefits:						
	Is it adequate for the question asked and the perspective?						
	Are the data on the effectiveness of alternatives adequately established?						
	Is the main assessment variable (endpoint) objective and relevant?						
	Is the time fixed for the evaluation sufficient and is it specified?						
	Are the results quantified by time?						
6	Measurement of costs:						
	Is it adequate for the question asked and the perspective?						
	Are the costs up to date and are the prices those of the market?						
	Is an adjustment for future costs and benefits performed?						
7	Is this type of analysis suitable?						
	Financial terms: cost/benefit						
	"Physical units": cost-effectiveness						
	Quality of life/utility: cost utility						
	Equal benefits: cost minimisation						
8	Analysis of results:						
	If intermediate variables are used, are they representative of the end benefit?						
	Is a marginal analysis performed?						
	Are the costs and consequences of adverse effects analysed?						
9	Is the evaluation suitable if made within a clinical trial?						
	Is the suitable methodology used?						
	Are the statistical methods used adequate?						
	Is an analysis according to "intention to treat" made?						
	Are costs resulting from the trial, which differ from those in normal practice, taken into account?						

(Appendix II continued)

Nr	Items	4	3	2	1	0	N/A [a]
10	Are the assumptions and limitations of the study discussed?						
	Is a sensitivity analysis performed?						
	Do the assumptions have a bias?						
	Is the execution of any important variable analysed or justified?						
	If intermediate endpoints are assumed, are limitations discussed?						
11	Are possible ethical problems discussed and identified?						
12	Conclusions:						
	Are they justified?						
	Can they be generalised?						
	Can they be extrapolated to daily clinical practice?						
13	Overall impression of the quality of the paper?						

a N/A = not applicable

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Chapter 6

Cost of illness of end stage renal disease in the Netherlands

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Abstract

Objective. To evaluate the cost of illness of end-stage renal disease in the Netherlands in 1994, to evaluate the number of Disability Adjusted Life Years (DALYs) associated with end-stage renal disease, and to predict developments in patient numbers and cost to society until 2003.

Setting. The Netherlands.

Methods. The costs of five dialysis modalities and renal transplantation were estimated using data from a clinical study (NECOSAD-I), data collection in dialysis centres, interviews with 165 patients and published data. Detailed 1994 data on patient numbers and changes between treatment modalities were derived from the Dutch Renal Replacement Registry. Indirect costs were estimated using the friction cost method. DALYs were calculated from death notifications to the Dutch Renal Replacement Registry and estimates of severity of renal disease. Predictions were made using a Markov-chain model. The predictions took account of expected demographic changes and trends in incidence and treatment of renal disease.

Results. In 1994, 7,340 persons were being treated with renal replacement therapy. The cost of renal replacement therapies varied between NLG 18,000 for renal transplantation and NLG 142,000 for centre haemodialysis, per patient per year. Total direct medical cost of care for renal patients were NLG 584 million in 1994, that was about 1 percent of total healthcare spending in that year. Indirect cost amounted to NLG 3.5 million. Renal diseases were associated with a loss of 14,000 DALYs. In 2003, the number of patients in the renal replacement programme will be around 11,500, with expected societal costs of more than NLG 900 million.

Conclusions. Renal insufficiency is a frequent health problem in the Netherlands, associated with a considerable loss of DALYs and high costs to society. Renal disease was not covered in recent health policy documents and underreported in other national studies and healthcare registries because disease classification systems are less suitable to describe diseases with multiple aetiology.

Introduction

According to the data of the Renal Replacement Registry of the Netherlands (Renine), 9243 persons were treated with a form of renal replacement on January 1, 1999 in the Netherlands.[1] Of these patients, about half lives with a functioning donor kidney, the other half is treated with dialysis.[1] Besides patients who have to rely on renal replacement therapy, some estimated tens of thousands of people suffer from reduced renal function. In future, dialysis or transplantation may be necessary for them. Approximately 1300 persons are admitted to the Dutch renal replacement programme annually, be it as a dialysis patient, or after having undergone a successful kidney transplant.[1] A multiplicity of illnesses can cause chronic renal failure. In the Netherlands, hypertension (21 % of new patients) and diabetics (16 % of new patients) are the most frequent causes of kidney failure.[1] In addition, age is a distinct determinant of kidney failure: the occurrence of chronic kidney failure increases from 49 per million in the age category of 0 to 15 years of age to 1290 per million among 65 to 74 year olds.[1]

Dialysis and transplantation are often, in particular in the popular media, described as examples of expensive medical technology. Research in the eighties has shown that, dependent on the form of treatment, dialysis cost NLG 60,000 to NLG 85,000 per patient per year.[2-3] At that time, the costs of kidney transplantation were estimated at NLG 69,000 in the first year after transplantation and NLG 6,200 in later years.[2] The total costs within public healthcare were estimated (1988) at NLG 380 million.[2] This estimate of direct medical costs of care for kidney patients deviates from the assessment of the costs of kidney disease in a study by the Department of Public Health of Erasmus University Rotterdam, in which the costs of all diseases in the Netherlands in 1994 are described in clusters derived from the International Classification of Diseases-9th version.[4] Within the group "Renal and Urogenital Diseases", a sum of 85 million was allocated to the diagnosis group "nephritis/nephrosis/nephropathy", the most obvious diagnosis group for patients with chronic kidney failure. The substantial difference in the two estimates can be explained mainly by the two completely different methods of approach that were used. The estimate of NLG 380 million was arrived at following the "bottom-up" method, the estimate of NLG 85 million was made according to the "top-down" method. The top-down method has an etiologic orientation: costs of medical care are classed as much as possible under the underlying disease, for instance renal care for a patient with diabetic renal failure will be registered under diabetes mellitus. Costs that are primarily made because of additional diseases are accounted for under the additional disease, so as to avoid double counts. In the bottom-up method, in which medical consumption is examined at a patient level, double counts cannot always be avoided.[5] Because chronic kidney failure is not a disease in itself, but a result of damage to the kidneys due to an array of various diseases, kidney patients have remained relatively invisible in the top-down method.

The technique of renal replacement has developed further since the eighties. The aforementioned cost estimates are therefore no longer up to date. Furthermore, in a report from the Health Council of the Netherlands it has been stated that the number of patients with renal replacement will rapidly increase in future years, especially in the older age groups.[6-7] The objective of our research is to determine the current costs of renal replacement

according to the bottom-up method, to estimate the societal costs of end-stage renal disease in 1994 and to make a prognosis of numbers of patients and cost developments for the period 1999-2003, based on demographic and epidemiological developments. In addition, we have made an estimate of the number of Disability Adjusted Life Years (DALYs) in the Dutch population, in order to provide insight in the public health burden of kidney disease and to compare it with the burden of other diseases.

Data and methods

Definitions. Included in the societal costs are the direct costs within and outside public healthcare, the costs resulting from absenteeism and incapacity for work. In this study kidney disease has been defined as the diseases that can lead to the application of renal replacement, such as dialysis and transplantation. 57 different underlying clinical pictures have been defined by the European Dialysis and Transplant Organisation.[8] Because of this divers aetiology, it is not possible to reproduce a defined codification of the International Classification of Diseases.

Patient numbers. Data of the number of patients with renal replacement in 1994, age and type of therapy of these patients and variations of the various therapies were obtained from the Renine Foundation. This registry has a percentage of cover of 100 percent.[9]

The cost research (general remarks). The costs of the five different forms of dialysis were analysed in a detailed cost research, in accordance with the guidelines of the Steering Committee on Future Health Scenario's.[10] Details of the cost research have already been described elsewhere.[11] [12] Three forms of haemodialysis (HD), namely full care centre haemodialysis (FCHD), limited care centre haemodialysis (LCHD) and home haemodialysis (HHD), and two forms of peritoneal dialysis (PD), namely continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), were included in the cost research. In the case of haemodialysis, the blood of the patient is purged of waste products two or three times a week by linking the patient up to an artificial kidney for a few hours. In the case of peritoneal dialysis, the patient himself purges the blood by applying a douche to the abdomen and removing it after a couple of hours. The costs entailed at start of dialysis and the costs of change of therapeutic modality were estimated separately, because of the additional costs of operations, hospitalisation, training of the patients and adjustments to the home.

Direct costs within the public health sector. For the cost research, among others data was used from a prospective study in which 250 new dialysis patients from 13 Dutch dialysis centres were monitored, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD- I).[13] In the Case Record Forms of this study, data was recorded of the use of medical care (hospitalisation and intake of medicine) by the patient. The monitored *hospitalisation* for the duration of NECOSAD (October 1993-December 1996) was itemised per patient group (HD versus PD), per indication (whether or not related to start of dialysis or change of therapeutic modality) and by age (younger than 45 years, 45-64 years of age, 65 and older). For each stratum, the total monitored hospitalisation in days was related to the duration of the follow-up in days, resulting in an estimate of the anticipated hospitalisation degree per patient per year. The costs per day in a hospital (NLG 568) were

taken from a Dutch study from 1996.[14] This cost estimate is exclusive of the costs of diagnostics and laboratory research. We calculated these costs separately (see below). The costs of *medication* were determined in two ways. In NECOSAD the percentage of patients that uses erythropoietin (EPO) was determined. The costs of use of EPO were taken from calculations of the Dialyse Groep Nederland (Dialysis Group of the Netherlands), a cooperation of all Dutch nephrologists (NLG 101 for FCHD, NLG 67.50 for LCHD and HHD, NLG 32 for PD patients, per day). Secondly, detailed information about the use of all other medication was obtained from 111 patients (89 HD and 21 PD patients) at one large dialysis centre. The costs of medication were estimated on an annual basis for each patient, using the recommended daily dose and prices as stated in the Farmacotherapeutisch Kompas.[15] The *labour costs* were calculated with the help of data provided by 13 dialysis centres participating in NECOSAD (2 academic hospitals, 7 general hospitals, 3 centres for active haemodialysis and 1 centre for home dialysis). For every dialysis centre, data concerning the number of haemodialyses performed in 1994, the number of available haemodialysis stations, the number of doctors, nurses (specialised in either HD or PD), social workers, dieticians and technicians, were related to the number of HD and PD patients that were treated in 1994. Thus, the average yearly "production" (number of patients/dialyses) per professional group was determined. For the calculation of the labour costs, the middle of the salary scale most frequently used (Functie Waardering Gezondheidszorg) was taken, including bonuses for irregular hours. Because detailed data concerning labour costs of dialysis centre employees who are not in immediate contact with the patients (e.g. reception, security and administration) were lacking, the staff expenses monitored in 1994 in two active dialysis centres were extrapolated to all other dialysis modalities. In the two centres these labour costs amounted to 20 percent of the total annual labour costs. The costs of equipment that is necessary for centre haemodialysis were obtained from two independent dialysis centres with a separate annual balance. The total costs of inventory, depreciation and maintenance of equipment over 1994 and 1995 were divided by the average number of patients that were treated during these years. The cost of equipment that is only used by one patient (with CAPD, APD and home haemodialysis) was depreciated in seven to ten years, depending on the kind of equipment. From the administrations of five dialysis centres information was gained about the costs of other *medical necessities*, such as artificial kidneys and dialysis fluids. For HD patients, the average cost per haemodialysis was multiplied with the number of dialysis treatments that a NECOSAD patient received on average per year (n=143). For PD patients the average costs per day were determined. The costs of *feeding during* HD treatment were taken from previous research.[16] *Laboratory tests* are performed regularly for dialysis patients. Previous research has shown that the cost of laboratory research differs greatly between dialysis centres.[16] In that study, the annual costs lay between NLG 2,145 and NLG 6,150 per patient. In the current cost estimate the average figure from this previous study (about NLG 4,000) has been included as the annual cost of laboratory tests. There were no observations available on the volume of *diagnostic services*, such as a thorax photo or an electrocardiogram. An approximate estimate of NLG 500 per patient per year was therefore included. Furthermore, 165 patients who participated in NECOSAD were interviewed about their *use of other medical and healthcare services* during the six previous months, so as to gain insight in medical consumption outside the dialysis ward. From patient recalls of such use of medical services over the

last 6 months, the consumption on an annual basis was estimated. Patients were asked how often they had been in contact with the following healthcare workers: general practitioner, social worker, physiotherapist, dietician, medical specialists and other workers to be specified further on. In addition, they were asked about assistance received at home from district nurses, home help, alpha help and other workers to be specified in hours per week. With the Mann-Whitney U test, it was examined whether the differences in medical consumption between HD and PD patients were statistically significant. The costs of medical consumption were determined by multiplying the volumes determined in this study by the tariffs that applied in 1994. To be able to offer a facility such as dialysis, costs are made that are difficult to differentiate to individual patients (*programme costs*), such as energy, cleaning and insurance. These costs have been estimated for haemodialysis patients by dividing the programme costs that were observed in two independent dialysis centres in 1994 and 1995 by the average number of patients that was being treated. For home dialysis, CAPD and APD, data were obtained from one centre that in particular treated these patient groups. Furthermore, certain costs are associated with onset of dialysis and changes in therapeutic modality. At onset of therapy, usually a few *adjustments* will have to be made to the *home* of those patients whose treatment mostly takes place at home, such as installation of electricity and waste outlet. Data concerning these costs were obtained from a centre for home dialysis. Costs of *surgical procedures,* such as the instalment of an appropriate vascular access for HD patients or the placement of a peritoneal catheter for PD patients, were taken from previous research.[17]

Direct costs outside the public health sector. During the interviews the patients were also asked how many kilometres they lived from the dialysis centre and how often and with what kind of means of transport they travelled to the centre. The cost of transport were estimated conform guidelines.[10] Time costs of patients were left aside.

Direct costs of transplantation. The costs of kidney transplantation have not been reassessed within the framework of this costing study, because a recent Dutch study was available.[18] This study estimated the costs in the first year after transplantation at NLG 54,000 exclusive of the costs of the transplantation operation. For the costs of mediation by the Eurotransplant Foundation, the transplantation operation and the post-surgical period until release from the hospital, the current COTG reimbursement rates were used (NLG 18,000). The single costs entailed in a kidney transplant were thus estimated at NLG 72,000. The annual costs of aftercare, including medication, are estimated to be approximately NLG 18,000 per patient.[18]

Total direct costs for kidney patients in 1994. In the estimation of the total costs of care for dialysis and transplantation (i.e. direct costs within and outside the public health sector), the fact that dialysis patients regularly experience changes in therapeutic modality was explicitly taken into account. This is a matter of concern to the cost estimation because variations of therapy involve high costs. The Renal Replacement Registry of the Netherlands provided data about the changes between therapeutic modalities in 1994 and the influx and efflux of patients per type of therapy. For the patients who did not change therapy during the whole year, the average costs per patient per year per dialysis modality were included in the estimation of the total costs of care. For those patients who started with a therapy or

changed therapy in 1994, the related extra costs were added to the average costs per patient per dialysis modality, in addition to which adjustments were made for the part of the year during which the patient was being treated.

Indirect costs outside the public health sector (productivity costs). Two methods of calculation are available for the estimation of the costs of absenteeism and more permanent incapacity to work (productivity costs): the "human capital method" and the "friction cost method". The last method was used in the current study. The friction cost method assumes that in a situation of structural unemployment the costs of absenteeism and incapacity to work are limited to a relatively short period, the so-called friction period. Because a person who up until that time has not been working can replace the sick employee, the costs for society are limited to the costs of absenteeism during the friction period and possibly to the costs of employment agencies and training of the new worker. In 1990 the friction period lasted for 96 days on average.[19] Because the economical climate largely remained unchanged between 1990 and 1994, the assumption was made that the friction period was also 96 days in 1994. To determine the productivity costs, 165 dialysis patients were presented with the Health and Labour Questionnaire during the aforementioned interviews.[20 21] Absenteeism during the weeks prior to the interview was thereby documented in detail. For each patient, absenteeism as a result of kidney disease was related (in hours) to the number of hours that the patient involved would normally work. Thus, an estimate could be made of which part of the absenteeism was related to the kidney disease and which part to other reasons. Absenteeism as a result of other disorders was left aside in this cost estimate. Only absenteeism that occurred during the friction period of 96 days was included in the calculation of productivity costs. A cost estimate was made by multiplying the kidney disease associated absenteeism recorded in the current study, with the 1994 average gross annual pay per sex, including employer's costs.[22 23] To make an estimate of the total costs of productivity losses of Dutch kidney patients, the per sex data from the sample survey were extrapolated to all known kidney patients in the Netherlands younger than 65 years of age.

Disability Adjusted Life Years (DALYs). The number of DALYs associated with kidney disease in the Dutch population was calculated as follows. On request, the Renine Foundation provided data concerning the number of deaths of kidney patients in 1994 and the average age at moment of death. To calculate the number of years of life lost in 1994, the remaining life expectancy at the time of death was calculated per sex from survival tables [24] and aggregated over all deceased kidney patients. The number of years lived with disability was calculated as follows. The 165 dialysis patients who were interviewed each answered the EQ-5D questionnaire to determine their health status.[11] A score system is available for the EQ-5Dprofile to translate the health state to a valuation of the quality of life of the patient.[25] In order to calculate the number of years lived with a disability, the reciprocal value (0.27) of the average valuation of the health state of the dialysis patient (0.73) was taken and multiplied by the average number of dialysis patients in 1994. The number of years lived with a disability of transplantation patients was calculated by multiplying the average number of transplantation patients in 1994 by a weight of 0.10, the reciprocal value of the presumed valuation of the health state of a transplanted patient.[11] The total num-

ber of DALYs related to kidney disease was calculated by aggregating the number of years of life lost and the number of years lived with disability of patients on renal replacement therapy in 1994.

Prognoses. With the help of a Markov chain model,[2 6] prognoses were made for the development of the number of kidney patients and the societal costs of care for these patients in the period between 1999 and 2003. The year 1999 was taken as point of departure because full information was available about patient numbers and types of treatment via the Renal Replacement Registry of the Netherlands (Renine Foundation). In the *Basic scenario* expected developments in demography and incidence are combined. For the calculation of the expected incidence in the period between 1999 and 2003, the trend observed in the period 1989-1998 was continued. This was done separately for three different age categories (0-44 years, 45-64 years, 65 years and older). The annual transition probabilities, the chance that a patient would make a transition from one treatment to another was simulated based on the observed transitions from one treatment to another in the period 1996-1999. To calculate the expected costs in the year 2003, the cost level of 1994 was used, so as to be able to compare both years. In the *IncidencePlus* scenario, the expected extra influx of new patients in the oldest age category (65 and older) has been taken into account.[6 7] In this scenario, additional incidence of 4 percent per year in the oldest age group was assumed, so that the influx of 65 year olds and older would be 20 percent higher after five years, compared to the Basic scenario.

Results

Direct costs within and outside of the public health sector. Table 1 shows the costs of 5 renal replacement therapies, per patient per year, excluding costs of start of therapy and changes between different types of dialysis. The estimated direct costs ranged from NLG 92,000 per year in the case of CAPD to NLG 142,000 per year for full care centre haemodialysis. The other three types of dialysis cost between NLG 111,000 and NLG 123,000 per patient per year. Table 2 shows the additional costs surrounding the start and change of therapy for five dialysis modalities. The single costs of the 5 types of dialysis varied from NLG 7,000 to NLG 15,000 and were the highest in the case of home haemodialysis, because of the necessary adjustments to the home.

Total direct costs of kidney patients in 1994. Table 1 shows the average number of patients in 1994 per type of therapy. Table 2 shows how many patients started dialysis or experienced a change of therapy per type of therapy. Multiplication of numbers of patients and costs per patient resulted in an estimate of the total direct costs of healthcare for kidney patients in 1994 of NLG 584 million, including all costs associated with changes in therapy. An estimated NLG 97 million thereof was related to kidney transplantation, and NLG 487 million regarded dialysis.

Indirect costs outside the public health sector. Of the 165 interviewed patients, 102 were younger that 65 years of age. Of these patients, 38 percent had a paid job, on average for 25 hours a week.

Table 1: Direct costs of renal replacement therapy in 1994 [a], per patient per year in NLG (excluding costs of start and change of therapeutic modality), and number of patients in 1994

Therapeutic modality [b]	FCHD	LCHD	HHD	CAPD	APD
Average number of patients [c]	2,056	516	93	971	132
Direct healthcare costs					
Hospitalisation	9,917	9,917	9,917	11,593	11,593
Medication	16,930	12,651	12,651	12,538	12,538
Personnel costs	47,662	36,473	48,056	19,101	19,101
Equipment	5,500	5,500	10,750	368	10,225
Medical supplies	18,590	16,445	18,590	34,675	54,750
Food	2,000	2,000			
Laboratory research	4,000	4,000	4,000	4,000	4,000
Other diagnostics	500	500	500	500	500
Extramural care	4,550	4,550	4,550	7,370	4,550
Programme costs	10,757	10,757	2,419	2,419	2,419
Direct costs outside healthcare					
Travel costs	22,097	22,097	986	986	986
Total per year	141,505	123,961	111,315	92,165	118,394

a The annual costs after kidney transplantation were estimated at NLG 18,000 per patient. The costs of transplantation were taken from the literature and therefore cannot be reproduced exactly in cost categories. The average number of persons who had a transplant in 1994 was 3,565.
b FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, HHD = home haemodialysis, CAPD = continuous ambulatory peritoneal dialysis, APD = automated peritoneal dialysis
c Data received on request from the Renine Foundation, Rotterdam

Table 2: Direct costs of start of renal replacement therapy and change of therapeutic modality, per patient per episode in NLG, and number of patients involved in 1994 [a b]

Therapeutic modality [c]	FCHD	LCHD	HHD	CAPD	APD
Number of patients [d]	1,242	262	32	588	121
Hospitalisation	4,409	4,409	4,409	5,640	5,640
Adjustments to the home			7,739	967	967
Surgery	2,419	2,419	2,419	1,451	1,451
Total costs at start / change of therapy	6,828	6,828	14,567	8,059	8,059

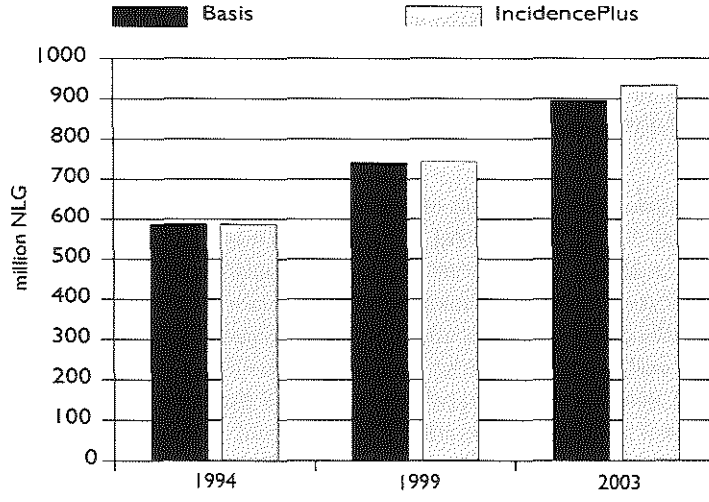
a This concerns patients who first started with a dialysis in 1994 and patients who changed between two types of therapy in 1994. Data concerning numbers of patients were obtained on request from the Renine Foundation, Rotterdam
b The single costs surrounding a kidney transplant were estimated at NLG 72,000 per patient. The costs of transplantation were taken from the literature and can therefore not be reproduced exactly in cost categories. In 1994 450 persons underwent transplantation
c abbreviations: see table 1
d number of patients who started with this therapeutic modality or who changed to this therapeutic modality

Men more often had a paid job (57%) than women (18%). Of the persons with a paid job, 5 persons (13%) had been absent from work because of their kidney disease (on average 2 days in a period of two weeks). An estimate was made that on an annual basis a person was absent for 3.4 percent of working hours because of kidney disease. For a male kidney patient, the cost of productivity loss amounted to NLG 1,820 a year, taking into consideration that the average appointment among working dialysis patients was 0.68 full-time equivalent. For women (part-time factor 0.58 full-time equivalent) the cost of productivity loss was estimated at NLG 1,120 per worker per year. Extrapolation of the kidney disease associated absenteeism found in this study to the Dutch population of kidney patients younger than 65 years of age (2,959 men and 2,166 women) resulted in a cost estimate of absenteeism of kidney patients of approximately NLG 3.5 million in 1994.

Disability Adjusted Life Years (DALYs). In 1994, 886 kidney patients died (531 men and 355 women) at an average age of 67.8 years. The remaining life expectancy of men of that age was 12.65 years, for women it was 16.93 years. As a result of premature death, 12,727 years of life were therefore lost (6,717 regarding men and 6,010 regarding women). In 1994 an average 3,768 patients were dialysed and an average 3,565 patients lived with a donor kidney (see table 1). The number of years lived with a disability for dialysis patients (disability weight 0.27) was 1,017 and for transplantation patients (disability weight 0.10) it was 356. The total number of DALYs of 14,100 is mostly caused by years of life lost (12,727) and to a lesser extent by years lived with a disability (1,373).

Prognoses. On 1 January 1999, some 9,250 patients in the Netherlands received renal replacement therapy. Expectations are that by 1 January 2004 this number will have risen to 11,300 in the basic scenario and to 11,600 in the *IncidencePlus* scenario. Figure 1 shows the expected development in the societal costs of care for kidney patients between 1994 and

Figure 1: Expected increase in health care cost of end stage renal disease patients between 1994 and 2003 in two scenarios (at cost level of 1994)



2003. In 2003 expectations are that the societal costs of care for kidney patients will have risen to around NLG 900 million. In the *IncidencePlus* scenario, that takes an additional influx of approximately 300 over 65 year olds into account, the costs will rise to NLG 934 million.

Discussion

In this study, the direct costs of care for end-stage renal disease patients were estimated at NLG 584 million in 1994. The indirect costs of kidney disease, estimated with the friction cost method, amounted to approximately NLG 3.5 million. In 1994, kidney disease was associated with a loss of about 14,000 DALYs. Prognoses show that as a result of ageing and trends in the influx in the dialysis programme, the intake of additional patients will be approximately 2000 patients up to and including 2003. Expectations are that the societal costs will increase to approximately NLG 900 million.

In 1994, about 1 percent of the total expenditure for healthcare that year (NLG 59.4 thousand million) was spent on end-stage renal disease treatment. It comes as no surprise that renal replacement, dialysis in particular, is expensive. In the eighties, Dutch researchers estimated dialysis costs at around NLG 60,000 to NLG 85,000 per patient per year.[2 3] The current cost estimate exceeds that by approximately NLG 30,000 to NLG 60,000, depending on the type of dialysis. However, the cost per dialysis remained roughly the same, as the cost per dialysis treatment in 1994 (NLG 593) is almost similar to the cost per treatment in 1983 (NLG 467 [2]), adjusted for the cost development in the public health sector between 1983 and 1994 (NLG 580).[26] The NLG 30,000 to NLG 60,0000 cost difference can mainly be accounted for by high travelling expenses, which were not included in previous research, the introduction of erythropoietin and the increased dialysis frequency. The travelling expenses of dialysis patients who dialyse in a centre amount to about NLG 20,000 a year, because the majority of the patients travel to the dialysis centre by taxi. Erythropoietin is an expensive medicine (NLG 8,700 - NLG 13,000 per patient per year) which stimulates the production of red blood cells in kidney patients and which is used by upwards of 80% of all dialysis patients. A further factor associated with the increase in costs is the fact that the average frequency of haemodialysis has risen since the eighties from more than two times per week (115 dialyses per patient per year) to nearly three times a week (143 dialyses per patient per year).

The indirect non-healthcare costs, costs of production losses as a result of absenteeism, were estimated at NLG 3.5 million in 1994. This estimate was arrived at by the extrapolation of observations in dialysis patients to the entire population of kidney patients. It is possible that this estimate is an underestimation of the actual costs, because the study population concerned stable dialysis patients and a lot of absenteeism takes place at the onset of renal replacement and during change of therapy. On the other hand, measurements in dialysis patients could also have led to an overestimation of the costs, because the percentage of active employees may be higher among transplanted patients than under dialysis patients. However, no data on this subject was available. Because the indirect non-healthcare costs form a small part of the total societal costs in comparison with the direct medical costs, the influence of an overestimation or underestimation of the productivity costs

on the total societal costs will not be substantial. However, our decision to value the productivity loss with the friction cost method rather than the human capital method has sincerely influenced our results. We have chosen this method because we believe that the friction cost method does more justice to the situation of structural unemployment seen on the Dutch labour market in 1994, than the human capital method. In our study, the indirect costs only form 0.6 percent of the total costs. Many kidney patients no longer have a paid job at the moment they start with renal replacement therapy. Of the population of dialysis patients interviewed by us, 41% had been declared wholly or partially disabled. The monetary value of absenteeism and the lifelong production losses of around 5,000 kidney patients in working life would certainly amount to a few hundred million guilders. According to the human capital method our estimate of societal costs would turn out to be much higher.

The current estimate of direct costs of care for kidney patients strongly deviates from the estimated costs of kidney disease in the report "Costs of Illness in the Netherlands, 1994" (further to be called iMGZ report).[4] In that estimate the total costs for the diagnostic group "nephritis / nephrosis / nephropathy" were NLG 85 million. This estimate includes kidney patients not yet dependent on renal replacement therapy. There are two ways to explain the large difference. Firstly, the hospital costs in the iMGZ report were analysed using admittance data from the Landelijke Medische Registratie (LMR), in which dialysis hardly occurs.[4] Secondly, the iMGZ report has an etiologic orientation: costs of care are classed as much as possible under the disease that lies at the root of the care so as to avoid double counts. Costs of kidney disease as a result of diabetes are therefore accounted for under diabetes. For a group of disorders with multiple aetiology, such as kidney disease, the iMGZ report therefore gives an underestimation of the actual costs. The discrepancy between both cost estimates is even more marked if it is taken into account that there is another group of a couple of ten thousand patients with limited kidney functioning, who in the future may need dialysis or transplantation (the so-called pre-dialysis patients).[27] Our bottom-up cost estimate only relates to those kidney patients who have reached the final stages of the disease and not to pre-dialysis patients. The costs for the care of predialysis patients, the indirect costs as a result of production losses and DALYs of this group have not been included in this paper due to a lack of available data. Fact is that our cost estimate of NLG 587 million would be much higher if these patients in the preliminary stages of renal insufficiency had been included in our calculations too.

The substantial differences between the costs of the various forms of dialysis and transplantation leads one to suspect that a policy aimed at substitution of patients from more expensive to cheaper types of treatment would be advisable. In a cost-effectiveness analysis, we demonstrated that such a policy only has a limited influence on the total costs of the renal replacement programme of the Netherlands.[11] By substituting patients from more expensive types of therapy such as centre haemodialysis to cheaper forms of therapy such as CAPD and kidney transplantation, more changes of therapy are induced overall. The savings resulting from substitution hardly weigh up to the additional costs of changes of therapy. The segmentation of patients over the various types of therapy is already reasonably optimal in the Netherlands, in a sense that patients that qualify for the use of less expensive types of therapy are already being treated with these modalities.

It is our opinion that far more attention should be paid to the secondary prevention of renal disease. The deterioration of the kidney function can be delayed in patients with a kidney disorder, among others by better control of hypertension, low-protein foods and the use of specific medication such as angiotensin-convertin enzyme (ACE)-inhibitors.[28 29] According to model calculations, dialysis and transplantation could be delayed for 5.8 years for insulin dependent diabetics who receive an intense treatment, in comparison with patients who receive a conventional treatment.[30] The feasibility of the realisation of results of such modelling studies in clinical practice should be object of further research.

The number of DALYs calculated by us, 14,000, indicates that the public health burden of kidney disease is substantial. In the Volksgezondheid Toekomst Verkenning (Public Health Status and Forecasts (PHSF)), which was published in 1997, the "burden of disease" of a large number of diseases and disorders was estimated.[31] The number of DALYs for kidney disease is of the same order of the number of DALYs associated with diseases as AIDS, Parkinson's disease, influenza and schizophrenia. Despite the high costs and the substantial burden of disease, kidney disease has hardly been visible in important research and policy documents, such as the iMGZ report,[4] and the Public Health Status and Forecasts.[31 32] In the 1993 and 1997 Public Health Status and Forecasts reports, diseases and disorders were predominantly selected based on mortality burden, disease burden, costs of disease and prevention possibilities.[31 32] Kidney disease was not selected as a subject for the PHSF, which illustrates the previously described invisibility of kidney disease in the various healthcare registrations and the fact that kidney disease is spread over several ICD-9 chapters. We conclude that a classification system such as ICD, entirely orientated towards the aetiology of diseases, is not suitable to classify diseases with multiple aetiology. In future versions of the ICD, kidney disease should not only be included in the diagnostic group "renal and urogenital diseases", but also incorporated as a complication of disorders in other chapters.

In the Netherlands, the prioritising of healthcare research on the basis of societal relevance has received a lot of attention over the past years.[33] The Advisory Council on Health Research, the Healthcare Insurance Board and the Council for Medical and Health Research all reflected on the selection of research subjects for the near future. Kidney diseases could hardly be found in these initiatives either. In this article, we have shown that kidney disease can lead to high societal costs and to a substantial burden of disease. As van Roijen en Rutten rightly remarked in an article in this journal,[34] this cannot in itself be a legitimisation to spend more healthcare resources for the prevention and treatment of kidney patients. The results of our study can however be helpful in establishing priorities in fundamental and applied studies. Kidney disease certainly deserves to be a subject of such studies.

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Chapter 7

Economic evaluation of End Stage Renal Disease Treatment

De Wit GA, Ramsteijn PG, de Charro FTh. Economic evaluation of end-stage renal disease treatment. Health Pol 1998; 44: 215-232.

Abstract

This paper examines the cost-effectiveness of end-stage renal disease (ESRD) treatments. Empirical data on costs of treatment modalities and quality of life of patients were gathered alongside a clinical trial and combined with data on patient and technique survival from the Dutch Renal Replacement Registry. A Markov-chain model, based on the actual Dutch ESRD program as of January 1st 1997, predicted the cost-effectiveness and cost-utility of dialysis and transplantation over the 5-year period 1997-2001. Total annual costs amounted to NLG 650 million (1.1 % of the healthcare budget). Full care centre haemodialysis was found to be the least cost-effective treatment, while transplantation and Continuous Ambulatory Peritoneal Dialysis were the most cost-effective treatments. The Markov-chain model was used to study the influence of substitutive policies on the overall cost-effectiveness of the ESRD treatment program. The influence of such policies was found to be modest in the Dutch context, where a high percentage of patients is already being treated with more cost-effective treatment modalities. In countries where full care centre haemodialysis is still the only or the major treatment option for ESRD patients, substitutive policies might have a more substantial impact on cost-effectiveness of ESRD treatment.

Introduction

Six major treatment modalities for patients with end-stage renal disease (ESRD) may be distinguished. Haemodialysis (HD), the cleaning of the blood from waste products through an artificial kidney, was introduced in 1960.[1] Haemodialysis can either be performed by the patient at home (home haemodialysis - HHD), or in a dialysis centre or hospital, with more (limited care haemodialysis - LCHD) or less active (full care centre haemodialysis - FCHD) input of the patient in the treatment. Kidney transplantation (TX) with non-related donor organs has been possible since 1962 and eliminates the necessity of dialysis as long as the graft is not irreversibly rejected by the recipient.[2] Peritoneal dialysis (PD), the removal of waste products through a cleaning fluid in the abdominal cavity, became clinically available in the late 1970s.[3] PD has two main treatment varieties, either with manual exchange of dialysis fluid (continuous ambulatory peritoneal dialysis - CAPD) or with automated exchange of dialysis fluid at night (automated peritoneal dialysis - APD).

Although many publications have considered the cost-effectiveness of ESRD treatment, few published studies were based on empirical data with regard to costs of treatment, survival and quality of life of patients. Most studies combined empirical data in one of these fields with literature-based evidence or estimations in the other fields.[4-11] One published cost-effectiveness analysis included utilities elicited from ESRD patients.[12] Most studies that have considered two or more treatment options for ESRD patients described a hierarchy in the cost-effectiveness of treatments. Kidney transplantation is described as having the best ratio between costs and effects of treatment, followed by either HHD or CAPD.[8-10] Most studies reported that haemodialysis, especially when the patient does not contribute actively to the treatment (FCHD), resulted in the highest cost per life year gained.[6-11 13] To the best of our knowledge, the cost-effectiveness of the more recently (1980s) developed technique of APD has not previously been studied.

We performed a cost-effectiveness analysis of ESRD treatments, alongside a clinical study on the adequacy of dialysis (the NECOSAD study). We collected empirical data on costs of treatment and quality of life and combined these with data on patient and technique survival from the Renal Replacement Registry of the Netherlands (RENINE).[14] A Markov-chain model was used to assess the cost-effectiveness and cost-utility of treatment modalities over a period of 5 years. We also used the Markov-chain model to estimate the costs of the ESRD treatment program nation-wide and to evaluate the influence of substitution between therapeutic modalities on the estimated societal costs and cost-effectiveness of the Dutch ESRD program.

Subjects and methods

The NECOSAD study

This cost-effectiveness analysis was performed alongside a clinical study on the adequacy of dialysis treatments, the NECOSAD study.[15] Thirteen Dutch dialysis centres (27 % of all centres) consecutively included all new dialysis patients who began treatment between

October 1993 and April 1995 in the NECOSAD study. Data for the cost-effectiveness analysis were gathered between October 1993 and December 1996.

Quality of life assessments

We interviewed 165 dialysis patients, of whom 135 participated in the NECOSAD study. It was known at the onset of the present study that only a few patients in the NECOSAD study were being treated with APD. Therefore, 30 extra APD patients were recruited from three hospitals with high numbers of APD patients. The Medical Ethical Committees of all 16 hospitals involved in the study approved the study. Inclusion criteria for participation in the quality of life interviews were: age above 18 years, written informed consent from the patient, the same treatment for at least 3 months, adequate eyesight to enable the completion of questionnaires and an adequate understanding of the Dutch language. Trained interviewers interviewed patients at home. Demographic data and data on number and type of comorbid diseases were collected at the interview. Quality of life of patients was assessed with the following instruments: EuroQol (EQ-5D) Instrument,[16 17] Standard Gamble,[18] and Time Trade Off.[19] The last two methods are preference based measurements, allowing the expression of quality of life as a single indicator, usually a number between 0 and 1, with 0 representing death and 1 representing full health. This single indicator can be used for the calculation of (cost per) Quality Adjusted Life Year (QALY). It is well-known that patients who actually experience an impaired health state value their own health state higher than healthy persons without experience of the disease.[20 21] In addition to the valuations elicited from ESRD patients, we applied data from a UK population sample on the valuation of health states [22 23] to the health status as described by ESRD patients in the present study. Therefore, we could dispose of both patient and general population valuations of the patients' health states. Differences between treatment groups have been tested by means of One Way Analysis of Variance, Pearson Chi-square test and Kruskall-Wallis test (where appropriate). A P-value of 0.05 was chosen as cut off for statistical significance.

The assessment of quality of life of transplanted patients fell outside the scope of this study. There were no published Standard Gamble or Time Trade Off scores from transplanted Dutch patients available to enable comparison with the scores of dialysis patients. Studies have shown that quality of life of transplanted patients is close to the quality of life as found in the general population.[24-25] A recent study found a 23 percent increase in Time Trade Off scores in dialysis patients who had received a successful kidney transplant.[12] Based on these studies, and in comparison with the valuations we found for dialysis patients (see results section) we have assumed a quality of life factor for transplanted patients of 0.90. The influence of this assumption was tested in sensitivity analyses.

Costs of treatment

The costing study was designed to include the total costs of care for dialysis patients, including both dialysis-related and other healthcare costs. We have distinguished costs in the first year of treatment, including extra costs at start of treatment, such as hospitalisations, vascular access operations and training of patients, from costs in second and later years of treatment. In general, resource use was valued at real costs, not charges. A societal perspective was taken for the cost-analysis. Time costs and indirect costs resulting from work

loss and inefficiency at work have not been included in this study. Costs were calculated at a 1996 price level. Costs will be expressed in Dutch Guilders (1 NLG = £ 0.31, 1 NLG = $ 0.50, conversion rates September 1997).

Data on volumes of resource use, including hospitalisations and use of medication, were obtained from the NECOSAD study. All registered hospitalisations in the study period were related to the total length of follow-up (the hospitalisation rate). Therefore, costs of hospitalisation were based on a calculation of hospital days per patient year at aggregate level. Hospitalisation is strongly related to the age of the patient.[26] We calculated the costs of hospitalisations separately for 3 age groups: 0-44 years, 45-64 years and 65 and older. If patients experienced a transition from one therapy to another, the hospitalisation in the first month after the change was attributed to the old treatment modality. Such hospitalisations are assumed to be associated with the failure of the old therapy and not with the start of the new therapy.[27] The costs of one day in hospital were taken from a recent Dutch study.[28]

Data on the work force in dialysis centres were gathered by means of a questionnaire sent to centres participating in the NECOSAD study. Labour costs were calculated using medium salaries from the gross salary scales for healthcare organisations. Nephrologists services were costed on the basis of the reimbursement rate of NLG 7,640 per patient per year, after correction for differences in time spent on patients in different treatment modalities. Costs of staff not directly working with patients, such as reception, safety and administration, were obtained from two independent dialysis centres. Costs of materials, equipment, meals, housing and energy were obtained from the cost-accounting systems of five of the sixteen dialysis centres participating. Recent data (1995) on the annual costs of laboratory services for dialysis patients were available from a study performed in 4 Dutch hospitals.[29] The annual costs of diagnostic services were estimated from standard protocols of the Dutch Organisation of Nephrologists. The costs of vascular access surgery were taken from a recent Dutch study.[30] Data on resource use outside the hospital and dialysis centre (primary care services) were obtained directly from patients at the quality of life interviews. The National Association for Home Care provided actual cost data of primary care. Travel distance and frequency of travelling from and to hospital and dialysis centres was covered at the patient interview. Travel costs were based on reimbursement rate (taxi rides) or valued at a level acceptable under Dutch tax laws (own transport). The costs of transplantation fell outside the scope of this study. A recent Dutch clinical trial documented costs after transplantation in 127 patients who received a renal transplant.[31] The costs of Eurotransplant and the cost of the transplantation operation, based on the reimbursement level, were added to the cost figures from that study. Total costs were estimated to be NLG 90,000 in the first year and NLG 18,000 in second and later years after transplantation.

Markov-chain model

A Markov-chain describes the dynamics in a population that is divided over a number of states and can be used to predict patient numbers in those states in the (near) future.[32 33] A Markov-chain is a discrete statistical process in which the future distribution of the population over the states depends on the present distribution, transition probabilities from one state to another and the inflow of new patients. Markov-chains have been used to predict resource requirements in renal units,[34] for regional planning of ESRD facilities [35] and to

assess the cost-effectiveness of immunosuppressive regimens after transplantation.[36] The actual patient numbers in the Dutch ESRD program as of 1st of January 1997 were used as a starting-point. Predictions were made for a period of 5 years (1997-2001). For a more detailed description of the Markov-process, see the Appendix.

Approximately 8300 patients were receiving ESRD treatment on January 1st 1997, equally divided between dialysis and transplantation.[37] In the Markov-model, 36 different states have been defined (combinations of 6 treatment modalities, 3 age-groups and 2 treatment stages). The 6 treatment modalities were FCHD, LCHD, HHD, CAPD, APD and TX. Patients were divided into three age-groups: 0-44 years, 45-64 years, and 65 years and older. Within each treatment two stages were distinguished: the first year versus the second and later years on the same treatment modality. Two irreversible states, death and recovery of kidney function, were added to the model. Patients who returned to dialysis after recovery of kidney function were regarded as new patients.

The matrix of transition probabilities was constructed based on the actual treatment histories of all patients in the Dutch Renal Replacement Registry between 1994 and 1996 (n=11,192). This registry covers all Dutch ESRD patients.[14] Death rates and technique failure rates, related to the necessity to change therapy because of irreversible problems, were incorporated in this matrix of transition probabilities. The expected inflow of new patients into the ESRD program is both dependent on the incidence of ESRD in the three age-groups and on demographic developments. A simple linear regression analysis with time as the independent variable showed that the inflow of new patients per million population over the 10-year period 1987-1996 increased significantly ($t > 2.34$, $df = 8$) in all 3 age-groups. These linear trends were extrapolated to the period 1997-2001. Figures on expected population numbers were derived from Statistics Netherlands.[38] The distribution of new patients over the 6 treatment modalities reflected the actual experience in the Dutch ESRD program between 1994 and 1996. The linear trend in the number of transplantations performed between 1987 and 1996 was also significant ($t = 7.22$, $df = 8$) and therefore extrapolated to the period 1997-2001.

The Base-case Markov-chain model that predicts future patient numbers in the 36 defined states was supplemented with information on costs of treatments and quality of life of patients in different treatment regimens. The cost per life year gained was calculated as total discounted costs over the 5 year period related to total discounted life years gained (see Appendix). The cost per Quality Adjusted Life Year (QALY) gained was calculated similarly. A discount rate of 5 percent was used, both for costs and effects of therapy. Box 1 summarises the input into the Base-case Markov-chain model.

Box 1: Input in Base-case Markov-chain model

- Period of prognosis: 1997-2001
- Patient population at start: Dutch ESRD population as at 1.1.1997
- Inflow of new patients in 3 age-groups: extrapolation of linear trend over period 1987-1996
- Population prognoses 1997-2001: estimates from Statistics Netherlands
- Division of new patients over six treatment modalities: as observed 1994-1996
- Number of transplantations per million population: extrapolation of linear trend over 1987-1996
- Division over five dialysis modalities after rejection of graft: as observed 1994-1996
- Transition probabilities: calculated with data of 11,192 prevalent ESRD patients in period 1994-1996
- Discount rate: 5%
- Cost of treatments in 1st and 2nd and following years: estimates from costing study
- Quality of life: $EQ\text{-}5D_{index}$ values as estimated from UK population sample [23]

Sensitivity analyses / Scenario-analyses

Several one-way sensitivity analyses were performed to assess the stability of the conclusions derived from the Base-case scenario. The Markov-chain model was used to study the predicted cost per QALY if quality of life valuations from different perspectives (patient versus general population) were incorporated in the model. The model was also used to explore several scenarios for cost reduction, such as substitution of patients to less expensive modalities.

Results

Quality of life

Table 1 lists the main patient characteristics of the treatment groups, average Standard Gamble scores, Time Trade Off scores and $EQ\text{-}5D_{VAS}$ scores, and general population values for the ESRD patients' health states. Because the number of HHD patients in the present study was very small (n=5) we have pooled the HHD and LCHD groups. Both treat-

Table 1: Main patient characteristics (mean, (SD) or %) according to treatment modality, quality of life outcomes and general population valuation for ESRD patients' health states

	FCHD group [a] (n=46)	LCHD group [a] (n=23) [b]	CAPD group [a] (n=59)	APD group [a] (n=37)
Age [c]	67 (9)	47 (15)	56 (13)	55 (13)
Male (%)	50	57	69	49
No. of comorbid diseases	2.6 (1.9)	1.9 (1.2)	2.6 (1.9)	2.3 (1.6)
Months on dialysis	15 (4)	15 (3)	15 (4)	15 (8)
Patient SG score	0.84 (0.21)	0.91 (0.13)	0.81 (0.24)	0.74 (0.24)
Patient TTO score	0.87 (0.20)	0.93 (0.11)	0.86 (0.23)	0.93 (0.14)
EQ-5DVAS [d]	0.58 (0.19)	0.65 (0.14)	0.61 (0.20)	0.61 (0.19)
General population valuation [e f]	0.66 (0.29)	0.81 (0.24)	0.71 (0.29)	0.81 (0.19)

a FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, CAPD = continuous cycling peritoneal dialysis, APD = automated peritoneal dialysis
b including 5 HHD patients
c $p < 0.01$
d divided by 100
e according to Dolan [23]
f $p < 0.05$

ments require active patient participation. Table 1 shows that the four treatment groups (FCHD, LCHD/HHD, CAPD, APD) were comparable with regard to sex, time on dialysis and number of comorbid diseases. LCHD/HHD patients were younger on average than patients treated with other dialysis modalities. Patients' SG, TTO and EQ-5DVAS scores were not statistically different across the four treatment groups, indicating that quality of life of patients in the four treatment groups was comparable. The general population valuations of the patients' health states were significantly higher for APD and LCHD/HHD patients (0.81) than for CAPD (0.71) and FCHD patients (0.66). The ranking of the quality of life of patients in the four treatment groups appeared to differ depending on the perspective (patient / general population) and valuation method. For instance, APD patients' TTO scores were equal to or higher than other groups' TTO scores, while APD patients' SG scores were lower than other groups' SG scores. Because of the somewhat conflicting results of quality of life measurements and because valuations derived from the general population are considered most appropriate in a cost-effectiveness analysis,[39] we decided to incorporate the general population valuations in the Base-case scenario and to apply patient valuations in sensitivity analyses.

Costs of treatment

Table 2 shows the results of the costing study. The start of PD treatment (CAPD and APD) was associated with higher hospitalisation costs than start of HD treatment, because approximately half of the PD patients received a clinical training to perform the fluid exchanges themselves. The average duration of hospitalisation at start of dialysis was 8.5 days. PD patients were hospitalised for 10.0 days and HD patients for 7.8 days on average. Patients in the oldest age group were hospitalised 3 more days at start of therapy than patients in the youngest age group. Patients who started with HHD therapy experienced

Table 2: Results of costing study (all figures in NLG)

	Haemodialysis			Peritoneal Dialysis	
	FCHD [a]	LCHD [a]	HHD [a]	CAPD [a]	APD [a]
Costs associated with start/change of therapy					
Hospitalisation at start of dialysis					
age < 45	2711	2711	2711	3733	3733
age 45-64	3047	3047	3047	5036	5036
age ≥ 65	6030	6030	6030	9003	9003
Surgery at start dialysis	2500	2500	2500	1500	1500
Housing adaptations			8000	1000	1000
Annual costs, excluding costs at start/change of therapy					
Total staff cost	49237	37671	49644	19714	19714
Total material cost	26090	23945	29340	35043	64975
Cost of hospital infrastructure	11120	11120	2500	2500	2500
Hospitalisation					
age < 45	7606	7606	7606	4385	4385
age 45-64	7918	7918	7918	10497	10497
age ≥ 65	12519	12519	12519	20380	20380
Laboratory services	4000	4000	4000	4000	4000
Other healthcare services	4550	4550	4550	7370	4550
Diagnostic services	500	500	500	500	500
Drugs	17501	13077	13077	12960	12960
Travel cost	22842	22842	1019	1019	1019

a FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, HHD = home haemodialysis, CAPD = continuous cycling peritoneal dialysis, APD = automated peritoneal dialysis

higher initial costs than other patient groups, because adaptation of water and electrical supplies at home was required.

Table 2 also shows the breakdown of the annual costs of treatment of five dialysis modalities. Staff costs were higher for any form of haemodialysis than for CAPD and APD. The average nurse to patient ratio was 1 to 2.29 for FCHD, 1 to 3.61 for LCHD and 1 to 13 for CAPD and APD. Nursing costs for HHD patients were high because patients received assistance from a nurse at home. Costs of equipment were found to be higher for HHD and APD patients, reflecting the fact that equipment at home is not shared among patients. Costs of medical supplies, such as dialysis fluids and disposables were higher for PD patients, especially APD, than for HD patients. Costs of infrastructure, such as housing, energy and cleaning were higher for LCHD and FCHD patients than for the three treatment modalities performed by patients at home. The use of primary care healthcare services was not significantly different across patient groups, with the exception of a higher use of district nurses by CAPD patients. It was found that 5 percent of CAPD patients needed the assistance of district nurses at the exchange of dialysis fluids. The higher costs of medications for FCHD patients were mainly associated with a higher use of Erythropoietin (EPO). Travel costs of FCHD and LCHD patients were higher than travel costs of other patients, reflecting the fact that these patients were transported to and from the dialysis centre by taxi. Cost differences between treatment modalities were also associated with differences in hospitalisation. The annual number of hospital days was highest in patients of

older age (average number of days in hospital per patient year 10, 16 and 27 for patients in the youngest, intermediate and oldest age-groups, respectively). PD patients were hospitalised more often than HD patients (20.5 days versus 17.5 days per patient year, respectively). This reflects a higher technique failure among PD patients.

Table 3 presents the cost figures that were entered into the Base-case scenario of the Markov-chain model, distinguished into three age-groups and two stages of treatment. The cost figures for the first year result from summing both the annual costs and costs associated with start and change of therapy. Average annual costs ranged from NLG 18,000 for transplantation to NLG 95,000 for CAPD to NLG 146,000 for FCHD. Annual costs of HHD, APD and LCHD varied from NLG 115,000 to NLG 128,000. This implies that the annual costs of the most expensive dialysis therapy (FCHD) were 50 percent higher than annual costs of the least expensive dialysis therapy (CAPD).

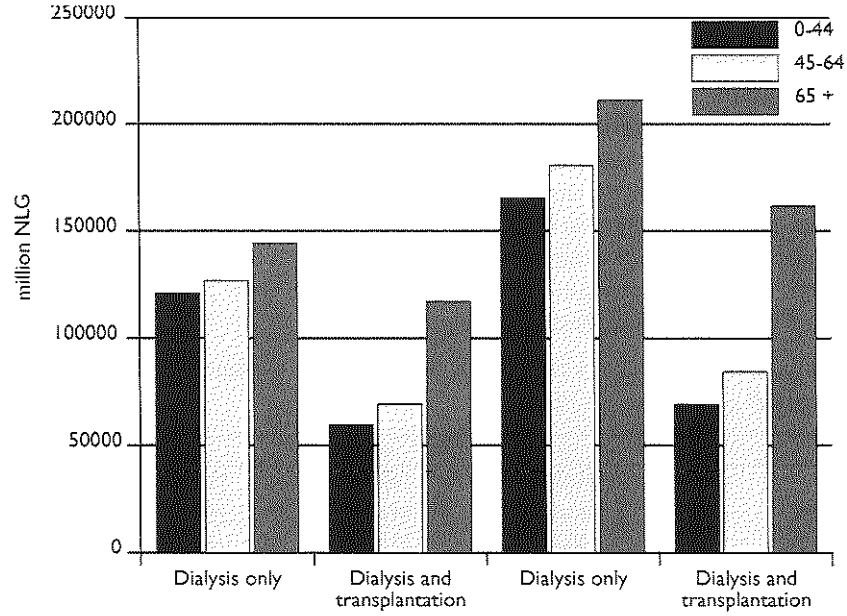
Table 3: Total cost of treatment in first versus later years, by treatment modality and age-groups (all cost figures in NLG)

	0-44	45-64	65+	average
FCHD year 1	148,700	149,300	156,900	152,666
FCHD later years	143,400	143,800	148,400	145,757
LCHD year 1	130,500	131,200	138,800	134,531
LCHD later years	125,300	125,600	130,200	127,622
HHD year 1	125,500	126,100	133,700	129,456
HHD later years	112,300	112,600	117,200	114,547
CAPD year 1	93,700	101,100	115,000	102,839
CAPD later years	87,500	93,600	103,500	94,699
APD year 1	120,800	128,300	142,100	129,951
APD later years	114,600	120,700	130,600	121,811
Transplantation year 1	90,000	90,000	90,000	90,000
Transplantation later years	18,000	18,000	18,000	18,000

Cost per life-year gained and cost per quality-adjusted life year gained

The predicted average cost per life year gained of all ESRD treatments over the 5-year period 1997-2001 was NLG 78,700, the predicted average cost per QALY was NLG 98,300. These predictions reflect the current and anticipated distribution of patients over the cheaper (transplantation) and more expensive (dialysis) treatments. The average cost per life year gained for the five dialysis modalities only was estimated to be NLG 133,100, versus NLG 25,000 for transplantation. The predicted cost per QALY was NLG 190,000 for dialysis and NLG 27,800 for transplantation. Figure 1 shows remarkable differences in cost per life year gained and cost per QALY for the 3 age-groups, reflecting the use of cheaper treatments (transplantation and CAPD) in the younger age groups and more expensive treatment (FCHD) in the oldest age group. Among the different dialysis modalities, the ratio of costs to life years gained and costs to QALY's was most favourable for CAPD and least favourable for FCHD, with intermediate positions for LCHD, HHD and APD. The estimated discounted costs of the Dutch ESRD treatment program over the 5 year period 1997-2001 were NLG 3.24 billion. This approximated an annual equivalent of NLG 650 million.

Figure 1: Cost per life year gained (two left sets of bars) and cost per QALY (two right sets of bars), according to three age groups – Base-case scenario



Sensitivity analyses / Scenario analyses

The Markov-chain model was run with the following deviations from the Base-case scenario:

1. ESRD patients' Standard Gamble valuations instead of societal valuations;
2. ESRD patients' Time Trade Off valuations instead of societal valuations;
3. Quality of life after transplantation not better than but equal to dialysis (QALY factor of 0.81 instead of 0.90);
4. Assuming a higher number of transplantations, from a current 30 transplantations per million population [40] to 38 per million population. This is due to take effect in 1998, when new donor legislation will be introduced.[41] This scenario resulted in 273 (= 10 %) more transplantations over the 1998-2001 period than in the Base-case scenario;
5. Assuming a level of 44 transplantations per million population, starting from 1998. This scenario resulted in 651 (= 25 %) extra transplantations compared to the Base-case scenario;
6. Assuming that 10 percent of the patients who start with the more expensive FCHD modality in the Base-case scenario will be able to start with LCHD;
7. Assuming a shift of 20 percent of new FCHD patients to LCHD;
8. Assuming a shift of 10 percent of new FCHD patients to CAPD;
9. Assuming a shift of 20 percent of new FCHD patients to CAPD;
10. Assuming a shift of 10 percent of new FCHD patients to APD;
11. Assuming a shift of 20 percent of new FCHD patients to APD.

The outcomes of the 11 scenarios are shown in Table 4. Because patients' valuations of health status were higher than general population valuations, the different quality of life indicators incorporated in the sensitivity analyses appeared to have a large influence on the cost per QALY. The introduction of patient Standard Gamble scores and Time Trade Off scores in the model resulted in an average reduction of the cost per QALY of NLG 10,300 (10.5%) and NLG 12,000 (12.2%), respectively. The Base-Case assumption that quality of life of TX patients is better than quality of life of dialysis patients was also found to influence cost per QALY. Scenario 3 showed a 6% increase in cost per QALY on the assumption that TX quality of life equals quality of life of dialysis patients. The number of transplantations per million population was found to have some influence on the total societal costs of the ESRD treatment program, as well as on cost per life year gained and cost per QALY. In a scenario with an increase in the annual number of transplants to the European maximum of 44 transplantations per million population,[40] the total societal costs over the 5 year period were reduced by 1.82% (NLG 59.3 million). In comparison with the Base-case scenario, the cost per life year gained was reduced by 2.06% (NLG 1,627) and the cost per QALY by 2.53% (NLG 2,491). The CAPD stimulating scenarios (scenarios 7 and 8) were found to dominate the Base-case scenario with less costs and better outcomes. In general, the influence of policies to substitute patients from more expensive treatment modalities (FCHD) to less expensive modalities (LCHD, CAPD and APD) was found to be small. In all six substitutive scenarios, the cost per life year gained was reduced by no more than 1 percent. The cost per QALY decreased by no more than 1.06 percent. The LCHD stimulating scenarios even resulted in higher societal costs and slightly higher cost per life year gained.

Table 4: Outcomes of the different scenarios over the 5 year period 1997-2001 (cost figures in NLG)

Scenario [a]	Δ Total costs	Δ Life-years gained	Δ QALY's gained	Δ Cost per life year gained	Δ Cost per QALY
Base-case-scenario	3,240,312,000	41149	32955	78,745	98,323
1. Patient SG valuations	-	-	+ 3864	-	- 10,318
2. Patient TTO valuations	-	-	+ 4583	-	- 12,004
3. TX quality of life = dialysis quality of life	-	-	- 1862	-	+ 5,891
4. 38 TX per million population	- 25,531,800	+43	+102	- 702	- 1076
5. 44 TX per million population	- 59,267,900	+100	+238	- 1627	- 2491
6. 10 % of new FCHD patients to LCHD	+ 12,694,500	+140	+168	+ 40	- 116
7. 20 % of new FCHD patients to LCHD	+ 25,402,900	+281	+337	+ 79	- 231
8. 10 % of new FCHD patients to CAPD	- 9,421,100	+85	+81	- 390	- 525
9. 20 % of new FCHD patients to CAPD	- 18,886,200	+170	+162	- 781	- 1050
10. 10 % of new FCHD patients to APD	+ 80,000	+72	+109	- 135	- 323
11. 20 % of new FCHD patients to APD	+ 128,000	+144	+219	- 271	- 646

a for a description of the scenarios, see Results paragraph, section sensitivity analyses /scenario analyses

Discussion

Dialysis is expensive. Average cost per life year gained in the Base-Case scenario was found to be NLG 133,000, the cost per QALY were NLG 190,000. The transplantation figures were estimated as NLG 25,000 per life year gained and NLG 27,800 per QALY. Total expenses of the ESRD treatment program were calculated at 3.24 billion guilders over the period 1997-2001 or NLG 650 million per annum. This equals 1.1 percent of the total 1997 healthcare budget of the Netherlands, which is spent on 0.0006 percent of the total population. Dialysis may be regarded as an expensive treatment, bridging the gap between the onset of end-stage Renal Disease and transplantation. However, transplantation and dialysis cannot be assessed separately. A successful transplantation program requires dialysis before a transplantation can be performed and again as back-up for patients who experience a rejection of the donor organ. The mutual dependency also applies to the different dialysis modalities: patients who have or gradually develop contraindications for one treatment modality may benefit from the availability of other modalities. The cost-effectiveness of ESRD treatments should therefore primarily be assessed at a more aggregate level, before considering the different therapeutic modalities.

Of the five dialysis modalities, CAPD is the most cost-effective treatment modality, followed by HHD, APD and LCHD. The current study was the first to take the cost-effectiveness of APD into account. The cost-effectiveness of APD was equal to that of other accepted treatment modalities, such as HHD and LCHD. On the aggregate level, FCHD was shown to be the least cost-effective treatment. FCHD was found to be the most expensive therapy and FCHD patients' quality of life, as valued by the general population, was lower than other patients' quality of life. The information from the quality of life study was somewhat confusing. The general population valuations of patients' quality of life was significantly different across groups. And although treatment group differences that were found in patients' own valuations were not significant, the three valuation methods resulted in different ranking of treatment modalities. For instance, APD ranked highest using the TTO instrument and lowest using the SG instrument. In view of these conflicting results, and considering the fact that quality of life differences across treatment groups are not huge anyway, it cannot be justified that quality of life of patients should play an important role in policy making with regard to the ESRD treatment program.

The more favourable outcomes of CAPD, LCHD, APD and HHD compared with FCHD suggest that a policy directed towards substitution of patients from the latter treatment modality to one of the former modalities could make sense. We have explored the influence of such substitutive policies. It was shown that the influence of substitution of patients from more expensive to less expensive treatments was only modest. The LCHD stimulating scenarios even resulted in higher societal costs, and slightly higher cost per life year gained. An important explanation is that there were more patient movements in the LCHD, CAPD and APD groups. More frequent movements from one therapy to another were associated with higher costs, because costs in the first year of therapy are higher than in later years. Patients in the FCHD group, especially in the older age groups, experienced fewer changes of therapy. Hence, the positive effect on costs and outcomes of the ESRD program that was expected from substitutive policies was reduced by increased costs asso-

ciated with more changes of therapy. A more substantive influence may be expected from an increase in the number of transplantations per million population. The Netherlands has reached a level of around 30 transplantations per million population. Many European countries have shown higher numbers over the past years.[40] The number of donor organs depends on a complex number of factors, including legislation, attitude towards organ donation among the population and healthcare workers and the number of traffic injuries. Because of the relatively low number of traffic injuries in the Netherlands, it cannot be expected that a high level of 44 transplantations per million people will easily be reached in the Netherlands. However, if the new donor legislation [41] provides for an increase in the number of donor organs, as anticipated, a positive influence on the societal costs of the ESRD treatment program and on the cost-effectiveness of the ESRD program may be expected.

The current study was stratified into different age-groups. Other patient characteristics, such as sex, employment status, life-style, marital status and comorbid diseases might influence the cost-effectiveness of treatment as well. A study by Smith and Wheeler [42] suggested that patients using FCHD may have lower charges than if they were using CAPD, and vice versa. This result supports the hypothesis that matching patient and treatment criteria is an efficient process, resulting in the best outcomes that are possible in individual patients. This would further reduce the usefulness of substitutive approaches. Cost reduction in general will have a much more significant influence on societal costs of ESRD treatment than substitution of patients to more cost-effective treatments. None of the substitutive policies explored were expected to have more effect on societal costs and cost-effectiveness of ESRD treatments as a cost reduction as low as 2 percent would have. It should be made clear that these results and conclusions only apply to the ESRD treatment situation as found in the Netherlands. There is equal access to all forms of dialysis. Nephrologists' fees are independent of the treatment modality of a patient. Without medical contraindications, patients in general are allowed to choose a treatment modality that best suits them. This means that circumstances to "match" patient and treatment characteristics are optimal in this country. The Netherlands has had relatively high patient numbers on CAPD from the beginning, and APD is now diffusing rapidly into dialysis centres as well.[37] Thirty percent of all dialysis patients are being treated with CAPD or APD.[37] It seems that a point of diminishing returns is being reached at this level of diffusion of PD treatment. The CAPD stimulating scenarios were still found to be dominant to the Base-Case scenario with less costs and better outcomes, but the reduction in cost per life year gained and cost per QALY in these scenarios was not impressive. The implication of this finding is that countries with a lower diffusion rate of PD treatments and similar cost profiles might benefit more from PD stimulating policies. This situation applies to many European countries. Within the 35 European countries covered by the Registry of the European Dialysis and Transplantation Association, only 8.8 % of patients received PD treatment in 1995.[43] PD was offered as a treatment option in only 45 percent of all dialysis centres covered by the European Registry, while there was access to HD in almost all dialysis centres.[43] In many European countries there is still room for substitution of patients to PD treatment and such substitutive policies might have a beneficial effect on the cost-effectiveness of the ESRD program in those countries.

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Appendix

A Markov-chain is a discrete statistical process in which the future distribution of the population (i.e. ESRD patients) over several states depends on the present distribution, transition probabilities from one state to the other and inflow of new patients. The model assumes that the patients in the system are always in one of a finite number of states. During each time interval, e.g. a month or a year, a patient is at risk of a transition to another state. In matrix notation, considering a situation of n different states patients can be in, the model can be described as follows:

- **A**, a **(n x n)** matrix of transition probabilities; $\mathbf{A}_{i,j}$ is the probability of transition from state i to state j, in the period between time t and time t+1;
- **X' (t)**, a n-sized row vector; $\mathbf{X'(t)}_k$ is the population at time t in state k;
- **I' (t)**, a n-sized vector; $\mathbf{I'(t)}_k$ is the flow of new patients into state k, in the period between time t and time t+1;

The forecast of the distribution of the population at time t+1, **X' (t + 1)** equals:

$$\mathbf{X'(t+1) = X'(t) \cdot A + I'(t)}$$

A vital assumption of the Markov chain model is:

1. The transition from state i to state j is independent of the history of the patient before arriving in state i ('Markovian assumption').

Further assumptions of the Markov-model include:

2. The transitions from one state to another all take place at the end of a period.
3. After applying the transitions to patients already in the system, new patients flow into the system.

The model allows for corrections in **A**, in order to match the total annual number of transplantations to a predefined number. The second assumption plays an important role in the calculation of the societal costs of treatment, because the number of patients at the beginning of a calculation-period equals the number of patients during that period. When there are X^t_k patients in state k at the beginning of period t and the costs per period t for treatment k are $c_{k,t}$ then the societal costs C^t_k in period t for treating patients in state k, equals:

$$C^t_k = c_{k,t} * X^t_k$$

Costs are discounted to the beginning of the forecast-period. The following assumption facilitates calculation:

4. All costs are made just before the end of a period.

The standard discounting formula applies in this situation and the discounted costs in period t for treatment k, D_k^t, using discount-rate r, equal:

$$D_k^t = C_k^t / (1 + r)^{(t-1)}$$

To calculate the number of life years gained it is assumed that the disease under consideration is an end-stage disease. This implies that:

5. In the absence of treatment a patient dies within one time period t.

The number of gained life years in period t for treatment k, L_k^t, equals:

$$L_k^t = X_k^t$$

Multiplication of L_k^t by a quality factor (indicator for quality of life) gives the number of QALY's gained in period t for treatment k. The discount-procedure for life-years and QALY's equals the one used to discount costs.

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Chapter 8

Sensitivity and perspective in the valuation of health status: whose values count?

De Wit GA, Busschbach JJV, de Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? Health Econ 2000; 9: 109-126.

Abstract

We studied the literature on the existence of differences in valuation for hypothetical and actual health states between patients and other-rater groups. We found that 9 different study designs have been used to study this question and applied 2 of these designs in a study involving dialysis patients and other rater groups. In the first study, both dialysis patients and students had to value hypothetical health states with Standard Gamble and Time Trade Off. Patients assigned higher values to hypothetical health states than students did. In the second study, dialysis patients who were being treated with 4 different dialysis modalities were asked to value their own health state with Standard Gamble, Time Trade Off and a visual analogue scale (EQ_{VAS}), and to describe their health state on the $EQ\text{-}5D_{profile}$. Several $EQ\text{-}5D_{index}$ values (health index values derived from general population samples) were calculated for the four dialysis treatment groups, based on the $EQ\text{-}5D_{profile}$. These health indexes could discriminate between treatment groups, according to clinical impressions. Treatment groups could not be differentiated based on patients' valuations of own health state. Our results suggest that general population samples, using $EQ\text{-}5D_{index}$ values, may be more able to discriminate between patient groups than the patients themselves are. The implications of this finding for valuation research and policy making are discussed.

Introduction

Values, sometimes also called utilities or preferences,[1] are quantitative expressions of preference for certain health states, on a scale on which 0 represents death and 1 represents full health. Values may have several applications in healthcare research and policy making. In the context of cost-effectiveness and cost-utility analyses, values may be used tot calculate (costs per) Quality Adjusted Life Years (QALYs).[1 2] In medical decision making, values may play a role when a patient or a healthcare professional has to make a choice between different treatment options.[3] Values may also be used as a direct outcome measure in clinical research, for instance in studies comparing different treatment options for a clinical condition, and for monitoring patient health. Values can be obtained from patients currently experiencing a certain health state, from people with past experience of that health state, close relatives of patients, healthcare professionals and from samples of the general public. But whose values count? This question has been described more as a political or ideological topic than as an empirical question.[4-6] Different disciplines have different perspectives on the issue "whose values count?". Historically, doctors provided ratings of patients' health status (e.g. the Karnofsky Performance Status [7]). With further development of quality of life research, this professional perspective was challenged and over the past two decades, the patient perspective has been a major perspective in clinically oriented research and in medical decision-making.[5 8] The rationale of the patient perspective is given by Froberg and Kane [5] as "(...) *it may be more appropriate to weight more heavily the preferences of those most directly affected by an intervention or policy. This seems especially true in clinical decision making*". At the same time, researchers oriented towards economic evaluation of healthcare have stated that the values of the general population may be more valid in the context of decisions on the alternative allocation of resources.[1 2 9] Hadorn explained this viewpoint as follows: "(...), *patients who rely on others to pay their medical bills (...) cannot expect that these others will pay for everything they (the patients) might wish to receive. Permitting patients unlimited access to care based on post-illness preferences would too often result in the provision of marginally beneficial care.*"[9] Furthermore, it is stated that rational citizens, when operating behind a "*veil of ignorance*", and thus ignorant of their own future health state and needs, would prefer that societal decisions lead to maximum aggregate benefit within that society.[2] The aggregate values of people without specific interest in particular health states would seem most appropriate from this perspective, because a higher level of solidarity with worse-off citizens will be guaranteed.

Hence, the health economists' perspective on the issue of "whose values count" is different from more clinically oriented perspectives. Williams has put forward that the issue of the patient perspective versus the general population perspective should not be regarded a matter of right or wrong.[4] Both perspectives may lead to legitimate outcomes, depending on the specific decision making context, and in fact the choice for the perspective is primarily a normative choice. However, if values given by patients and other rater groups differ in magnitude, this normative choice could also have empirical implications. We studied the literature on this subject, with a limitation to those papers that compared patient values with values of at least one other rater group. We found 35 different publications aimed at answering the question whether experience with illness influences the valuation of health.[6 10-43] These 35 publications included 38 separate studies, in which nine different research

designs were applied. These nine designs differ with respect to the amount of experience with disease of the rater, the distance of the rater to the patient and the resemblance between the health state to value and the actual health state of the rater. Because we experienced that it was sometimes quite difficult to get a grip on the exact method that was applied in each of the study reports, we have made a classification of study designs. This classification is not meant as an exhaustive enumeration of possible research designs, but merely to present the subtle differences in designs that were found in the literature. The 9 different study designs found are described in Box 1. Details on design and conclusions of the 38 separate studies can be found in Appendix I.

Box 1: Classification of different study designs that were found in the literature to address the question of the existence of differences in values between patients and other rater groups

(1) Patient and others (non-patients: doctors, nurses, family members, general population, students, convenience samples) value hypothetical health states related to the actual health state of the patient (e.g. breast cancer patients value cancer related health states) [6 10-16]

(2) Patient and other rater-groups value hypothetical health states unrelated to the actual health state of the patient (thus entirely hypothetical to both groups) [17-20]

(3) Different patient groups (with different stages of disease) value hypothetical states related to the actual health state of the patients [11 21-23]

(4) Different patient groups (with different stages of disease) value hypothetical states unrelated to the actual health state of the patient [24]

(5) General population samples value hypothetical health states. Values of those in a dysfunctional health state are compared with values of those in normal/perfect health. The division between healthy and non-healthy individuals is made afterwards [25-29]

(6) Patients and proxies (familiar with the patient, such as caregiver, nurse or doctor) value the actual health state of the patient involved [13 20 30-34]

(7) Patients and non-patients are interviewed on hypothetical treatment choices. The choice they make is thought to reflect the value for the hypothetical health states associated with the treatment choice [35-37]

(8) Values for hypothetical health states are elicited from patients before they enter that hypothetical health state. Values are elicited again from the same patient after they have obtained experience with the hypothetical health state. The stability of the values is studied [38-40]

(9) A patient describes his health state on a classification system or profile and subsequently values his actual health state. The patient value is compared with a population value for the actual health state of the patient (i.e. in terms of the EQ-$5D_{profile}$) of the patient [41-43]

The results of the 38 studies do not facilitate a univocal conclusion on the subject. Twenty-seven of the 38 studies concluded that patient values are different or sometimes different from other groups' values. Eleven studies found no differences in values between rater groups. The studies reporting differences in valuations found in general that patients gave higher values than other groups: 22 studies reported higher patient values, 2 studies showed lower patient values and 3 studies found contradictory results. Some studies only have small sample sizes, and thus may lack power to detect differences between groups, should they exist. Some study designs, such as design 7 (treatment choices) may measure more features than the value of the health state alone. For instance, cancer patients' treatment choices may reflect their current (impaired) health state at the moment of questioning or may include the perceived chances of survival with the respective treatment options. These drawbacks further hamper a clear-cut conclusion, but current evidence would be most supportive of the conclusion that patients' values are higher than values of other rater groups. The Panel on Cost-Effectiveness in Health and Medicine recently supported this conclusion.[2]

If we assume that patients' values are different from other rater-groups' values, then does this have implications for the sensitivity of value measurements? This is a less addressed issue. The term "sensitivity" is being used differently by different disciplines, but is used by us to refer to the capacity to distinguish health states on the basis of values attached to those health states.[44 45] If it is true that patients in general assign higher values to their health state in comparison with other rater groups, then loss of sensitivity to discriminate between patient and treatment groups might be the result. If patients give higher values in general, they will use a smaller part of the scale ("ceiling effect") in comparison with healthy people. On the other hand, when healthy people have to value very worse health states, a similar phenomenon ("floor effect") may be observed at the bottom end of the scale. If a particular rater group uses a relatively small part of the scale, a reduction of sensitivity to differentiate across (treatment) groups could be a consequence.

In the context of a clinical study involving four different dialysis treatments, we were able to study the existence of inter-rater differences and possible consequences for the sensitivity to discriminate between patient groups. Our data allowed for the application of two of the nine research designs that were found in the literature.

Subjects and methods

General approach

First, we compared the valuations for hypothetical health states of dialysis patients and students, using both Standard Gamble and Time Trade Off instruments (study design 2, as described in Box 1). A sample of dialysis patients and a sample of volunteer students were asked to value three hypothetical health states. Outcomes from both rater groups were compared. Second, we compared the valuations of four different groups of dialysis patients for their actual health status with general population valuations for similar health states (study design 9, as described in Box 1).

Valuation methods used

Health-related quality of life of dialysis patients was assessed using the EuroQol Instrument (EQ-5D).[46 47] The EQ-5D is a generic questionnaire, suitable for collecting data on health related quality of life. The clinical version of the EQ-5D includes a classification system ($EQ\text{-}5D_{profile}$) and a visual analogue scale (EQ_{VAS}). The $EQ\text{-}5D_{profile}$ records the level of self-assessed problems on 5 domains of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with three levels of functioning: (level 1: no problems; level 2: some problems; level 3: unable to perform/extreme problems). The EQ_{VAS} records the respondents rating of his/her overall health status on a graduated, vertical visual analogue scale. The EQ_{VAS} is anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). The combination of 5 dimensions with 3 levels of functioning yields 243 [35] unique health states. These 243 health states may be converted to a single summary index (EQ-5Dindex), by applying scores from a standard set of preference weights. The $EQ\text{-}5D_{index}$ is constructed from values that have been assigned to the health states by subjects from the general public. Several methods are available for such valuation research,[1] among which the Standard Gamble (SG),[48] Time Trade Off (TTO)[31 48] and visual analogue scales. The essence of the *Standard Gamble* (SG) is that the respondent is presented with two alternatives and asked to choose the one most preferred.[48] The first alternative offers the certainty of staying in the described health state for the remainder of the respondent's life. The second alternative is a gamble with specified probabilities for both the positive outcome of the gamble (a normal health state for the remainder of time) and the negative outcome (immediate death). The SG score, a score between 0 and 1, is calculated as 1 minus the risk percentage chosen divided by 100. The *Time Trade Off* method (TTO) asks responders whether they are prepared to give up some remaining time of their life, in order to improve an impaired health state to normal health.[31 48] The time perspective that is presented to the respondent corresponds with statistical life expectancy for people of the same age and sex. The quotient of the chosen number of years in a normal health state over statistical life expectancy yields the TTO score. Our operation of the TTO method did not allow for negative values.[31] The visual analogue scale that was used in our valuation research was the EQ_{VAS}, as described above. These three valuation methods may be used for the valuation of both *hypothetical* health states and the actual health status of the respondent, as was done in the present study.

Patients' versus students' valuations of hypothetical health states

The patient sample consisted of 165 dialysis patients who were being treated with four different dialysis modalities, with differing impact on patients. Patients participated in a clinical study on the adequacy of dialysis.[49] Starting from three months after inclusion in the clinical study, patients became eligible for a quality of life study. One of four interviewers (trial nurses) visited the patient at home for an interview on the patient's health status and their valuations for hypothetical health states and their own current health state. The student sample consisted of 105 students of Erasmus University who volunteered to participate in a study that was set up to compare different methods to elicit values for health states.[50] The students were all interviewed by one of the authors (JJB). Both dialysis patients and students, using TTO and SG according to protocols described above, valued

three imaginary health states. The three imaginary states were framed within the EQ-$5D_{profile}$ and represented a wide spectrum of severity of health states. The three health states are presented in Table 1.

Table 1: Three hypothetical health states as defined by EQ-$5D_{profile}$

EQ-$5D_{profile}$ dimension	Mild state	Moderate state	Severe state
Mobility	No problems	Some problems	Confined to bed
Self-care	No problems	No problems	Unable to wash/dress self
Usual activities	Some problems	Some problems	Unable to perform
Pain / discomfort	No pain	Extreme pain	Extreme pain
Anxiety/depression	Not anxious	Moderately anxious	Extremely anxious
Abbreviated state [a]	11211	21232	33333

a 1 = no problems, 2 = some problems, 3 = unable to perform / extreme problems

The comparison of patients' and students' valuations for hypothetical health states in fact was a byproduct of the clinical part of the study. The valuation of hypothetical health states was used to introduce the valuation methods to the patients and to make patients feel at ease with the interview situation. Because the valuation methods used with patients and students were identical, we were able to combine the results of both valuation studies.

Patients' versus general public's valuations of the actual health state of the patient

After the valuation of hypothetical health states, dialysis patients were asked to classify themselves on the EQ-$5D_{profile}$. They were also asked to value their own current health state using EQ_{VAS}, SG and TTO, analogous to the valuation of hypothetical health states described above. After the interview, the interviewer completed the Karnofsky Performance Status [7] for that patient, as an indicator of functional status of the patient.

The patients' valuations of their own current health state were compared with valuation data (EQ-$5D_{index}$) obtained from several European general population studies. In most countries participating in the EuroQol Group,[46 47] including the United Kingdom,[51] the Netherlands,[52-54] Finland,[55] and Spain,[56 57] EQ-$5D_{index}$ weights have been estimated. The general background to estimating these EQ-$5D_{index}$ weights is described by Brooks et al.[47] and is summarized here briefly. Samples from the general population were asked to value hypothetical sets of health states in terms of the EQ-$5D_{profile}$, using either visual analogue scale or Time Trade Off methods. This process resulted in sets of values for a sample of the 243 possible health states that can be described by the EQ-$5D_{profile}$. The health index weights for the remaining EQ-5D health states were estimated using mathematical modeling. The main characteristics of these European valuation studies of the EuroQol Group are summarized in Table 2.

Based on the EQ-$5D_{profile}$ as provided by the patient, we calculated 6 different EQ-$5D_{index}$ weights (as described in Table 2) for each dialysis patient. Thus, for each dialysis patient, we had 3 scores reflecting the SG, TTO and EQ_{VAS} valuations of the patient him/herself, and 6 scores reflecting outsiders' valuations for the actual health status of that

patient. We compared the four dialysis treatment groups (full care centre haemodialysis - FCHD, limited care centre haemodialysis - LCHD, continuous cycling peritoneal dialysis - CAPD, automated peritoneal dialysis - APD) with regard to these scores.

Statistical analysis

Differences in valuations for hypothetical health states between the patient and student groups were univariately tested by means of Mann-Whitney U tests. In addition, using a Manova repeated measurements procedure, the pooled scores were tested for the presence of a group effect. The latter analysis was performed twice, with and without adjustment for age differences between the two groups. In the part of the empirical study that was concerned with the valuation of actual health status by patients, we used non-parametric Kruskall-Wallis tests to test for differences across the four dialysis treatment groups. A P-value of 0.05 was chosen as the cut-off point for statistical significance in all analyses.

Table 2: Main characteristics of valuation research within the EuroQol Group

Country	Population	Number of respondents	Number of health-states	Hypothetical vs. own health	valuation method
UK [51]	General	2997	42	Hypothetical	TTO
Netherlands [52,54]	General	217	25	Hypothetical	EQ_{VAS}
Netherlands [53]	Students	126	243	Hypothetical	EQ_{VAS}
Finland [55]	General	1634	43	Hypothetical	EQ_{VAS}
Spain [57]	General	300	75	Hypothetical	EQ_{VAS}
Spain [56]	General	15000	243	Own health [a]	EQ_{VAS}

a Note that this Spanish general population study was different from the others in that respondents were asked to value their own current health state instead of hypothetical health states

Table 3: SG and TTO scores of dialysis patients and students, for 3 hypothetical health states (as shown in Table 1)

Method / health state	Dialysis patients (n=165)		Students (n=103)		P-value [a]
	n	Mean (SD)	n	Mean (SD)	
SG mild	159	0.90 (0.13)	103	0.97 (0.06)	< 0.01
TTO mild	148	0.94 (0.11)	103	0.91 (0.10)	< 0.001
SG moderate	157	0.76 (0.21)	103	0.67 (0.25)	< 0.01
TTO moderate	146	0.78 (0.19)	103	0.55 (0.24)	< 0.001
SG severe	155	0.42 (0.31)	103	0.31 (0.32)	< 0.01
TTO severe	146	0.50 (0.28)	103	0.20 (0.24)	< 0.001

a Mann-Whitney U-tests

Results

Patients' versus students' valuations of hypothetical health states. All 165 patients completed the EQ-$5D_{profile}$ and EQ_{VAS}. From the sample of 165 dialysis patients, 146 (88.5%) patients were able to answer all SG and TTO questions. Six patients (3.6%) did not respond to any of the 8 valuation tasks using SG and TTO methods. Thirteen patients (7.9%) answered some of the SG and TTO valuation tasks, but not all eight questions. Reasons for not cooperating in the valuation tasks were cognitive problems, tiredness and religious beliefs. Two students out of 105 students (1.9%) were not willing to respond to the TTO and SG questions. The average age of the dialysis patients was 57 years, the average age of the students was 22.5 years.

The mean scores of the two groups are presented in Table 3. In 5 of the 6 valuation tasks, patients gave higher scores than students. The Standard Gamble valuation of the mild health state was scored lower by patients than by students. Differences between students and patients were relatively small when the mild health state was valued, and relatively large when valuing the moderate and severe health state. The largest difference was found at the TTO valuation of the severe health state. Students gave a score of 0.20, indicating that they were willing to sacrifice 80 percent of their life expectancy in order to avoid the severe health state. Patients scored much higher, i.e. an average score of 0.50. We observed that patients used a smaller part of both SG and TTO scales than students did. Patients used 48 % of the range of possible scores on the SG scale, and 40 % of the TTO scale, while students used 66 % and 71 % of these scales, respectively. Univariate analysis of the differences between students' valuations and dialysis patients' valuations showed that all differences were significant. The multivariate analysis showed that there was a significant effect of the group ($P < 0.001$) and that an interaction between the rater-group and the health state existed ($P < 0.001$), implying that differences between the two rater groups are not constant over the hypothetical health states. Adjustment for age differences between the two groups did not change the results of the analysis.

Patients' versus general public's valuations of the patients' actual health state. Table 4 shows both the Karnofsky score, EQ_{VAS}, SG and TTO scores of patients in 4 dialysis treatment groups and the 6 European health indexes that were calculated on the basis of the dialysis patients' EQ-$5D_{profile}$. The first entry of Table 4 shows that significantly different Karnofsky scores were given by the interviewers to the 4 dialysis treatment groups, indicating that functional status of patients in the 4 treatment groups was different. No differences were found across the 4 patient groups as for their SG, TTO and EQ_{VAS} scores. However, five out of six EQ-$5D_{index}$ weights were significantly different across the 4 patient groups. The only EQ-$5D_{index}$ that was not different across the 4 groups was one of the Spanish indexes. However, this Spanish index was fundamentally different from the 5 others, because it is based on own actual health status, not hypothetical health status.

Table 4: Mean (SD) valuations for actual health status from dialysis patients (upper part) and mean EQ-5D$_{index}$ weights (lower part), according to treatment modality

	FCHD [a] (n=46)	LCHD [a] (n=23)	CAPD [a] (n=59)	APD [a] (n=37)	P-value[b]
Nurses' rating of performance status of dialysis patients					
Karnofsky Performance Status	66 (17)	78 (11)	71 (14)	76 (13)	0.01
Dialysis patients valuation of actual health state					
EQ_{VAS} [c]	0.58 (0.19)	0.65 (0.14)	0.61 (0.20)	0.61 (0.19)	0.49
SG	0.84 (0.21)	0.91 (0.13)	0.81 (0.24)	0.74 (0.24)	0.13
TTO	0.87 (0.20)	0.93 (0.11)	0.86 (0.23)	0.93 (0.14)	0.33
General population EQ-5D$_{index}$ value based on hypothetical health states					
United Kingdom general population [d]	0.66 (0.29)	0.81 (0.24)	0.71 (0.29)	0.81 (0.19)	0.04
The Netherlands general population [d]	0.69 (0.22)	0.82 (0.19)	0.73 (0.21)	0.80 (0.17)	0.05
The Netherlands students [d]	0.62 (0.19)	0.72 (0.17)	0.64 (0.19)	0.71 (0.16)	0.05
Finland general population [d]	0.75 (0.20)	0.86 (0.17)	0.78 (0.20)	0.85 (0.16)	0.05
Spain general population [d]	0.65 (0.27)	0.79 (0.20)	0.71 (0.24)	0.78 (0.18)	0.03
General population EQ-5D$_{index}$ value based on self-rated health					
Spain general population [d]	0.76 (0.18)	0.83 (0.16)	0.76 (0.18)	0.81 (0.15)	0.12

a FCHD = full care centre haemodialysis, LCHD = limited care centre haemodialysis, CAPD = continuous cycling peritoneal dialysis, APD = automated peritoneal dialysis
b Kruskall-Wallis test
c divided by 100
d see table 3 for a description of characteristics of the valuation study

Discussion

We studied the literature on the existence of differences in valuations between patients and other rater-groups. Our conclusion was that evidence that patients assign different values to *hypothetical* health states than "outsiders" is growing compared to the 1989 review of Froberg and Kane.[5] Studies that found differences reported higher values from patients in most cases. This was affirmed in the present study. We compared the SG and TTO values for three hypothetical health states from dialysis patients and students and found that in five out of the six valuation tasks, patients assigned higher values than students. These differences could not be explained by age differences between the two groups, as has been found elsewhere.[11 58-59] One of the six hypothetical health states was valued lower by patients than by students. This was the SG valuation of the mild health state. The MANOVA analysis showed that there was an interaction between the group effect and the health state effect. The implication of this finding is that, although patients in general do value health states higher than students do, this may be different for specific health states, especially the better health states. As a result, patients used a smaller part of the scale for their valuations of the three health states than did students. Kind and Dolan [26] and Badia et al.[20] gave some evidence for a similar phenomenon of lower valuations for mild states and higher valuations for more severe states. They called this "valuation compression". The word "compression" carries the implication of error associated with patient valuations, at least when general population valuations are considered the gold standard. However, the opposite

could also be true: given the values of the patients, the general public seems to stretch out the scale ("valuation expansion"). We will probably never be certain which of the two phenomena is responsible for the observed differences in valuation between patients and other rater groups. In this paper, we have focused on the implication of the observed differences, rather than speculating about the "true" cause of the existence of differences.

In our study, patients were first asked to value the three *hypothetical* health states using SG and TTO. Thereafter, they had to describe their own current health using the EQ-$5D_{profile}$ and to value the description of their own *actual* health using EQ_{VAS}, SG and TTO. Many patients described their health state in terms of "some problems" in several domains. Such health states resemble the "moderate" hypothetical health state, that was just before valued on average with 0.76 (SG) or 0.78 (TTO). But once the valuation task concerned *themselves*, they did not want to take risks or trade-off life years anymore. A ceiling effect at the valuation of own current health state has also been found in other patient populations with serious conditions. Tsevat et al. applied the Time Trade Off in 1438 seriously ill patients with a projected 6-month mortality rate of 50 percent and found that 35 percent was unwilling to sacrifice any longevity.[30] Fowler and colleagues showed that 35 percent of a sample of 291 AIDS patients had a high reluctance to give up life; they wanted life extension under all circumstances.[60] Bosch and Hunink described a median TTO value of 0.80 and a median SG value of 0.91 in patients with intermittent claudication.[61] The most common explanation for this phenomenon is coping: patients have gradually learned to adjust their expectations to their actual possibilities. Once a (chronic) disease is detected, patients change their internal standards to evaluate the situation and the yardstick of what is acceptable and what is not is lowered substantially.[62] As a consequence, their evaluation of own health status may be leveled off at the upper end of the scale, with a consequent reduction in the variance of the distribution and the statistical power to detect an effect of clinical differences in health status on health values. Besides coping behavior, other explanations for high valuations can be found in the literature. Time preferences, religious beliefs, risk aversion and reluctance to give up any possible life at all may have influenced the SG and TTO scores.[60 63-65] Furthermore, our interviewers notified that patients, although explicitly instructed only to consider their present health state while answering SG and TTO, referred to other domains of life to explain the choices they made. For instance, family circumstances such as a future wedding anniversary or the wish to see grandchildren grown up were mentioned. In answering SG and TTO, it possibly is very difficult for responders to strictly separate their impaired health state from other, more flourishing, domains of life.

Table 4 shows that the SG, TTO and EQ_{VAS} valuations lead to different results within the patient-groups. The EQ_{VAS} valuation was much lower than SG and TTO valuations. This is in accordance with previous research aiming at the comparison of the three valuation methods.[64 66 67] The differences in health-index values are caused by different scaling methods, different modeling techniques to estimate the health-index values and population differences. However, the ranking of the 4 different dialysis treatments is similar with all health-indexes, with highest ratings for LCHD patients, intermediate ratings for CAPD and APD patients, and lowest ratings for FCHD patients. The Karnofsky score that was rated by trial nurses did differ significantly across groups, also with highest scores for LCHD patients. The Karnofsky score has relatively less meaning in itself, because the higher score

for LCHD patients could be attributable to the *idea* that LCHD patients perform better or *should* do better than other patients. However, this explanation cannot be applied to the valuation research that was done in the general population, since health states were framed in the general terms of the $EQ\text{-}5D_{profile}$, without reference to a specific patient group. Nevertheless, all health indexes applied to dialysis patients' health states ranked LCHD as the treatment with the highest "quality of life" and thus were in accordance with the clinical impression of the nurse who provided the Karnofsky score.

It is often thought that general population valuations are less sensitive than patients' valuations, because patients experience all the subtleties of their health status that can never be explained in sufficient detail to an outsider. Although this is unmistakably true, patient valuations may also be contaminated for reasons discussed above. Our tentative conclusion is that "outsiders" may be more able to differentiate across treatment groups than patients are themselves, at least when the EQ-5D is used. Five out of six estimated EQ-5D health indexes showed significant differences across patient groups. The only EQ-5D health index that did not show significant differences was the Spanish study of 15,000 people from the general population.[56] As previously stated, that study was based on the valuation of *own* health state, whereas the other five EQ-5D health indexes are based on ratings of *others'* (*hypothetical*) health states. The same phenomenon that is held responsible for loss of sensitivity to discriminate between patient groups, namely concentration of ratings in the upper end of the scale once the valuation is concerned with oneself, might be responsible for the fact that this Spanish EQ-5D health index is not able to differentiate across treatment groups, while the others are. So, the essential point of the valuation task seems to be whether the task is related to *self* or *others*. Similar observations were made in two other recent studies.[68-69] Once the valuation is concerned with *others*, coping mechanisms that prevent people from using the whole range of the scale are less relevant. Overall, it may seem unlikely, and even counterintuitive, that a simple instrument such as EQ-5D could be more able to pick up subtle differences between health states than more sophisticated methods such as Time Trade Off. Another recently published study also provided with evidence that sensitivity of the EQ-5D was better than the sensitivity of SG and TTO.[70] In fact, there is increasing evidence that instruments such as TTO do not pick up clinically meaningful changes in health status of the patient. Researchers have reported stable TTO values, despite distinct changes in health status over time.[71-73]

One important explanation for our findings has largely remained undiscussed: the standard error associated with the valuations of different rater groups. For example, prejudice against certain aspects of impaired health status may cause a focus of the general public on that aspect, thereby reducing standard error of the response and increasing discriminatory power. Also, patients may find that the reality of their actual health is far more complex than suggested by the hypothetical health state presented, with numerous other attributes effecting their valuation. This would increase the standard error and reduce the discriminatory power. Furthermore, when the $EQ\text{-}5D_{index}$ weights are attached to the $EQ\text{-}5D_{profile}$, they are treated as constants without variances, although in the valuation studies variance exists. Thus one can say that one layer of variance is stripped out, making it more likely that

particular differences will appear statistically significant. However, if this was an entirely satisfying hypothesis, it should also hold for the Spanish EQ-$5D_{index}$ that was based on own, not hypothetical, health states. This is not the case.

It might be argued that the present study, with relatively few patients in the 4 treatment groups, might lack power to detect differences across patient groups. However, the EQ-5D health index values were based on the same patient numbers and at least were better able to differentiate across treatment groups than patients were themselves. The present study could easily be replicated in other clinical studies in which the EQ-$5D_{profile}$ and EQ_{VAS} scores are obtained directly from patients, to see whether our results hold in other circumstances.

What are the implications of this study? The discussion on the subject of "whose values count" seems to be subtler than was previously thought. Critics have questioned whether outsiders are knowledgeable enough to make judgments that could have far-reaching consequences, for instance in a resource allocation context. Of course, no outsider knows exactly what it is like to be a dialysis patient. But outsiders may be able to make subtle differences between health states. If patient values are used in societal decision making, "valuation compression" and its possible consequence, reduction of sensitivity to discriminate between treatments, could diminish the (possible) marginal benefit of healthcare interventions. This reduction in possible marginal benefit of treatment may lead to higher costs per QALY gained than if population values were used. When patient values are used in studies aimed at the comparison of different therapeutic modalities for one clinical problem, the "valuation compression" at the upper end of the scale might result in loss of sensitivity to discriminate between the therapeutic modalities, when in fact differences between those modalities exist. Our study does not present the solution to the "whose values count?" discussion, but suggests that use of patient values might be more complicated than previously thought.

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Appendix I

Author/year	Design	Number of respondents	Conclusion	Patients versus other rater groups [a]
Sackett 1978 [10]	1	246 general population 29 dialysis patients	Patients' values were higher than general population values	>
Wolfson 1982 [6]	1	14 physicians 15 physical therapists 13 family members 10 stroke patients	No inter-rater differences in values were found	=
Boyd 1990 [11]	1	40 physicians 59 healthy volunteers 40 patients with colostomy	Patients' values were higher than other groups' values	>
Ashby 1994 [12]	1	49 nurses 20 hospital physicians 24 general practitioners 28 university staff 17 breast cancer patients	Patients valued scenarios with good psychosocial response higher than other groups, no differences in other scenarios	≥
Revicki 1996 [13]	1	49 schizophrenic patients 49 primary caregivers 12 psychiatrists	Some statistically significant differences between the groups' values for hypothetical states were found, but in general few differences	≥ ≤
Dominitz 1997 [14]	1	46 colorectal cancer patients 114 patients at risk for colorectal cancer 24 patients scheduled for sigmoidoscopy 62 patients with unrelated conditions	Patients with related conditions gave higher values to colon cancer screening scenarios than patients with other conditions. No differences between groups for cancer scenarios	≥
Jalukar 1998 [15]	1	49 head and neck cancer patients 50 healthcare professionals 86 students	Patients valued head and neck cancer health states higher than students, and equal to or higher than health workers	≥
Clarke 1997 [16]	1	32 patients with Gaucher Disease (GD) 38 chronically ill patients 39 healthy subjects	Patients with GD valued hypothetical GD scenarios similar or higher than the two other rater groups	≥
Rosser 1978 [17]	2	10 medical patients 10 psychiatric patients 10 medical nurses 10 psychiatric nurses 20 healthy individuals 10 doctors	Differences between rater groups were found: medical patients gave highest scores but psychiatric patients lowest scores	< >

(Appendix I continued)

Author/year	Design	Number of respondents	Conclusion	Patients versus other rater groups [a]
Balaban 1986 [18]	2	26 RA patients General population sample	No differences between the values of both groups were found	=
Selai 1995 [19]	2	23 acutely ill hospital patients general population samples from 3 countries	Patients gave higher values than the general population	>
Badia 1996 [20]	2	103 ICU patients 360 healthy individuals	Patients tended to rate the worst health state higher and the better health states worse than healthy individuals	< >
Boyd 1990 [11]	3	40 patients with colostomy 11 patients without colostomy	Colostomy patients' values were higher than other patients' values No differences found between groupsusing category rating. Women	>
Daly 1993 [21]	3	21 menopausal women without symptoms 25 menopausal women mild symptoms 25 menopausal women severe symptoms	with severe symptoms gave lower values to severe health state using TTO, but similar values for mild health state	≤
Samsa 1998 [22]	3	415 patients with stroke 184 patients with TIA 654 asymptomatic patients at risk for stroke	A hypothetical major stroke scenario was valued higher by stroke patients than by other patient groups	>
Hall 1992 [23]	3	60 breast cancer patients 44 women without breast cancer	Cancer scenarios were valued higher by patients than by non-patients	>
Llewellyn-Thomas 1991 [24]	4	30 women with benign breast disease 60 women with malignant breast disease	No relationship between actual health status and health values was found	=
Badia 1995 [25]	5	600 visitors of a primary care centre	Valuations for actual health state did not influence ratings for hypothetical health states	=
Kind 1995 [26]	5	1900 individuals from general population	Those who described their current health as impaired gave higher valuations for all health states, especially severe states	>
Hadorn 1995 [27]	5	612 individuals from convenience samples	No systematic differences in preferences for health states according to health status or disease experience were found	=
Gudex 1996 [28]	5	3395 individuals from general population	Current self-reported health was found to have influence on ratings in 14 % of hypothetical states: those in worse health gave higher valuations in these cases. No differences found in 86 % of ratings.	≥
Dolan 1996 [29]	5	1181 individuals from general population	Higher valuations for hypothetical states were given by responders who described their current health as dysfunctional	>
Revicki 1996 [13]	6	49 schizophrenic patients 49 primary caregivers 12 psychiatrists	No differences in ratings for patients' own health between the 3 groups were found	=
Badia 1996 [20]	6	103 ICU patients	No differences in valuations of the health state of the patient were	=

(Appendix I continued)

Author/year	Design	Number of respondents	Conclusion	Patients versus other rater groups [a]
		103 proxies	found	
Tsevat 1995 [30]	6	1438 seriously ill patients 1041 family members 1079 physicians	Patients rated their current health state higher than their family members and their physicians	>
Churchill 1987 [31]	6	194 dialysis and transplant patients nurses and nephrologists	Patients gave higher ratings to own health than nephrologists and nurses	>
Molzahn 1997 [32]	6	215 dialysis and transplant patients 42 nurses 7 physicians	Patients valued their own health higher than their nurses did, but physicians' values were equal to patients' values	≥
Dorman 1997 [33]	6	152 stroke patients 152 proxies	No differences in valuations of the health state of the patient were found	=
Tsevat 1998 [34]	6	300 hospitalized patients > 80 years 300 proxies	Patients valued their own health higher than their proxies	>
O'Connor 1989 [35]	7	154 cancer patients 129 healthy volunteers	Patients choose more often for a toxic treatment over a non-toxic treatment than healthy volunteers	>
Slevin 1990 [36]	7	100 cancer patients 100 matched controls 60 oncologists 88 radiotherapists 790 general practitioners 303 cancer nurses	Patients were much more likely to opt for radical treatment with minimal chance of benefit than the other respondent groups	>
Llewellyn-Thomas 1989 [37]	7	60 women with breast cancer 60 women with benign breast disease	Women with cancer were much more likely to undergo adjuvant radiotherapy, even with a small extra chance ofprevention of recurrence	>
Llewellyn-Thomas 1993 [38]	8	66 patients with laryngeal cancer	Values for possible treatment outcomes remained consistent when those outcomes were experienced	=
O'Connor 1987 [39]	8	54 cancer patients undergoing chemotherapy	patient preferences remained stable after treatment	=
Christensen-Szalanski 1984 [40]	8	18 pregnant women interviewed on preferences to avoid anesthesia during labor	Long-term preferences were stable, but preferences shifted during labor , patients were more likely to choose anesthesia	≤
Jenkinson 1997 [41]	9	152 BPH patients general population surveys	Patient and general population valuations were similar	=
Zethraeus 1999 [42]	9	104 patients with hormone replacement therapy general population surveys	Mild hypothetical scenarios were valued similar, but severe scenarios were valued higher by patients than by the population	≥
Hurst 1994 43	9	55 patients with rheumatoid arthritis general population surveys	Patients rated their actual health status higher than the general population	>

Appendix I continued

a < patient values lower than other groups' values, = patient values identical to other groups' values, > patient values higher than other groups' values, ≤ patient values lower than or identical to other groups' values, ≥ patient values higher than or identical to other groups' values

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Chapter 9

Conclusions and discussion

Introduction

This thesis deals with an economic evaluation of renal replacement therapies in the Netherlands. In the previous chapters, the topics of quality of life of patients, costs of therapy, societal costs and cost-effectiveness have been discussed. This chapter presents a general discussion of the main results of each study. In addition, some methodological and theoretical ideas based on the findings are given and recommendations for future research are made. The main conclusions on the studies are discussed below by topic. A more chronological presentation of study questions, results and main conclusions can be found in the *Summary* section of this thesis.

Comparison of the quality of life of haemodialysis and peritoneal dialysis patients (chapters 2 and 3)

One of the aims of the literature review on quality of life of end-stage renal disease patients (chapter 2) was to summarise the current knowledge on differences in quality of life between patients undergoing various therapeutic modalities. Our review was limited to well-known generic quality of life instruments (i.e. Short-Form 36, Nottingham Health Profile, Sickness Impact Profile, Quality of Life Index, Standard Gamble and Time Trade Off). Most of these instruments became available in the late 1980s or early 1990s. Inherently, our review was *a priori* limited to studies performed in this period. This guaranteed that major therapeutic improvements (such as the introduction of cyclosporin for transplanted patients and erythropoietin for renal anaemia) were included in the results. The literature review clearly showed quality of life advantages of transplanted patients compared with dialysis patients.[1-9] However, these results do not justify the choice of one dialysis modality over the other based solely on perceived quality of life benefits. Most studies that addressed this issue concluded, when differences in case-mix between patient groups were statistically controlled for, that dialysis treatment modality is not a determinant of quality of life.[1 2 5 7 10 11]

The absence of a difference in quality of life between haemodialysis (HD) and peritoneal dialysis (PD) found in the literature review was confirmed by our empirical study (chapter 3). Using four quality of life measures in a sample of 135 patients from the NECOSAD-I study, no differences were found between the two patient groups. Although the similarity in quality of life fits the overall experience reported in the literature, the wide variance in scores, especially scores on the two health preference methods, may have obscured possible differences between patient groups. Additional problems in the interpretation of health preference scores from dialysis patients will be discussed later in this chapter.

Quality of life measurement in dialysis patients is hampered by the fact that no randomised studies have yet been performed. Such a study design is preferable to the observational designs that were selected in our review, irrespective of how well statistical control for the influence of background variables may have been. Even if quality of life differences between treatment groups were found, it would remain unclear whether these are due solely to a therapy effect or to patient selection. Only a randomised trial can largely exclude the influence of patient selection. However, experience with the NECOSAD-II study,[12] intend-

ed to be the first randomised controlled trial comparing HD and PD, demonstrates how difficult it is to randomise patients over different treatment modalities. Even when patients have no specific indications or contra-indications for either HD or PD, the patients and their nephrologists generally have implicit or explicit ideas about the relative advantages of a specific therapy in their particular circumstances. In the absence of randomised trials, longitudinal studies, which follow patients for a considerable time from the onset of dialysis, are the best alternative. The minimum set of background variables that should be controlled for in such studies also emerges from our literature review (chapter 2). Important independent factors impacting on quality of life of patients are the presence of concurrent diseases,[2 8 10 13-20] age,[2 8 10 11 13 15-18 21] education,[2 10 11 19 21] gender,[8 10] race,[15 16] time on dialysis / total time with end-stage renal disease,[8 11 20] haemoglobin level,[8 10 13] haematocrit level,[10 22] serum albumin,[14 17 19] and residual renal function.[18] However, a recent study of Korevaar et al. in the Netherlands showed that multivariate adjustment for know case-mix differences at the start of dialysis therapy was not sufficient to adjust for all differences in quality of life of patients starting with HD and PD.[12] After proper case-mix adjustment, pre-HD patients scored significantly lower than pre-PD patients, indicating that there are other unknown variables (possibly difficult to quantify) that influence the process of fitting patients to treatments. Korevaar et al. conclude that in future non-randomised studies to compare HRQOL of HD and PD patients, assessment of HRQOL just before start of dialysis and subsequent adjustment for baseline values should be performed.[12]

Quality of life of Automated Peritoneal Dialysis patients (chapters 2 and 4)

Although Automated Peritoneal Dialysis (APD) as a modification of Continuous Ambulatory Peritoneal Dialysis (CAPD) was developed in the early 1980s,[23] surprisingly little is known about quality of life of APD patients. However, the number of patients using APD has been growing fast in the Netherlands:[24] on January 1 2000, 376 APD patients were registered in the Netherlands, representing more than 25% of all peritoneal dialysis patients (n = 1,438). Between 1998 and 2000 the number of patients on APD rose from 280 to 376, a 34% increase.[24] The growing use of the APD technique is, however, not yet reflected in the quality of life literature, because our review (chapter 2) revealed only five studies that had included APD patients.[25-29] Unfortunately, four of these five studies reported quality of life data at aggregate level only, hampering assessment of study results at the level of treatment modality. Only one study, a small randomised trial in 25 APD and CAPD patients published in 1999, reported data by treatment modality;[28] no differences in quality of life between APD and CAPD patients were found. Another randomised clinical trial performed in the Netherlands in the early 1990s compared CAPD and Continuous Cycling Peritoneal Dialysis (CCPD), a variant of APD with an extra daytime exchange of dialysis fluid.[30] As part of this study, emotional wellbeing of patients was measured with the Affect Balance Scale,[31] and overall wellbeing and overall satisfaction were measured using a 7-point Likert scale. Although these measures do not fit into our operationalisation of health-related quality of life (chapter 2), it is interesting to note that no differences were found between the two patient groups.

Because little was known about health-related quality of life of APD patients at the time we performed our quality of life studies, an exploratory study was conducted (chapter 4).

Because the NECOSAD-TAS study included only 7 APD patients, additional interviews were held with 30 APD patients from three dialysis centres with relatively large numbers of APD patients. To ensure comparability of the two groups, the inclusion and exclusion criteria for APD patients were similar to those for the NECOSAD-PD patients. After adjustment for case-mix variables, APD treatment appeared to be an independent indicator of better mental health (measured with the SF-36 mental health summary score) and of the absence of anxiety and depression (measured with the EQ-$5D_{profile}$). Especially the social functioning of APD patients was better than that of CAPD patients; this might be because during the day APD patients are free from treatment, allowing a more normal social/working life. That APD patients were less anxious and depressed than CAPD patients is more difficult to explain, but treatment selection may have played a role. Patients with higher basic anxiety levels may avoid choosing the APD technique out of fear if being attached to a machine while asleep. Treatment selection in general must be considered when interpreting the positive quality of life results of the APD patients in our study. The results of this first exploratory study warrant a larger and better controlled study, preferably a randomised trial. It may be less difficult to randomise PD patients to CAPD or APD, than to randomise dialysis patients to haemodialysis or to peritoneal dialysis. The small randomised study by Bro et al.[28] and the Dutch study by de Fijter et al.[30] have shown that, in principle, it is possible to randomise patients over both forms of peritoneal dialysis.

High health preferences of dialysis patients (chapters 2, 3 and 4)

Health preferences reported by 165 Dutch dialysis patients revealed relatively high values for the actual health status of patients (chapters 3 and 4). Values elicited with Standard Gamble (SG) and Time Trade Off (TTO) methods indicate that patients on average value their current health state as 74 to 93% of normal health. Typical values of prevalent dialysis patients reported in the literature (Appendix 3A and 3B of chapter 2) range from 0.40 to 0.70, with the exception of two studies reporting values above 0.80.[32 33] The average TTO value found for all 165 dialysis patients interviewed in our studies (0.89), was even somewhat higher than that found after renal transplantation (0.87) in another study.[1] What could be the reasons for the differences in scores between previous studies and our work?

Chapters 3 and 4 present several possible explanations. First, because all previous studies were performed in Canada or the USA, one obvious explanation is that health values are not comparable across national or international borders. This explanation is supported by Veenhoven et al. who found that the perception of happiness and wellbeing differed between countries and continents.[34] In their study, which included over 50 countries, the Netherlands was identified as having the second highest level of wellbeing. Additional evidence for the incomparability of health values comes from an American population study: the Beaver Dam Health Outcomes Study.[35] Their random sample of 1,356 healthy persons (mean age 64 years) had a mean TTO values of 0.86 (s.d. 0.23), even lower than the mean TTO score from Dutch dialysis patients (0.89). Although to our knowledge TTO values have never been elicited in healthy Dutch persons, basic values around 0.86 seem highly unlikely, as long as the median value of dialysis patients in the same age range equals 1.

Even within the same country, important quality of life differences between patients from different dialysis centres have been described.[19] Thus, another explanation may be the dif-

ferences in healthcare and social security systems between the Netherlands and north American countries. One obvious difference is that the drop in income after the onset of serious disease is much greater in the USA than in the Netherlands. Moreover, data reported by Matas et al. suggest that patient populations in the USA and the Netherlands are incomparable.[36] They describe the long-term quality of life after kidney and pancreas-kidney transplantation in a cohort of 1,138 recipients of donor organs. The mean SF-36 scores in this transplanted population, supposedly better than scores of dialysis patients (chapter 2), are similar to the mean SF-36 scores reported from the baseline quality of life measurements of dialysis patients in the NECOSAD-I study.[13] The better quality of life scores may be attributable to the selection of healthier patients in the Netherlands, a higher level of healthcare for end-stage renal disease patients, or a higher general level of quality of life in the Netherlands. Another indication of the incomparability of patient populations between the continents is that the mortality rate of patients undergoing dialysis in the USA is 25-50% higher than in Europe.[37] Acceptance in the USA of older and sicker patients with more coexisting conditions may explain these differences.[37] Whatever the explanation for the differences, it clearly is difficult to extrapolate health preferences from one country to another, because it is unlikely that patient populations are comparable. TTO and SG values from north American end-stage renal disease patients may not be extrapolated to European patients. The influence of cultural differences on health preferences and the transferability of study results to other countries remain a subject for future study.

(Societal) cost of renal replacement therapies (chapters 6 and 7)

Although there is no lack of studies on the costs of renal replacement, Peeters et al. have shown that the quality of most studies is doubtful.[38] A major problem identified by Peeters et al. was that the perspective of the cost study was often not mentioned. Furthermore, important cost categories (e.g. hospitalisation or costs of nurses assisting with home therapy) were often ignored. According to international and recently issued Dutch guidelines on the different types of costs that should be included in economic evaluations, all relevant costs, irrespective of the payer, should be measured.[39-44] All relevant costs include direct healthcare costs, direct non-healthcare costs, indirect non-healthcare costs and indirect healthcare costs. In our analysis of costs of renal replacement therapy (chapters 6 and 7), we have attempted to adhere to these guidelines. For major direct healthcare cost drivers such as hospitalisation and staff costs, we used primary data from the NECOSAD trial. We believe that our estimates of direct healthcare cost are rather complete, although our cost figures for health service use outside dialysis centres (e.g. community nursing and general practitioner contacts) may be less reliable because we had to rely on patients' recall during face-to-face interviews.

In our costing study, direct non-healthcare costs were rather high for centre haemodialysis patients, mainly due to high travel costs. One limitation of our costing study is that help from the partner or other family members with home-based treatment was not valued in monetary terms. This may have led to an underestimation of the direct non-healthcare costs, and thus to an underestimation of total societal cost of kidney diseases.

For indirect non-healthcare costs, we used the friction cost method to value productivity losses, as recommended in recent Dutch guidelines for costing studies.[43] For end-stage

renal disease patients still participating in the paid work, the estimated annual productivity losses ranged from NLG 1,120 (€ 510 for females) to NLG 1,820 (€ 827 for males) (chapter 6). Total extrapolated indirect non-healthcare costs were small (NLG 3.5 million / € 1.59 million in 1994), mainly because most end-stage renal disease patients are older than 65 years or stopped working long before the onset of renal replacement therapy. Therefore, the indirect non-healthcare costs were subsequently excluded from our economic evaluation (chapter 7). In economic evaluation studies with a societal perspective, which should include indirect non-healthcare costs as part of the analysis, it is easier to demonstrate the cost-effectiveness of therapeutic interventions. Including the effects on absenteeism and disablement payments, low net costs or even cost savings may be demonstrated. This is certainly not the case with renal replacement therapies, partially because most patients are around 65 years of age, and partially because younger patients seldom have full-time jobs. Thus, the effects of renal replacement therapy on indirect non-healthcare costs are negligible at group level.

Especially in the case of ESRD patients, who die more or less immediately without RRT, it can be argued that all healthcare use not directly related to dialysis should be valued. We have attempted to include indirect healthcare costs by the valuation of costs of hospitalisation, medication and other healthcare services, irrespective of the indication for which it was used. However, we may have missed considerable cost drivers, such as costs of diagnostic and surgical procedures. Interestingly, none of the economic evaluation studies identified in our literature review (chapter 5) included indirect healthcare costs. In the absence of data for such estimates, average healthcare costs for age and gender, for instance as identified in top-down cost of illness studies,[45] could serve as a proxy for indirect healthcare costs.

Future cost studies should give more attention to direct non-healthcare costs. In particular, help given by partners and relatives should be valued because most home-based therapies, such as home haemodialysis and peritoneal dialysis, require some assistance. In our study, only 5% of peritoneal dialysis patients received help from community nurses, implying that most received assistance from relatives. Information on financial contributions from the patients themselves, e.g. for special diets, alternative therapies or adaptations to the house for home-based therapies, could further improve the current cost estimates.

Together with Dutch incidence and prevalence data, our cost estimates per treatment modality were combined into a bottom-up estimate of the 1994 cost of illness of end-stage renal disease in the Netherlands (chapter 6). Total direct healthcare costs of kidney diseases were estimated at NLG 650 / € 295 million annually, equivalent to over 1% of total healthcare spending in 1994. Although our actual cost study was performed in 1996 (at 1996 price levels) (chapter 7), the 1994 disease-specific estimate (chapter 6) was adapted later from the 1996 estimate, to allow a comparison with estimates presented in a general cost of illness study for the Netherlands in 1994.[45] In this study (the KVZ study), costs of all diseases in the Netherlands in 1994 were categorised into 62 disease clusters derived from the International Classification of Diseases-9th revision (ICD-9). Within the group "renal and urogenital diseases", NLG 85 / € 38.6 million was allocated to the diagnosis group "nephritis/nephrosis/nephropathy", the most obvious disease cluster for patients with chronic kidney failure. The substantial difference between the two estimates warranted the study pre-

sented in chapter 6. It appeared that the difference between both estimates is mainly explained by the completely different approaches of general and disease-specific cost of illness methods. The estimate of NLG 650 / € 295 million was arrived at following the disease-specific estimation, basically a multiplication of incidence and prevalence data by annual cost figures for new and existing patients. The estimate of NLG 85 / € 38.6 million was arrived at in a general cost of illness study using a "top-down" method. The aim of general cost of illness studies is to categorise healthcare expenses into disease clusters, to gain insight into the relative cost of different diseases.[46] The top-down method has an etiologic orientation: costs of medical care are classified (as far as possible) according to the underlying disease. For instance, renal care for a patient with diabetic renal failure will be classified under diabetes mellitus. Costs that are primarily related to comorbid conditions are classified under the comorbid condition. Otherwise, healthcare expenses for disease clusters would amount to more than 100% of total healthcare expenses.[47] Because chronic kidney failure is not a disease in itself but a result of damage to the kidneys due to various diseases, kidney patients have remained relatively "invisible" in the general cost of illness study. Furthermore, it appeared that haemodialysis was seriously underreported in the Landelijke Medische Registratie (LMR), the national registration of hospital care in the Netherlands. Less than 1% of all haemodialysis treatments in 1994 were registered in the LMR. In the absence of LMR data on dialysis, it was decided to divide the amount of money that was earmarked for haemodialysis in the 1994 annual healthcare budget for the Netherlands "Jaaroverzicht Zorg" (NLG 227 / € 103.1 million) pro-rata over all 62 ICD-9 disease clusters. As a result, the substantial spending for haemodialysis patients disappeared completely in the KVZ study. In future reports of the KVZ study, this shortcoming should be addressed. One partial solution would be to assign the amount of money earmarked for haemodialysis in the national healthcare budget only to diagnostic groups covering end-stage renal disease patients. Data from the Dutch Renal Replacement Registry (RENINE), which registers the primary disease of all Dutch end-stage renal disease patients, could be used for this purpose. A "translation" of the 60 different primary diagnoses used to classify end-stage renal disease patients in RENINE to the diagnostic groups of the ICD-9 (such as used in the KVZ study) has been published by us elsewhere.[48] It appeared that only 12 of the 62 diagnostic groups that were distinguished in the KVZ study covered end-stage renal disease patients. Moreover, analysis of the allocation of all prevalent end-stage renal disease patients over these 12 diagnostic groups revealed that two third of all patients originate from only three disease clusters, namely hypertension (25%), diabetes mellitus (19%) and nephritis/nephrosis/nephropathy (22%). These data could be used to assign end-stage renal disease expenses pro-rata to relevant diagnostic groups only. Such an approach would, to some extent, reduce the "invisibility" of end-stage renal disease treatment in future general cost of illness studies. Furthermore, the reporting of data by Dutch dialysis centres to the LMR should be drastically improved.

We have limited our cost of illness study to end-stage renal disease, although originally we planned to report on cost of illness of kidney diseases. The latter includes all patients with reduced kidney functioning, without the necessity of renal replacement therapy (predialysis patients); however, many uncertainties surround the cost of illness of this patient group. First, the exact number of predialysis patients is unknown because many persons may be unaware of reduced kidney functioning. Based on the annual National Health Survey, it is

estimated that between 30,000 to 45,000 persons have kidney diseases, including those already using renal replacement therapy.[48] However, many more may have a sub-clinical kidney disease. In the future, data from the PREVEND study [49] may allow a more precise estimate of the number of patients at risk for end-stage renal disease. PREVEND is a cohort study in the general population of Groningen, aiming at the assessment of the prevalence of (different levels of) microalbuminuria. Also, unknown is the volume and cost of healthcare provisions for predialysis patients. An American study on predialysis patients and end-stage renal disease patients showed similar hospitalisation rates and similar duration of hospital stay.[50] Patients identified with limited kidney function may use expensive "cocktails" of medication, such as ACE-inhibitors, calcium antagonists, diuretics, cardiovascular and lipid-lowering medication. Besides, regular blood and urine monitoring, renal biopsies, ultrasonography and other diagnostic procedures may increase the already high annual costs. More studies are needed to identify the number of predialysis patients and the level of healthcare use and associated costs. In addition, economic evaluations should quantify the benefits (economic and otherwise) of postponement of renal replacement therapy by appropriate management of predialysis patients.

Cost-effectiveness of renal replacement therapies (chapters 5 and 7)

The literature review on economic evaluations of renal replacement therapies presented in chapter 5 showed the flaws of most published studies. Considering the absolute cost of treatments and the relatively large proportion of the entire healthcare budgets spent on renal disease treatments (chapter 6), it is surprising that so few good quality economic evaluations of these programmes have been published.

In chapter 7, the conclusion was drawn that it makes little sense to further concentrate on substitution policies to improve the cost-effectiveness of the end-stage renal disease program. This conclusion is certainly valid for the Netherlands where the cheaper treatment modality, peritoneal dialysis, is widely accepted and patients are generally able to choose freely between different dialysis therapies. In the Netherlands as much as 30 percent of the patients are being treated with peritoneal dialysis.[24] Once this high level of peritoneal dialysis use is reached, further substitution from more expensive haemodialysis to less expensive peritoneal dialysis no longer serves to improve the cost-effectiveness of the end-stage renal disease treatment program. Higher technique failure,[51] associated with more frequent changes of therapy and higher cost, is thought to be responsible for this result. However, use of peritoneal dialysis is not so widespread in other European countries (e.g. Belgium, Italy and France) where 10% or less of all end-stage renal disease patients are being treated with peritoneal dialysis.[52] Wider diffusion of peritoneal dialysis in such countries might contribute to improvement of overall cost-effectiveness of renal replacement therapies and may also decrease the total absolute amount spent on end-stage renal disease treatments. This assumption is supported by data from de Vecchi et al. who listed the overall amount of the national healthcare budget that is spent on dialysis treatment (hence, excluding renal transplantation) for several European countries: this ranges from 0.7% (United Kingdom) to 1.8% (Belgium), with most countries spending around 1.5% of healthcare budgets on dialysis.[53] The Dutch estimate of the national healthcare budget that was spent on all renal disease treatments including renal transplantation (1.1%) as presented in chapter 7, is in the

lower part of the range reported by de Vecchi et al.[53] Two explanations for the large differences in healthcare spending are: the overall prevalence of end-stage renal disease treatments in terms of the percentage of the population receiving treatment, and the relative amount of home-based therapies such as peritoneal dialysis and home haemodialysis. Countries where peritoneal dialysis has hardly diffused into the end-stage renal disease treatment programme consistently show relatively high spending on the renal replacement programme.[53] The only European country where peritoneal dialysis rates are higher than in the Netherlands is the United Kingdom, where 45% of dialysis patients are being treated with peritoneal dialysis. In the U.K. "only" 0.7% of the healthcare budget is spent on dialysis treatments. The Markov-chain model that was presented in chapter 7 could be used to further explore the issue of the rationality of substitutive policies for countries other than the Netherlands. An example of such an investigation would be to construct a base-case scenario where only 2% of the incident and prevalent patients are being treated with peritoneal dialysis, while keeping all other model inputs constant. Then, it could be assumed that 10, 20 and 30% of new patients start with peritoneal dialysis. Such modelling work could shed further light on the possibility to further increase the cost-effectiveness of dialysis provision. Recently, a similar approach was reported by Kirby and Vale [54] who employed a Markov-model to determine which method of dialysis (CAPD or haemodialysis) a patient should have as the initial method of RRT in the U.K., where approximately 50% of new patients beginning dialysis receive CAPD. Of the 16 different scenarios explored, they found HD to be the dominant strategy (more effective at less cost) in 8 scenarios, while HD was more effective at higher cost than CAPD in the other 8 scenarios. In a literature review, they consistently found more treatment changes and lower technique survival rates for CAPD patients. Kirby and Vale concluded that in the U.K., investing in more haemodialysis facilities could improve the overall cost-effectiveness of end-stage renal disease treatment. Our finding that, given a rate of PD use of 30% in the Netherlands, transfer of more HD patients to PD would not improve overall cost-effectiveness of the RRT programme, is in accordance with Kirby and Vale.

Two scenarios explored in chapter 7 proved to be totally unrealistic: i.e. scenarios 4 and 5, which assumed a higher number of transplantations after the introduction of new donor legislation in 1998. This legislation encouraged active registration of the willingness to be a post-mortem donor for every Dutch citizen aged 18 years or older. It was expected that the number of renal transplantations would rise from 30 to 38 per million of the population,[55] and perhaps even rise to 44 per million of the population (scenario 5). However, the number of post-mortem kidneys available for transplantation dropped from 412 in 1997 to 338 in 1999. The total number of kidney transplants dropped from 505 in 1997 (32 per million of the population) to 454 in 1999 (29 per million population), despite a simultaneous increase in the number of living-related transplants.[24] Thus, the new donor legislation did not contributed to a further increase in the cost-effectiveness of the Dutch end-stage renal disease programme, as was expected at the time of writing chapter 7. On the contrary, the new donor legislation may be regarded as very cost-ineffective because, apart from the cost of maintaining the registration, additional dialysis stations are needed to keep eligible patients in optimal condition, with associated intangible costs of sub-optimal health status and prolonged waiting time to transplant. The donor system may be characterised as a costly way of causing patient distress.

As was shown in chapter 5, most economic evaluation studies simply count the annual cost of therapy and claim this as the cost per life year gained, assuming that this investment yields one additional year of life. However, this approach does not reflect the clinical reality of changes between modalities, which occur frequently and at relatively high cost (chapter 7). Moreover, to state that renal transplantation or CAPD is the most cost-effective therapy simply because it is cheaper than other treatments fails to take into account that a transplantation programme can not exist without the back-up of a dialysis programme. The dialysis programme is needed to keep patients in optimal condition for the awaited transplant and to serve as a back-up in case the donor organ is rejected. This mutual dependency applies to all different dialysis modalities: patients who have or gradually develop contraindications for one treatment modality may benefit from the availability of other modalities. The cost-effectiveness of end-stage renal disease treatments should, therefore, primarily be assessed at an aggregate level, before considering the different therapeutic modalities. For such an aggregate analysis, data on typical treatment patterns and changes between the different treatment modalities are needed. We were able to use real-life data on patient and technique survival, as well as treatment histories of some 20,000 end-stage renal disease patients, from the Dutch Renal Replacement Registry. Our approach, an integrated analysis of the cost-effectiveness of the total end-stage renal disease treatment programme, is different from most other studies because the mutual dependencies in the overall treatment programme are accounted for.[56] In the treatment of end-stage renal disease, renal transplantation is generally regarded as the gold standard. However, the lack of donor organs and the necessity of a dialysis programme as back-up hampers the application of renal transplantation for all patients, despite its cost-effectiveness. Our approach acknowledges the reality that without renal replacement therapy, patients with end-stage renal disease will die and that, at present, clinicians tend to consider all patients with end-stage renal disease for dialysis, regardless of age or comorbidity. Future economic evaluations should report cost-effectiveness of treatment at the level of sub-groups of patients with identical case-mix, e.g. patients of similar age and with similar concurrent diseases. Such data reporting can contribute to existing knowledge on the cost-effectiveness of renal replacement therapy.

One intriguing question is whether dialysis, if developed nowadays, would be reimbursed by public health insurance. Similar to 40 years ago, the strongest argument for reimbursement is the life-saving capacity of this new medical technology. On the other hand, a cost-effectiveness ratio as high as NLG 100,000 / € 45,500 per life-year gained compares unfavourably with most other new healthcare services. A recent technology with a similar high cost-effectiveness ratio that is reimbursed under Dutch health insurance is lung transplantation.[57] Although this is an expensive technology, the budget implications are only a fraction of those of the introduction of dialysis, because the scarce availability of donor lungs severely restricts its use. Another example is Viagra; despite its relatively favourable cost-effectiveness profile it was not reimbursed, presumably because of the high number of possible users.[58] For dialysis, given the enormous budget implications and unfavourable cost-effectiveness profile, it is likely that its diffusion would be severely restricted to specific patient groups, should a reimbursement decision be needed nowadays.

Methodological problems with health preference methods and the use of patient preferences in economic evaluations (chapters 2, 3, 4 and 8)

Surprisingly few economic studies incorporating quality of life aspects were identified (chapter 5). However, because of the far-reaching consequences of being a RRT patient, intangible costs/quality of life losses should be valued in a study. Thus, cost-utility analysis seems to be the best research design for the evaluation of interventions for end-stage renal disease patients. Preferences to be used in cost-utility analysis can be derived from patients, relatives, health professionals and the general population, using methods such as Time Trade Off (TTO), Standard Gamble (SG) and rating scale. Although the TTO is claimed to be a psychometrically sound measure in general [59 60] and in end-stage renal disease patients,[61] our literature review (chapter 2) revealed doubts about this instrument. Application of the TTO as a valuation method of the own health state was hampered by relatively high non-response,[1 62 63] and the TTO was not responsive to clinical changes.[64-66] Our own studies (chapters 3,4, and 8) added doubts about the use of both TTO and SG as methods for the valuation of the patient's own health status.

We have used TTO and SG as measures of health-related quality of life (HRQOL). The variance in all HRQOL outcomes was only poorly to moderately explained by the clinical, socio-demographic and treatment-related variables included in our study (chapters 3 and 4), and found by others.[2 10 14 16 19] This implies that HRQOL outcomes may be determined by factors other than the ones we explored. As in other studies using SG and TTO, patients were explicitly instructed to value their current health status only. However, we doubt whether patients have followed these instructions, or whether patients can follow these instructions. For instance, respondents referred to their wish to see grandchildren grow up, or to celebrate a future wedding anniversary when they refused to trade-off time for quality or to accept a gamble with a small chance of dying immediately. Other respondents considered it impossible to trade-off any lifetime at all or to accept a gamble, because such decisions (even though hypothetical) were not considered appropriate in the context of their religion. This may imply that responders are unable to distinguish between the hypothetical nature of the question and their personal or family situation, demonstrating the presence of confounding factors in the valuation of health status. It is difficult to control for these confounding factors because the sources of bias are very complex. In summary, a serious problem with both the TTO and SG is that they fail to distinguish health-related quality of life (as influenced by the health problem to be valued) from other factors that contribute to overall wellbeing. Health is only one factor that influences the health preference scores, and often not the most important one.

In chapter 8, we discussed the sensitivity of TTO and SG to discriminate between therapeutic modalities. As described in chapters 3 and 4, no differences in valuations for the own health states were observed at the level of the different treatment groups. However, using several general population data sets for the valuation of health states, we observed differences in the valuation of health states of different patient groups. It was hypothesised that outsiders may identify subtle differences in the health status of patients, whereas the patients themselves "compress" their valuations in a small (upper) part of the scale, with inherent loss of discriminatory power. An obvious explanation for this phenomenon is that patients have been successful in applying coping strategies. They have incorporated their

expectations of the future into the valuation of their current health status and accept that their health status will most likely not improve. The valuation compression adds to the problems in the interpretation of preference scores from patients.

At the time of designing our study (1994-1995), we planned to use patient preferences in the economic evaluation, together with general population values. However, ranking of the quality of life scores of patients in the treatment groups appeared to differ depending on the perspective (patient/general population) and valuation method. This observation, as well as problems in the interpretation of scores as (described above) and the methodological problems identified in the literature review (chapter 2), strongly advocates not to use patient valuations in cost-utility analysis. Also, guidelines for and textbooks of economic evaluation published in the last five years have advocated the use of general population values.[39 44] However, this advice is often ignored in recent economic evaluations.[67 69] Researchers planning economic evaluations alongside clinical studies should incorporate HRQOL instruments for which general population weights have been determined, such as the EQ-5D [70] or the SF-36.[71] In comparison with patient interviews using TTO, SG or similar instruments, this is a relatively easy, inexpensive and reliable way to elicit values to be used in economic evaluations.

General remarks and directions for further research

This thesis presents information on the economic evaluation of renal replacement therapies. In the 40 years of its history, this is not the first attempt to collect data on cost and outcomes of end-stage renal disease treatment. On the contrary, our literature reviews (chapters 2 and 5) showed much research in this field. The current research builds on earlier Dutch evaluation studies,[72 73] but provides more accurate and up-to-date figures. Inevitably, areas for further research remain.

With respect to quality of life aspects, more studies are needed to gain a better understanding of quality of life of APD patients. Although we have shown some benefits in HRQOL from APD treatment, these tentative results need confirmation. Furthermore, the issue of the relatively high health preferences of Dutch dialysis patients remains a challenge. Ideally, the relationship between health preference scores and health profile scores should be assessed within patient groups from different countries, to assess whether patient groups with similar health profiles differ with respect to their valuation of own health status. Data sets including at least either the SF-36 or the EQ-5D, and SG or TTO are needed for such research. Also, the observation that general population samples may better differentiate between patient groups than the patients themselves (as described in chapter 8), needs further investigation. The study could easily be replicated with patient data sets including the $EQ\text{-}5D_{profile}$. Finally, our literature review showed that the relationship between the process of care and HRQOL outcomes of patients has yet hardly been investigated. Why do patients in one dialysis centre show better HRQOL than in another centre? Can differences in the process of care be identified and quantified? These questions remain to be answered by future research.

With regard to economic aspects, the question remains whether cost advantages of home-based techniques will remain when the help of relatives with therapy are valued in monetary terms. Furthermore, the current study focused more on dialysis than on renal transplantation. For transplantation, we used estimates of the quality of life and cost figures published earlier. EQ-5D data are needed to better estimate patient and general population values of transplanted patients' health states. The Markov-model employed in chapter 7 could be improved with better empirical data on renal transplantation, although it is unlikely that the cost and outcome advantages of transplantation would change substantially. Recent developments in the field of renal replacement therapy have revealed new research topics. For example, daily home haemodialysis may be more costly but also more effective, as postulated recently in a small study;[74] this claim should be further investigated. In addition, in future studies, cost-effectiveness of renal replacement therapy should be reported at the level of patient groups with similar case-mix profiles. Finally, the issue of the optimal mix between treatments in order to organise the end-stage renal disease treatment programme at national level in the most cost-effective way, warrants additional study. As was shown by Kirby and Vale,[54] a 50% peritoneal dialysis rate nationally may not be the most cost-effective way to organise the programme. We found that at a 30% peritoneal dialysis rate, the overall cost-effectiveness of the treatment programme could not be much improved. Future modelling studies should aim to quantify the optimal mix of treatments to ensure that end-stage renal disease treatment is offered in the most cost-effective way, not only in the Netherlands but also in countries where peritoneal dialysis has hardly diffused into the healthcare system.

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Summary

Patients with end stage renal disease are dependent on one of the three major types of renal replacement therapy currently available: haemodialysis, peritoneal dialysis and renal transplantation. In the Netherlands on January 1 2001, approximately 9,850 patients were being treated with renal replacement therapy. Each year more than 1,400 new patients have to start renal replacement therapy, which is a lifelong, complex and costly treatment with a serious impact on the patient's quality of life.

The main objective of this thesis is to evaluate the costs and outcomes of end stage renal disease treatments in the Netherlands. The material presented in this thesis consists of literature reviews, empirical research on quality of life of dialysis patients and costs of different therapies, and modelling studies. The empirical work was performed in the context of an ongoing clinical cohort study on the adequacy of dialysis treatment, the NECOSAD-I study (Netherlands Cooperative Study on Adequacy of Dialysis). As a sub-study of NECOSAD-I, the present study, called NECOSAD-Technology Assessment Study (NECOSAD-TAS), was initiated in 1995.

The thesis comprises nine chapters. Chapter 1 gives background information on renal replacement therapies and on the epidemiology of renal failure in the Netherlands. The research questions addressed in the subsequent chapters are also briefly introduced in chapter 1.

Chapter 2 addresses quality of life measurements in renal failure patients. A systematic review of the literature on health related quality of life (HRQOL) of end stage renal disease patients is presented. The review focuses on six well-known HRQOL instruments used in renal populations: i.e. four health profiles (Short-Form 36, Nottingham Health Profile, Sickness Impact Profile and Quality of Life Index) and two health preference methods (Standard Gamble and Time Trade Off). Studies were identified using bibliographic databases. Of the 114 publications that were initially selected because at least one of the six HRQOL instruments were applied, 57 remained after further selection based on study quality criteria. The main conclusions of the literature review are: (1) the methodological soundness of the use of the Short-Form 36 and the Sickness Impact Profile in renal patients is best documented, (2) HRQOL of end stage renal disease patients is worse than HRQOL of the general population, especially in the physical dimensions of HRQOL, (3) a higher age and the presence of comorbid diseases are strong determinants of lower HRQOL of renal disease patients, (4) HRQOL of transplanted patients is better than that of dialysis patients, but no major HRQOL differences exist between patients treated with the different dialysis modalities.

Chapter 3 presents a cross-sectional study on HRQOL of 69 haemodialysis and 66 peritoneal dialysis patients participating in NECOSAD-TAS. HRQOL was assessed with two health profiles (Short-Form 36 and EQ-5Dprofile) and two health preference methods (Standard Gamble and Time Trade Off). Few studies have applied these two different types of HRQOL instruments simultaneously. The main objective of this study was to assess the relationship between information acquired from the two different types of HRQOL instruments in dialysis patients. A second aim was to compare HRQOL between the two dialysis groups and also to compare HRQOL of dialysis patients with a general population sample of similar age. The relationship between socio-demographic, patient-related and treatment-

related background variables and HRQOL outcomes was also investigated. HRQOL of dialysis patients, as measured with health profiles, was severely impaired. The health preference scores of patients however were higher (0.82 to 0.88) than previously reported in the literature. Correlations between health profiles and health preferences were poor to modest. HRQOL outcomes were poorly explained by background characteristics. There were no significant differences in HRQOL between the haemodialysis and peritoneal dialysis groups. It is concluded that health profiles and health preference methods represent different aspects of HRQOL. An impaired health status may not be reflected in the preference scores. Coping strategies and other attitudes towards health may have a stronger effect on the preference scores than on the health profile outcomes. It is concluded that the added value of health preference methods in clinical research may be limited.

Chapter 4 investigates HRQOL of Automated Peritoneal Dialysis (APD) patients. Because APD is a relatively new technique, data on HRQOL of APD patients are scarce. The objectives of this cross-sectional study were (a) to explore HRQOL of APD patients, (b) to compare this outcome with HRQOL of continuous ambulatory peritoneal dialysis (CAPD) patients and a general population sample, and (c) to study the relationship between HRQOL outcomes and background variables. The study sample comprised 37 APD patients and 59 CAPD patients from NECOSAD-TAS. HRQOL instruments used were similar to those in the study reported in chapter 3. Physical functioning of both APD and CAPD patients was more impaired than in the general population, but there were no differences in mental functioning. Multivariate analyses showed that the mental health of APD patients was better than that of CAPD patients. In addition, APD patients were less anxious and depressed than CAPD patients. There were no differences between APD and CAPD patients concerning the physical aspects of HRQOL and role functioning. Other variables that influenced HRQOL outcomes were age, the number of comorbid diseases, and type of primary kidney disease. It was concluded that HRQOL of APD patients is at least equal to that of CAPD patients.

Chapter 5 presents a systematic literature review on economic evaluations of renal replacement therapy published between 1988 and 2000. The aim of this study was to review and compare current knowledge on the costs and effects of renal replacement therapies, and to assess the methodological quality of the economic evaluations in the field. Of the more than 1,700 references found in six bibliographic databases, 127 publications were assessed using a standardised quality rating system. Of these, only 11 papers were of sufficient methodological quality. In general, studies were particularly weak with regard to the costing parts, including lack of discounting and not applying the opportunity cost principle. Renal transplantation and CAPD were consistently found to be more efficient than haemodialysis. The interpretation of this conclusion is, however, hampered by the fact that most studies did not correct for differences in casemix between patients being treated with different renal replacement therapies.

Chapter 6 evaluates the cost of illness of end stage renal disease in the Netherlands in 1994, including an estimation of the number of Disability Adjusted Life Years (DALYs) associated with end stage renal disease. Projections of patient numbers and costs to society up to 2003 are also presented. The costs of five dialysis modalities and of renal transplantation were estimated using data from NECOSAD-I, additional data collection in dial-

ysis centres, published data, and interviews with 165 dialysis patients. Cost per treatment modality was combined with detailed 1994 data on incident and prevalent patient numbers and treatment changes from the Dutch Renal Replacement Registry, to estimate total direct healthcare cost of renal replacement therapy. The cost of renal replacement therapies ranged from NLG 18,000 (€ 8,182) for renal transplantation to NLG 142,000 (€ 64,545) for centre haemodialysis, per patient per year. Total direct medical cost of care for renal patients were NLG 584 million (€ 265.45 million) in 1994, representing about 1% of total healthcare spending in that year. Indirect costs amounted to NLG 3.5 million (€ 1.59 million). Renal diseases were associated with a loss of 14,000 DALYs. In 2003, we expect around 11,500 patients in the renal replacement programme, with associated societal costs of more than NLG 900 million (€ 409.1 million). It is concluded that renal insufficiency is a major health problem in the Netherlands, associated with a considerable loss of DALYs and high costs to society.

Chapter 7 examines the cost-effectiveness of end stage renal disease (ESRD) treatments. Empirical data on costs of treatment modalities and quality of life of patients were collected alongside a clinical trial and combined with data on patient and technique survival from the Dutch Renal Replacement Registry. A Markov-chain model, based on the actual Dutch ESRD program as at January 1 1997, was employed to estimate the cost-effectiveness and cost-utility of dialysis and transplantation over the 5-year period 1997-2001. At the aggregate level, full care centre haemodialysis was found to be the least cost-effective treatment, while transplantation and CAPD were the most cost-effective treatments. Using the Markov-chain model, the influence of policies to transfer patients from more to less expensive dialysis modalities on the overall cost-effectiveness of the Dutch ESRD treatment program was studied. The influence of such policies in the Dutch context was found to be modest, because a high percentage of patients is already being treated with more cost-effective treatment modalities. In countries where haemodialysis is still the only or the major treatment option for ESRD patients, transfer of patients from haemodialysis to CAPD might have a more substantial impact on overall cost-effectiveness of ESRD treatment.

Chapter 8 returns to the topic of the quality of life of patients, but now focusing on implications of the use of patient values (or patient utilities) in evaluative research. The chapter is rooted in the observation that for all dialysis treatment groups, patients showed similar Time Trade Off and Standard Gamble scores for their own health state, whereas the general population valuations for the same health states were found to differ across treatment groups. First, we summarise the literature on differences in valuation for hypothetical and actual (own) health states between patient groups and between patient groups and other rater groups. It was found that patients' values are generally higher than outsiders' values. Second, two empirical studies on dialysis patients and other rater groups are reported. In the first study, dialysis patients and students had to value hypothetical health states with Standard Gamble and Time Trade Off. Patients assigned higher values than the students to hypothetical health states. In the second study, dialysis patients being treated with four different dialysis modalities were asked to value their own health state with Standard Gamble, Time Trade Off and a visual analogue scale (EQ_{VAS}), and to describe their health state on the $EQ\text{-}5D_{profile}$. Several $EQ\text{-}5D_{index}$ values (health index values derived from general population samples) were calculated for the four dialysis treatment groups, based on their EQ-

$5D_{profile}$. These health indexes discriminated between treatment groups, according to clinical impressions. However, treatment groups could not be differentiated based on the patients' own valuations of their health state. Whereas outsiders use almost the entire scale for their valuation of different health states, patients' valuations are compressed in the upper part of the scale; this may be due to the patients' successful coping behaviour. These results suggest that, using EQ-$5D_{index}$ values, general population samples may better discriminate between patient groups than the patients themselves. The valuation compression found in the patient groups may hamper the use of patient values in economic evaluations.

Chapter 9 summarises the most important findings of the studies addressed in this thesis and presents recommendations for further research. The results indicate that there are no major differences in HRQOL between haemodialysis patients and peritoneal dialysis patients. HRQOL of dialysis patients, as measured with health profiles, is more severely impaired than that of the general population. However, the high patient preferences elicited with Time Trade Off and Standard Gamble indicate that HRQOL is much less impaired than suggested from the application of health profiles. The fact that health preferences measure more than HRQOL alone may explain this contradiction. Factors influencing Standard Gamble and Time Trade Off scores include coping behaviour and personal circumstances. This hampers the interpretation of patient valuations. Therefore, patient valuations of own health status should not be used in evaluative research. A study on the cost of illness showed relatively high societal cost and a high public health burden of end stage renal disease. A scenario study revealed that there is little room for improvement in the overall cost-effectiveness of the Dutch end stage renal disease treatment programme. Future studies should focus on elucidation of the high health preference scores of Dutch dialysis patients, on improvement of cost estimates, especially direct non-health care costs, and on economic evaluation of renal replacement therapy for specific patient groups with a similar casemix.

Samenvatting

De belangrijkste functie van de nieren is om afvalstoffen en overtollig vocht te verwijderen uit het lichaam. Hoewel een mens ook goed kan functioneren met niet optimaal werkende nieren is er een stadium dat het vasthouden van afvalstoffen, zouten en water fataal kan worden. We spreken dan over terminale nierinsufficiëntie. In dat stadium van nierziekten moet gestart worden met nierfunctievervangende behandelingen, anders zullen patiënten spoedig overlijden. Drie belangrijke vormen van nierfunctie vervangende therapie zijn haemodialyse, peritoneale dialyse en niertransplantatie. Bij haemodialyse wordt het bloed ontdaan van afvalstoffen doordat het gespoeld wordt door een kunstnier in een dialyseapparaat. De patiënt wordt meestal drie keer per week gedurende enkele uren gedialyseerd in één van de circa 50 Nederlandse dialysecentra. Bij peritoneale dialyse wordt het bloed continue gezuiverd omdat er enkele malen per dag nieuwe spoelvloeistof in de buikholte wordt ingebracht. Het buikvlies fungeert bij peritoneale dialyse als een filter, dat het bloed van afvalstoffen zuivert. De patiënt kan deze handeling zelf thuis verrichten. Bij niertransplantatie krijgt de patiënt een "nieuwe" nier van een donor. Een succesvolle niertransplantatie maakt de continue behandeling van nierinsufficiëntie door dialyse overbodig. Vanwege een schaarste aan donororganen is niertransplantatie niet voor alle personen die daarvoor in aanmerking zouden komen mogelijk. Op 1 januari 2001 werden in Nederland circa 9850 personen behandeld met een van de drie vormen van nierfunctievervangende therapie. Jaarlijks starten circa 1400 nieuwe patiënten met nierfunctievervangende behandelingen. Deze complexe en dure behandelingen moeten levenslang worden volgehouden en beïnvloeden de kwaliteit van leven van de patiënt in hoge mate.

Het doel van het in dit proefschrift beschreven onderzoek is om de kosten en effecten van nierfunctievervangende behandelingen in Nederland te evalueren. Daarvoor werd gebruik gemaakt van literatuuronderzoek, empirisch onderzoek naar de kwaliteit van leven van patiënten en de kosten van diverse behandelmethoden, en van modellering. Het empirische deel van het onderzoek werd uitgevoerd in de context van een groot klinisch patiëntgebonden cohortonderzoek, de zogenaamde NECOSAD-I studie (Nederlandse Coöperatieve Studie naar de Adequaatheid van Dialyse). In 1995 ging de NECOSAD – Technology Assessment Study (NECOSAD-TAS) van start, als onderdeel van de NECOSAD-I studie. De resultaten van NECOSAD-TAS beschrijf ik in dit proefschrift.

Dit proefschrift bestaat uit negen hoofdstukken. Hoofdstuk 1 geeft achtergrondinformatie over de epidemiologie van nierziekten in Nederland en beschrijft de belangrijkste nierfunctievervangende behandelingen. Tevens biedt dit hoofdstuk een introductie op de onderzoeksvragen die in de verschillende hoofdstukken aan bod komen.

Hoofdstuk 2 gaat over het meten van de kwaliteit van leven bij nierpatiënten. Het geeft de resultaten weer van een systematisch literatuuronderzoek op het terrein van gezondheidsgerelateerde kwaliteit van leven van nierpatiënten. Dit literatuuronderzoek richt zich op zes bekende instrumenten om de kwaliteit van leven te meten. Alleen toepassingen van die meetinstrumenten bij nierpatiënten zijn meegenomen. Vier van de zes meetinstrumenten zijn gezondheidsprofielen (Short-Form 36, Nottingham Health Profile, Sickness Impact Profile en Quality of Life Index), waarbij aan de patiënt gevraagd wordt om op een aantal aspecten van kwaliteit van leven aan te geven hoe goed of slecht het met hem of haar gaat. De twee andere meetinstrumenten (Time Trade Off en Standard Gamble) zijn instrumenten om de subjectieve waardering van de patiënt voor zijn of haar gezondheidstoestand

te meten. Aan de respondent wordt gevraagd om aan te geven hoe deze zijn of haar gezondheid waardeert. Daarvoor wordt gebruik gemaakt van een vraag- en antwoordspel, waarbij de keuzes die de respondent maakt geacht worden de onderliggende waardering voor zijn of haar gezondheidstoestand te reflecteren. Dergelijke metingen worden ook wel utiliteitsmetingen genoemd.

Relevante studies voor het literatuuronderzoek werden geïdentificeerd met behulp van bibliografische databases. Op basis van vooraf geformuleerde kwaliteitscriteria bleven 57 van de 114 gevonden studies over voor dit literatuuronderzoek. De voornaamste conclusies ervan zijn: (1) dat voor de toepassing van de zes meetinstrumenten bij nierpatiënten de methodologische eigenschappen van Short-Form 36 en Sickness Impact Profile het best zijn gedocumenteerd, (2) dat de gezondheidsgerelateerde kwaliteit van leven van patiënten met nierinsufficiëntie slechter is dan die van groepen uit de algemene populatie, vooral voor wat betreft de fysieke component van kwaliteit van leven, (3) dat een hogere leeftijd en de aanwezigheid van andere ziekten sterke determinanten zijn van een lagere kwaliteit van leven, en (4) dat de kwaliteit van leven van patiënten die een niertransplantatie hebben ondergaan beter is dan die van dialysepatiënten, maar dat tussen de verschillende dialysebehandelingen geen duidelijke verschillen in kwaliteit van leven worden gevonden.

Hoofdstuk 3 beschrijft de resultaten van een cohortstudie naar de kwaliteit van leven van 69 haemodialysepatiënten en 66 peritoneale dialysepatiënten die aan NECOSAD-TAS meededen. De kwaliteit van leven werd geëvalueerd met twee gezondheidsprofielen (Short-Form 36 en EQ-$5D_{profile}$) en twee waarderingsmethoden (Standard Gamble en Time Trade Off). De EQ-$5D_{profile}$ is een veelgebruikt instrument om de gezondheidstoestand te meten, maar werd niet eerder bij nierpatiënten toegepast. Ook zijn er weinig studies gepubliceerd waarbij zowel gezondheidsprofielen als waarderingsmethoden gelijktijdig worden gebruikt om de kwaliteit van leven van één groep patiënten te beschrijven. Daarom was het voornaamste doel van dit onderzoek om de relatie te bestuderen tussen informatie die respectievelijk met behulp van gezondheidsprofielen en waarderingsmethoden verkregen wordt. Andere doelen van het onderzoek waren de vergelijking van de kwaliteit van leven van beide groepen dialysepatiënten onderling en die van dialysepatiënten met leeftijdgenoten uit de algemene populatie. Ook werd de relatie tussen socio-demografische kenmerken van patiënten, patiëntgerelateerde en behandelingsgerelateerde variabelen en kwaliteit van leven onderzocht. De gezondheidsprofielen lieten zien dat dialysepatiënten op een aantal terreinen van kwaliteit van leven aanzienlijke problemen kennen. De scores op de waarderingsmethoden waren echter hoger dan eerder in de literatuur beschreven. De correlatie tussen de scores op de gezondheidsprofielen en de scores op de waarderingsmethoden was zwak tot matig. Beide vormen van kwaliteit van leven uitkomsten konden niet goed worden verklaard door de onderzochte achtergrondkenmerken. Ook waren er geen significante verschillen in kwaliteit van leven tussen de beide groepen dialysepatiënten. In hoofdstuk 3 wordt de conclusie getrokken dat gezondheidsprofielen en waarderingsmethoden verschillende aspecten van kwaliteit van leven representeren. Een slechte gezondheidsstatus hoeft blijkbaar niet gereflecteerd te worden in een waardering voor de kwaliteit van het leven. Aanpassing (coping) en preferenties voor andere zaken dan gezondheid alleen lijken de waardering voor de kwaliteit van het leven veel sterker te beïnvloeden dan de scores op de

gezondheidsprofielen. In klinisch onderzoek is de meerwaarde van toepassing van patiëntwaarderingen voor de kwaliteit van het leven boven het gebruik van gezondheidsprofielen daardoor waarschijnlijk beperkt.

De kwaliteit van leven van patiënten die behandeld worden met automatische peritoneale dialyse (APD) is het onderwerp van Hoofdstuk 4. Omdat APD een relatief nieuwe vorm van peritoneale dialyse is zijn hierover nauwelijks kwaliteit van leven gegevens beschikbaar. Daarom is het lastig om kwaliteit van leven overwegingen mee te nemen bij de therapiekeuze. De doelstellingen van het in dit hoofdstuk beschreven onderzoek zijn: (a) de kwaliteit van leven van APD patiënten te beschrijven, (b) deze te vergelijken met de kwaliteit van leven van patiënten die behandeld worden met continue ambulante peritoneale dialyse (CAPD), (c) de relatie tussen kwaliteit van leven en achtergrondkenmerken te onderzoeken. De onderzochte groep bestond uit 37 APD patiënten uit drie Nederlandse dialysecentra en 59 CAPD patiënten die aan NECOSAD-TAS meededen. De gebruikte kwaliteit van leven meetinstrumenten waren hetzelfde als in het in hoofdstuk 3 beschreven onderzoek. Het fysieke functioneren van zowel APD als CAPD patiënten was slechter dan dat van de referentiegroep uit de algemene populatie, maar qua psychologisch functioneren werden geen verschillen met de algemene populatie gevonden. Multivariate analyses lieten zien dat de mentale gezondheid van APD patiënten beter was dan die van CAPD patiënten. Daarnaast waren APD patiënten minder angstig en depressief dan CAPD patiënten. Qua fysiek functioneren en op het gebied van zowel emotionele als fysieke rolfuncties werden geen verschillen tussen beide groepen gevonden. Achtergrondvariabelen die geassocieerd waren met kwaliteit van leven uitkomsten waren leeftijd, het aantal bijkomende ziekten en de primaire nierziekte. De conclusie die in hoofdstuk 4 getrokken wordt is dat de kwaliteit van leven van APD patiënten op zijn minst gelijk is aan die van CAPD patiënten.

In Hoofdstuk 5 worden de economische aspecten van behandeling van nierfalen geïntroduceerd. In dit hoofdstuk wordt een systematisch literatuuronderzoek gepresenteerd van alle goede economische evaluaties van nierfunctievervangende behandelingen die gepubliceerd werden tussen 1988 en 2000. Het doel hiervan was om de stand van zaken op het gebied van onderzoek naar kosten en effecten van nierfunctievervangende behandelingen weer te geven en om de methodologische kwaliteit van dit onderzoek te beoordelen. Van de ruim 1700 referenties die ik vond in zes bibliografische bestanden, werden 127 relevante publicaties beoordeeld met behulp van een kwaliteitsbeoordelingssysteem. Slechts 11 studies bleken op de meest essentiële punten aan de eisen die aan economisch evaluatieonderzoek gesteld mogen worden te voldoen. De grootste manco's in de niet geselecteerde studies bleken op het gebied van het kostenonderzoek te liggen; zo werd er vaak niet gedisconteerd en ook werd het opportuniteitskostenbeginsel niet toegepast. Vrijwel alle onderzochte studies concludeerden dat niertransplantatie en CAPD de meest kosten-effectieve behandelvormen zijn. De interpretatie van de conclusies in de 11 studies wordt echter bemoeilijkt doordat vrijwel nooit rekening gehouden werd met het feit dat de verschillende behandelvormen worden gebruikt voor patiëntengroepen die vaak heel verschillend zijn qua leeftijd, aantal en aard van bijkomende ziekten en gezondheidsstatus.

Hoofdstuk 6 beschrijft de maatschappelijke kosten en ziektelast van terminale nierinsufficiëntie in Nederland. In dit hoofdstuk wordt een raming gemaakt van het aantal Disability Adjusted Life Years (DALY's) dat hiermee samenhangt. Tevens wordt een raming gemaakt

van de ontwikkelingen in aantallen patiënten en maatschappelijke kosten van behandeling van nierziekten tot aan het jaar 2003. De kosten van vijf verschillende vormen van dialyse en niertransplantatie en de kosten van overgang naar een andere behandelvorm werden geraamd met gegevens uit NECOSAD-I, aanvullende dataverzameling in een aantal dialysecentra, gepubliceerde data en een interview met 165 dialysepatiënten. De Nederlandse registratie van niervervangende behandelingen (Stichting Renine) leverde gedetailleerde gegevens uit 1994 over het aantal nieuwe en bestaande Nederlandse patiënten per behandelvorm en over het voorkomen van wisselingen tussen de diverse behandelvormen. Deze epidemiologische gegevens werden gecombineerd met de opgestelde kostenraming per behandelvorm en de kosten van verandering van therapievorm om de totale directe gezondheidszorgkosten van nierfunctievervangende behandelingen in 1994 te ramen. De kosten van nierfunctievervangende therapie variëren van NLG 18000,- (€ 8182,-) voor niertransplantie tot NLG 142000,- (€ 64545,-) voor passieve centrum haemodialyse (een vorm van centrum haemodialyse waarbij alle noodzakelijke handelingen door verpleegkundigen worden verricht), per patiënt per jaar. De totale directe medische kosten van zorg voor nierpatiënten waren 584 miljoen gulden (€ 265,45 miljoen) in 1994, oftewel ongeveer 1% van de totale uitgaven aan gezondheidszorg in dat jaar. Kosten van productieverliezen als gevolg van de nierziekte werden geraamd op ongeveer 3,5 miljoen gulden (€ 1,59 miljoen). Nierziekten waren geassocieerd met een verlies van 14000 DALY's in dat jaar. DALY is een maat waarmee aangegeven kan worden hoe groot de volksgezondheidslast is van een bepaalde ziekte, in vergelijking met andere ziektes. De volksgezondheidproblematiek als gevolg van nierziekten blijkt vergelijkbaar te zijn met die van bijvoorbeeld AIDS, influenza en schizofrenie. Naar verwachting zullen er in het jaar 2003 ongeveer 11500 patiënten met nierfunctievervangende therapie behandeld worden, en zullen de maatschappelijke kosten van nierziekten oplopen tot circa 900 miljoen gulden (€ 409 miljoen). De conclusie van dit onderzoek is dat nierinsufficiëntie in Nederland een belangrijk gezondheidsprobleem is met een aanzienlijk verlies aan DALY's en hoge kosten voor de samenleving.

Hoofdstuk 7 behandelt de kosten-effectiviteit van niervervangende behandelingen. Voor deze studie werden gegevens verzameld over de kosten van vijf verschillende dialysebehandelingen. Om het effect van de verschillende behandelingen in kaart te brengen werden de gegevens die over de kwaliteit van leven van patiënten verzameld zijn (zie hoofdstukken 3 en 4) gecombineerd met gegevens over de overlevingsduur van patiënten en de "technische overlevingsduur" van behandelingen (dit is de tijdsduur totdat een definitieve overstap naar een andere behandelingsvorm wordt gemaakt). Deze gegevens werden verkregen van de Stichting Renine, die een registratie bijhoudt van alle nierfunctievervangende behandelingen die in Nederland worden uitgevoerd. Met behulp van een Markov-keten model werd de kosten-effectiviteit en kosten-utiliteit van alle niervervangende behandelingen, inclusief transplantatie, geraamd over de vijfjaarsperiode 1997-2001. Uitgangspunt van deze modelleringsexercitie waren de empirische gegevens over nierfunctievervangende behandelingen in Nederland per 1 januari 1997. Op geaggregeerd niveau bleek haemodialyse de behandeling te zijn met de hoogste kosten-effectiviteitsratio (dat wil zeggen de hoogste kosten per gewonnen levensjaar), terwijl CAPD en niertransplantatie relatief lage kosten-effectiviteitsratio's hadden. Met behulp van het Markov-keten model werd onderzocht of beleid gericht op substitutie van patiënten van duurdere naar goedkopere behandelvormen invloed zou hebben op de kosten-effectiviteit en kosten-utiliteit van het totale Nederlandse

niervervangingsprogramma. Deze studie wees uit dat dergelijk beleid waarschijnlijk weinig zal verbeteren aan de totale kosten-effectiviteit van nierfunctievervangende behandelingen, omdat in Nederland reeds een relatief groot deel van de patiënten behandeld wordt met de meer kosten-effectieve behandelvormen zoals CAPD. Slechts een drastische verhoging van het aantal transplantaties zal de doelmatigheid van het Nederlandse niervervangingsprogramma verbeteren. Er zijn echter veel landen waar haemodialyse de enige of verreweg belangrijkste behandelvorm voor nierfalen is. In deze landen zou dergelijk substitutiebeleid wellicht de kosten-effectiviteit van het totale behandelprogramma kunnen doen toenemen.

In Hoofdstuk 8 keren we weer terug naar het thema kwaliteit van leven. In dit hoofdstuk gaat het om de vraag wat de gevolgen zijn van het gebruik van patiëntwaarderingen (zogenaamde patiëntutiliteiten) in evaluatieonderzoek. Het idee voor dit hoofdstuk werd geboren uit de observatie dat patiënten uit alle dialysegroepen ongeveer dezelfde Time Trade Off en Standard Gamble scores hadden, terwijl de waarderingen van buitenstaanders (groepen uit de algemene populatie) voor de gezondheidstoestand van die verschillende patiëntengroepen wel degelijk heel verschillend waren. Allereerst wordt in dit hoofdstuk een samenvatting gegeven van de bestaande literatuur op het terrein van waarderingsverschillen voor de eigen dan wel een hypothetische gezondheidstoestand, zowel tussen groepen patiënten onderling als tussen patiënten en buitenstaanders. Een buitenstaander kan zowel een volledig gezond persoon zijn als een patiënt die een andere dan zijn eigen gezondheidstoestand waardeert. Voorts worden twee empirische studies gepresenteerd waarbij patiëntwaarderingen vergeleken worden met waarderingen van buitenstaanders. In de eerste studie werd aan dialysepatiënten en gezonde studenten gevraagd om hypothetische gezondheidstoestanden te waarderen met behulp van Standard Gamble en Time Trade Off. Patiënten gaven hogere waarderingen aan deze hypothetische toestanden dan studenten. In de tweede studie werd aan vier groepen dialysepatiënten, die allen met een andere vorm van dialyse behandeld werden, gevraagd om hun eigen gezondheidstoestand van dat moment te waarderen met Time Trade Off, Standard Gamble en een Visueel Analoge Schaal (EQ_{VAS}). Tevens werd gevraagd om de eigen gezondheidstoestand te beschrijven met behulp van het $EQ\text{-}5D_{profile}$. Gebaseerd op die door de patiënt zelf beschreven gezondheidstoestand werden voor de vier dialysegroepen $EQ\text{-}5D_{index}$ waarden berekend. $EQ\text{-}5D_{index}$ waarden weerspiegelen de waarderingen van de algemene populatie voor bepaalde gezondheidstoestanden die beschreven worden met het $EQ\text{-}5D_{profile}$. Er werden verschillende beschikbare $EQ\text{-}5D_{index}$ waarden gebruikt, afkomstig van populatiestudies uit verschillende Europese landen en gebaseerd op verschillende meetmethoden, zoals Time Trade Off en Visueel Analoge Schaal. Op basis van de $EQ\text{-}5D_{index}$ Time Trade Off waarderingen kon een rangorde in de vier dialysegroepen aangebracht worden die overeen kwam met klinische observaties. Op basis van de directe patiëntwaarderingen (ook Time Trade Off) was echter geen onderscheid tussen de vier behandelgroepen te maken. Waar buitenstaanders (i.c. de algemene populatie) vrijwel de hele beschikbare schaal gebruiken voor de waardering van de verschillende gezondheidstoestanden, worden de waarderingen van patiënten gecomprimeerd in het bovenste gedeelte van de schaal, het gedeelte waarin de betere gezondheidstoestanden zich bevinden. Dit zou het gevolg kunnen zijn van succesvol coping gedrag van patiënten. Deze resultaten suggereren dat buitenstaanders beter in staat zijn om gezondheidstoestanden te onderscheiden in termen van kwaliteit van leven dan de patiën-

ten zelf. Het gebrek aan sensitiviteit van patiëntwaarderingen voor kwaliteit van leven beperkt de toepassing van patiëntwaarderingen. Gebruik hiervan als primaire uitkomstmaat bij economisch evaluatieonderzoek moet dan ook worden ontraden.

In Hoofdstuk 9 worden de belangrijkste bevindingen van de verschillende studies uit dit proefschrift samengevat en bediscussieerd. Ook worden aanbevelingen voor verder onderzoek gedaan. De resultaten van dit onderzoek laten weinig verschillen in kwaliteit van leven zien tussen haemodialyse en peritoneale dialyse patiënten. De kwaliteit van leven van dialysepatiënten, zoals gemeten met gezondheidsprofielen, is aanmerkelijk lager dan de kwaliteit van leven van leeftijdgenoten uit de algemene populatie. Ondanks de problemen op het gebied van kwaliteit van leven werden voor alle patiëntgroepen hoge waarderingen voor de kwaliteit van het leven gevonden.

Hoewel dat formeel niet de bedoeling is, meten de waarderingsmethoden meer dan de waardering voor de gezondheidsgerelateerde kwaliteit van leven alleen. Dit zou de kloof tussen de uitkomsten van de gezondheidstoestandmeting en de waarderingsmethoden kunnen verklaren. Persoonlijke omstandigheden en karakteristieken, waaronder coping gedrag, familieomstandigheden en religie, hebben invloed op Time Trade Off en Standard Gamble scores. Dit bemoeilijkt de interpretatie van patiëntwaarderingen en mede daarom zou het gebruik van patiëntwaarderingen in (economisch) evaluatieonderzoek moeten worden afgeraden. Een studie naar de maatschappelijke kosten van nierziekten liet zien dat nierbehandelingen in Nederland leiden tot hoge maatschappelijke kosten en een flinke ziektelast. Uit een scenariostudie bleek dat er weinig ruimte is voor verdere verbetering van de kosteneffectiviteit van het totale nierbehandelprogramma in Nederland. Alleen een drastische verhoging van het aantal niertransplantaties kan de doelmatigheid van nierfunctievervangende behandelingen in Nederland verder verbeteren. Nader onderzoek is nodig om op te helderen waarom de Standard Gamble en Time Trade Off scores van Nederlandse nierpatiënten hoger zijn dan die van nierpatiënten uit andere landen. Op het terrein van kostenonderzoek is er behoefte aan verbeterde kostenramingen, in het bijzonder op het nu nog onontgonnen gebied van directe kosten buiten de gezondheidszorg, zoals kosten van informele zorg voor nierpatiënten. Verder zouden toekomstige economische evaluaties zich moeten richten op de kosten-effectiviteit van niervervangende behandelingen voor specifieke groepen patiënten met vergelijkbare achtergrondkenmerken.

Abbreviations

APD	Automated Peritoneal Dialysis
CAPD	Continuous Ambulatory Peritoneal Dialysis
CBA	Cost Benefit Analysis
CCPD	Continuous Cycling Peritoneal Dialysis
CEA	Cost Effectiveness Analysis
CMA	Cost Minimisation Analysis
CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
EDTA ERA	European Dialysis and Transplant Association - European Renal Association
EQ-5D	EuroQol-5D Instrument
$EQ\text{-}5D_{VAS}$	EQ-5D Visual Analogue Scale
$EQ\text{-}5D_{profile}$	EQ-5D classification system
ESRD	End Stage Renal Disease
FCHD	Full Care Centre Haemodialysis
HD	Haemodialysis
HHD	Home Haemodialysis
HRQOL	Health Related Quality of Life
HYE	Healthy Years Equivalent
ICD-9	International Classification of Diseases-9th revision
KVZ	Kosten van Ziekten Studie
LCHD	Limited Care Centre Haemodialysis
LMR	Landelijke Medische Registratie
MCS (SF-36)	Mental Component Summary score
MTA	Medical Technology Assessment
NECOSAD-I	Netherlands Cooperative Study on Adequacy of Dialysis - I
NECOSAD-TAS	Netherlands Cooperative Study on Adequacy of Dialysis - Technology Assessment Study
NHP	Nottingham Health Profile
NLG	Dutch guilder
PCS (SF-36)	Physical Component Summary score
PD	Peritoneal dialysis
QALY	Quality Adjusted Life Year
QLI	(Spitzer's) Quality of Life Index
RENINE	Renal Replacement Registry of the Netherlands
RRT	Renal Replacement Therapy
SF-36	Short-Form 36
SG	Standard Gamble method
SIP	Sickness Impact Profile
TTO	Time Trade Off method
TX	(Kidney) Transplantation

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About the author

Ardine de Wit was born on April 20th, 1965 in Stiphout (Noord-Brabant), the Netherlands. After completing secondary school (Peelland College in Deurne) in 1983, she studied Health Sciences at Rijksuniversiteit Limburg in Maastricht (currently Maastricht University) with a major in Health Policy and Administration. She graduated in 1989 and won the Catharina Pijls award for her student research on the diffusion of in vitro fertilisation in the United Kingdom and the Netherlands. After graduation she worked for a few months at the department of Health Economics of Rijksuniversiteit Limburg, and focused on the diffusion of lasers in health care. In October 1989 she moved to Erasmus University Rotterdam (Centre for Health Policy and Law) where she started research on the use of minimally invasive therapies in gynaecology. In 1990 she was sent on secondment to the Health Council of the Netherlands, to author a background study on this subject. At Erasmus University, she continued to work on various research topics, including the costs of lung transplantation, cost-effectiveness of growth-hormone therapy in small children, cost-effectiveness of hyperthermia in the treatment of pelvic tumours, and quality of life of lung cancer patients. In 1995, she started to work on the "NECOSAD – Technology Assessment Study". These research activities on economic and quality of life aspects of renal replacement therapy are described in this thesis. From February 1998, she works at the National Institute of Health and the Environment (RIVM) in Bilthoven, first at the Department of Public Health Forecasting (VTV), and from 1999 at the Department for Health Services Research (CZO). Here, her main research interest is the economic evaluation of preventive activities, especially immunisation strategies. At present, she is project leader of the project "Cost-effectiveness of prevention and health care interventions". Furthermore, she is member of several national and international societies in the field of health economics and technology assessment in health care.