MODELING OUTCOME OF PATIENTS ON RENAL REPLACEMENT THERAPY

Ylian Liem

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MODELING OUTCOME OF PATIENTS ON RENAL REPLACEMENT THERAPY

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	Prof.dr. J.F.M. Wetzels
	Dr. F.Th. de Charro
Copromotoren:	Dr. W.C. Winkelmayer
	Dr. J.L. Bosch

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Kidney Int. 2007 Jan;71(2):153-8.

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4.1 Living renal donors: optimizing the imaging strategy - decision- and cost-effectiveness analysis.
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1

General introduction

END-STAGE RENAL DISEASE

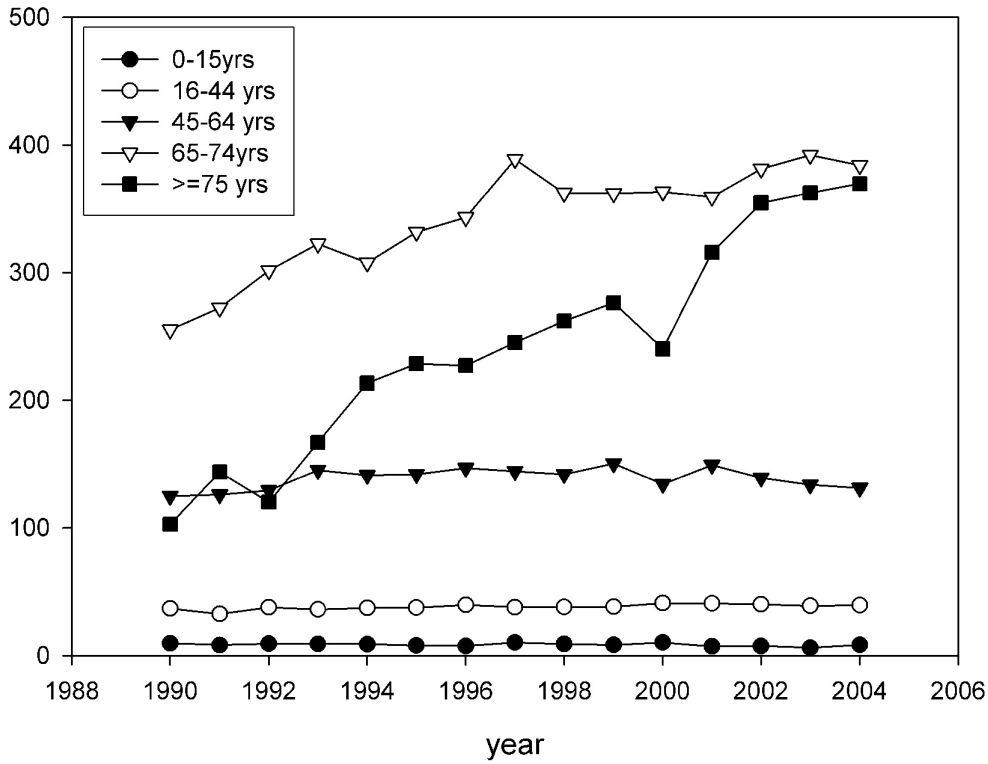
End-stage renal disease (ESRD) is a major health problem, affecting over 11,500 patients in the Netherlands.[1] A large spectrum of diseases may result in ESRD; the European Renal Association – European Dialysis and Transplant Association grouped these into eight categories: glomerulonephritis or -sclerosis, pyelonephritis, polycystic kidney disease, hypertension, renal vascular disease, diabetes and miscellaneous and unknown categories.[2] These diseases vary widely in the rate of development from chronic kidney disease into ESRD and in their associated prognosis once ESRD has developed. In the US, diabetes and hypertension are the most common causes of ESRD.[3] In the Netherlands, the proportion of patients with diabetes as the cause of ESRD is much lower, but has been growing in recent years.[4]

To decrease the burden of ESRD, its prevention is very important. Research has focused mainly on patients with diabetes and hypertension. For diabetes patients, strict regulation of blood glucose levels has shown to slow progression and to even reverse kidney damage.[5,6] For hypertensive patients, control of blood pressure has shown to slow progression of kidney disease as well.[7] Microalbuminuria is an important marker of kidney damage. Independent of their effect on blood pressure, inhibitors of the Renine-Angiotensin-Aldosteron System, Angiotensin-Converting-Enzyme-Inhibitors (ACE-Is) or Angiotensin-Receptor-II-blockers (ARBs), have been shown to reduce microalbuminuria, and to slow progression of most types kidney disease.[8] Lastly, reduction of dietary protein intake reduces progression in several disease categories.[7] Although these principles have been adopted in clinical practice guidelines,[9,10] many patients with chronic kidney disease still continue to progress to ESRD. The incidence in the Netherlands rose from 85.2 per million population (pmp) in 1994 to 103.7 pmp in 2004, and this increase was mainly due to a higher incidence among patients over 65 years of age (Figure 1).[11]

RENAL REPLACEMENT THERAPY MODALITIES

ESRD entails the need for Renal Replacement Therapy (RRT). Three major categories of RRT can be distinguished: hemodialysis (HD), peritoneal dialysis (PD) and renal transplantation (RTx). In HD therapy, blood is pumped into the dialyzer, into hollow fibers or parallel sheets which are suspended in a crystalloid solution (dialysate) and function as semi-permeable membranes.[12] Exchange of solutes is achieved through concentration gradients during counter transport, allowing for correction of fluid and electrolyte

FIGURE 1. The incidence of end-stage renal disease by age in the Netherlands over time (per million population)



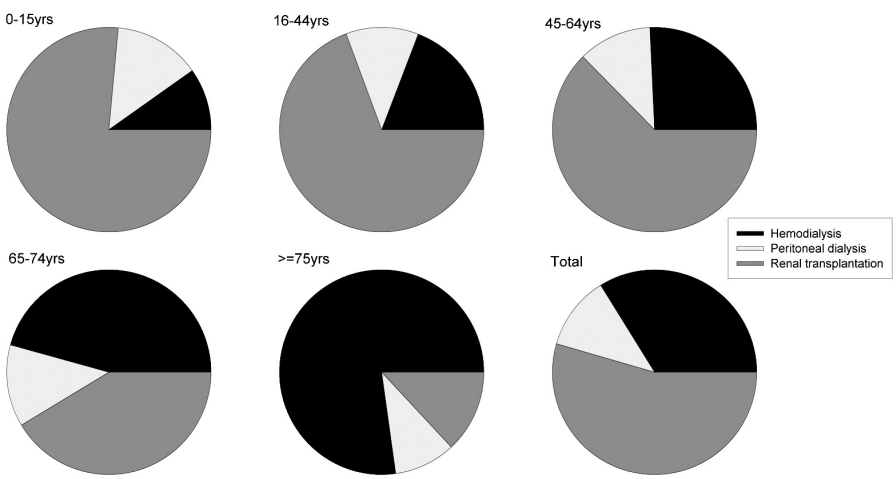
imbalances. Dialyzed blood is then returned to the body. Hemodialysis requires a vascular access. Usually, an arteriovenous fistula is constructed surgically for this purpose, anastomizing the radial, brachial or femoral artery to an adjacent vein. Gore-tex grafts may function as an arteriovenous fistula if the vessels are too fragile to create a fistula. Generally, patients need to be dialyzed for 3 to 5 hours, 3 times weekly. The treatment can be received at a dialysis center with full care, at centers with limited-care requiring active participation from patients, and in some cases at home.[13] The most common complications of HD include hypotension and vascular access thrombosis.[12]

The second form, PD, makes use of the peritoneum as a semi-permeable membrane, though which solutes can be exchanged.[12] Dialysate is instilled into the peritoneal cavity through a catheter; it is left to dwell and is subsequently drained. Of the total estimated resting splanchnic blood flow of 1200ml/min, merely around 70ml is in contact with the peritoneal membrane. Therefore, exchange occurs slowly and dialysis is needed

almost continuously. The two most commonly used forms of PD in the Netherlands are Continuous Ambulatory PD and Continuous Cyclic PD. Continuous Ambulatory PD requires the patient to manually infuse 2 to 3L of dialysate every 4 to 6 hours. Continuous Cyclic PD allows a 12 to 15 hour daytime dwell and 3 to 6 nighttime exchanges by an automated cycler. The most common and important complications are peritonitis and catheter-exit-site infections.

The third form of renal replacement therapy is RTx. A renal transplant or graft is usually placed in the iliac fossa.[12] The kidney can be donated by either a post-mortem or a living donor. To accrue wait time for a kidney transplant from a post-mortem donor in the Netherlands (which is part of the Eurotransplant organ procurement system), a patient must already have initiated dialysis treatment.[14] In living-donor RTx, there have been many developments in recent years. Not only living-related, but also living-unrelated (often spousal) donation and even cross-over transplantation (exchange of kidneys by two or more incompatible donor-recipient pairs), are currently being performed.[15] The living donor undergoes an extensive work-up to exclude contraindications for donation and to depict renovascular anatomy in order to guide the transplant surgeon in the peri-
 operative planning of the nephrectomy.[16,17] The depiction of the renal vasculature has become especially important because of the introduction of minimally invasive surgical techniques, such as laparoscopic donor nephrectomy. An RTx necessitates immunosuppressive therapy; currently various regimens are being used. Complications include

FIGURE 2. The treatment distribution of End-Stage Renal Disease patients by age in the Netherlands on January 1st 2005



graft rejection and complications from long-term immunosuppressive therapy, such as various cancers.

In the Netherlands, transplantation rates have been rising over the years and on January 1st 2005, more patients were alive with a functioning graft (6,292) than there were patients being treated with dialysis (5,259).[1] In recent years, 25 to 30% of dialysis patients were being treated with PD.[1] The treatment modality distribution varies highly with age, with RTx comprising almost 70% and HD 10% of patients 16-44 years of age, while of patients older than 75 years only 13% had an RTx and 77% were treated with HD (Figure 2).[1]

SURVIVAL OF PATIENTS ON RENAL REPLACEMENT THERAPY

Although survival of dialysis patients has improved over time, it is still considerably worse than for RTx patients. The United States Renal Data System (USRDS) reported a 5-year survival probability of 35% for dialysis and 75% for RTx patients initiating therapy in 1996-2000.[3] Studies comparing HD and PD survival have yielded conflicting results. Patient selection complicates the comparison: HD patients have been reported to have more co-morbidity at initiation of dialysis therapy.[18] Furthermore the difference in survival has been reported to change over time and to differ with age.[19-22]

The access to the RTx waitlist depends on patient characteristics. Lower rates of waitlisting have been reported for older patients, non-caucasian patients, and patients with co-morbidity such as congestive heart failure, lung disease or cancer and with late nephrologist referral.[23,24] Therefore, the mortality rate is considerably lower among patients waitlisted for transplantation, compared to all patients on dialysis.[25] Once waitlisted, different factors may influence the access to transplantation. A higher rate of transplantation has been reported for younger and Caucasian patients, men, patients with a higher income or education level and patients with early referral and greater intensity of nephrologist care prior to RRT.[23,24] Patients with a co-morbid condition, smokers and nursing home patients had lower rates of transplantation.[23] In addition, several studies indicated that PD patients have a better access to RTx than HD patients.[26,27] Patients from the waitlist who do get transplanted were reported to have less immunization, to have had a shorter pre-transplant dialysis duration and to be in a better clinical condition.[28]

As a result, the comparison of survival of dialysis versus RTx patients is biased by selection of patients with a better prognosis for RTx. Efforts have been made to compare the survival of waitlisted dialysis patients to the survival of transplanted patients for a more valid comparison.[25,29,30] Results show that cadaveric transplantation is associated with a worse survival in the first months following transplantation, but with a better survival in the years thereafter.[25,29]

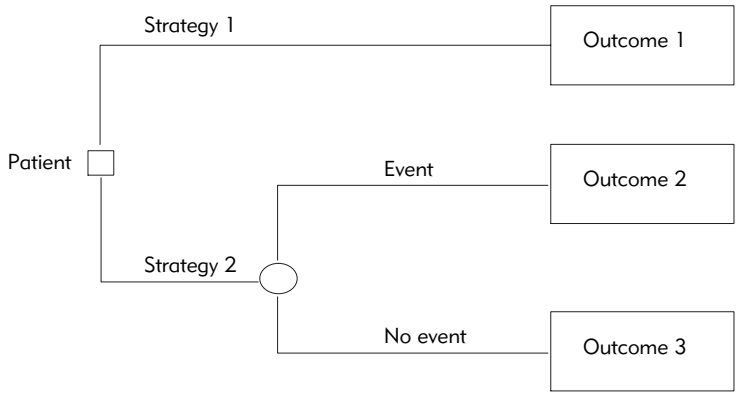
As RTx is associated with a higher survival compared to renal dialysis, it is considered to be the first choice for the treatment of ESRD patients. Due to scarcity of organ donors, however, this therapy option is only available for a limited number of patients. Because it has proven to be difficult to increase the number of post-mortem donations, it would be important to promote living-related renal transplantation. Other interventions to improve overall survival of patients with ESRD, in a cost-effective manner are also warranted.

Comparison of interventions is time consuming. In ESRD, randomized controlled comparisons of the different treatment options are not feasible because of the clinical importance of patient selection. Nonetheless, evidence-based practice is of great importance to this patient group and therefore proper observational studies are indicated. Results from observational studies can be used in decision analytic models to assess the effect of interventions.

DECISION ANALYSIS

Decision analysis provides a systematic, explicit, quantitative method for making decisions under uncertainty in health care.[31] Uncertainty may arise due to erroneous or ambiguous observations, and to a variety in effects of treatments. A framework that is commonly used in decision analysis is the PROACTIVE approach: Problem, Reframe, Objectives, Alternatives, Consequences and Chances, Trade-offs, Integrate, (Expected) Value and Explore and Evaluate.[32] This means that after defining a Problem, one should Reframe it from different perspectives and determine the Objectives of the intervention. Different Alternatives to attain these objectives should be identified and the Consequences and Chances of each alternative must be explored. A decision tree is usually constructed to visualize the different alternatives and their consequences (Figure 3). Each alternative strategy is represented by a branch emanating from a decision node

FIGURE 3. Example of a decision tree

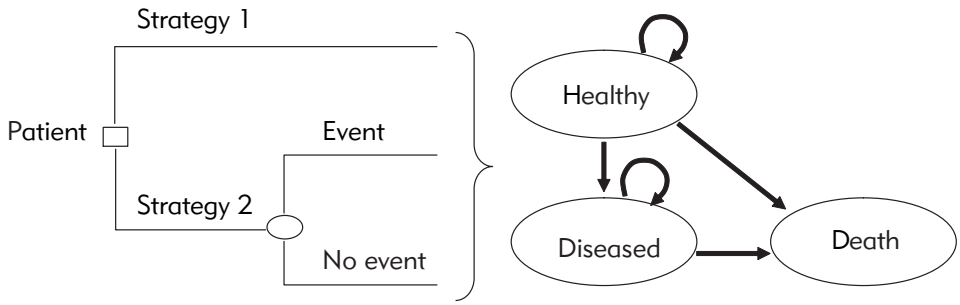


and from each strategy, all consequences or events branch off. Trade-offs resulting from the harms and benefits of these consequences are quantified. Subsequently, the Trade-offs are Integrated by calculating the Expected Value associated with each alternative using a multiplication-and-addition procedure: the probability of each outcome is multiplied by its value, and for each alternative, these products are added. The alternative with the highest Expected Value constitutes the optimal strategy. Lastly, assumptions need to be Explored and uncertainty should be Evaluated.

MARKOV MODELING

A Markov model (Figure 4) is used when the decision problem involves risk over time, when the timing of events is important, or when events may happen more than once.[31] In such a model, different states can be distinguished, which are defined by the possible health states that a patient may experience. These states should be mutually exclusive and collectively exhaustible. In the example of ESRD, one may define the states HD, PD, RTx and death. The time of the analysis is divided into time intervals of an equal length, referred to as cycles. Patients may transition from one state into another according to the transition probability. For example, in a model with a cycle length of 1 year, RTx patients transition to the dialysis state according to the 1-year probability of graft failure. When these transition probabilities do not vary over time, a Markov chain model with constant probabilities can be defined, but when they do vary, a Markov process model should be employed. The transition probabilities can be estimated from

FIGURE 4. Example of a Markov model within a decision tree



literature data, and from patient-level data. If patient level-data are available, survival probabilities can be derived from the data using conventional statistical modeling techniques, such as the Cox proportional hazards regression model.

The Markov model can be analyzed in different ways. In a cohort simulation, mean transition probabilities for the entire cohort are used. The model is run for a number of cycles until most patients have died and the model calculates life expectancy on the basis of all transition probabilities. The model can also be analyzed using Monte Carlo simulations. These types of simulation allow for the addition of distributions around the mean estimates of either patient characteristics (1st order Monte Carlo) or parameters, such as transition probabilities (2nd order Monte Carlo). As a result, the uncertainty around the estimated life expectancy can be assessed.

QUALITY OF LIFE

Quality of life (QoL) estimates can be used to adjust life expectancy for morbidity in decision analytic modeling. QoL is increasingly recognized as an important clinical outcome measure, especially in chronic diseases. There are general as well as disease-specific instruments to measure QoL. Among the general instruments, two types can be distinguished: health-profiles and preference-based methods. Health-profile measures assess health status on a number of domains, for example physical, emotional or social domains. The Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) is a well-known example. Preference-based methods assign a single index value or 'utility' to QoL. This value reflects a subject's preference for the QoL in a given health state, expressed on a ratio scale, with length of life as the metric. An example is the

time trade-off method. This method involves asking a patient to think about his kidney disease over the past 2-3 weeks and then choose between two hypothetical options: either remaining in his current health state for the patient-specific life expectancy or to trade-off a number of years to live in full health. The number of years to be traded-off is varied between 0 and the total life expectancy and the question is iterated until the patient is indifferent between the two options. The utility is then calculated by dividing the number of years that the patient would not be willing to trade-off by the total life expectancy at the point of indifference. From several health-profile methods, a utility can be calculated, by use of a tariff or set of preference weights. Such tariffs have been estimated by deriving general population utilities for all possible health states that may result from a health-profile method.[31] Utilities can be used in economic evaluations to adjust expected life years for QoL.[31]

QoL of ESRD patients has been studied increasingly. As early as the 1980s, Evans et al reported that QoL was higher among RTx recipients compared to dialysis patients.[33] Others, however, reported that this might be explained by pre-existing differences between patients selected for the different forms of RRT.[34] Similar to studies on the difference in survival between HD and PD patients, studies on the difference in QoL of HD and PD patients remain controversial. Whereas some studies have shown a higher QoL for PD patients as compared with hospital HD patients,[33,35] others found comparable physical QoL for PD and HD patients, but a higher mental QoL for PD patients.[36]

AIMS AND OUTLINE

The aim of this thesis is to study the long-term outcome of renal dialysis and RTx patients in the Netherlands and to integrate their expected survival with QoL estimates from the literature into a decision analytic model that can be used to study the effect of therapeutic or policy interventions.

We compare survival of HD and PD patients in the Netherlands in chapter 2.1. The predictors of waitlisting and its influence on mortality are studied in chapter 2.2; additionally, we describe the predictors of access to cadaveric renal transplantation for waitlisted patients. In chapter 2.3, we assess the short-term consequences in terms of living donors' return to work after nephrectomy for different surgical techniques.

QoL of RRT patients as measured with the SF-36 is summarized in a meta-analysis in chapter 3.1. As the SF-36 cannot be used for quality-of-life adjustment in decision analyses, we summarize values for utility measures in HD, PD and RTx patients in chapter 3.2 and additionally, assess the differences in utility-values between the RRT-groups.
We integrate literature data with the results from the chapter 2.3 in chapter 4.1 to estimate the optimal diagnostic imaging technique for living donors. In chapter 4.2, we quantify the survival benefit in terms of (quality-adjusted) life expectancy of early transplantation versus dialysis with waitlisting and possible cadaveric RTx. For this purpose we integrate the survival studies of dialysis patients (chapters 2.1 and 2.2) and RTx patients in a decision analytic model and use the utilities from the meta-analysis (chapter 3.2) to adjust life expectancy for QoL.

In chapter 5.1, we explore the application of propensity scores, in the estimation of HD and PD survival in the Netherlands.

We integrate and discuss our main findings and describe limitations and methodological issues relevant to our studies in chapter 6. In addition, we offer suggestions for future research.

2

Clinical outcomes in renal replacement therapy: patients and donors

2.1

Comparison of hemodialysis and peritoneal dialysis survival in the Netherlands

ABSTRACT

Objective: Considerable geographic variation exists in the relative use of hemodialysis (HD) vs. peritoneal dialysis (PD). Studies comparing survival between these modalities have yielded conflicting results. Our aim was to compare the survival of Dutch HD and PD patients.

Methods: We developed Cox regression models using 16,643 patients from the Dutch End Stage Renal Disease Registry (RENINE) adjusting for age, gender, primary renal disease, center of dialysis, year of start of renal replacement therapy, and included several interaction terms. We assumed definite treatment assignment at day 91 and performed an intention-to-treat analysis, censoring for transplantation. To account for time dependency, we stratified the analysis into three time periods, >3-6, >6-15, and >15 months.

Results: For the first period, the mortality hazard ratio (HR) of PD compared with HD patients was 0.26 (95% confidence interval (CI) 0.17-0.41) for 40-year-old non-diabetics, which increased with age and presence of diabetes to 0.95 (95% CI 0.64-1.39) for 70-year-old patients with diabetes as primary renal disease. The HRs of the second period were generally higher. After 15 months, the HR was 0.86 (95% CI 0.74-1.00) for 40-year-old non-diabetics and 1.42 (95% CI 1.23-1.65) for 70-year-old patients with diabetes as primary renal disease.

Conclusion: We conclude that the survival advantage for Dutch PD compared with HD patients decreases over time, with age and in the presence of diabetes as primary disease.

INTRODUCTION

The relative use of hemodialysis (HD) vs. peritoneal dialysis (PD) for treatment of end-stage renal disease varies considerably across countries. In 2002, 0.5% of dialysis patients in Luxembourg underwent PD, whereas 48.4% used this modality in New Zealand.[37] Practice varies not only among but also within countries, as has been reported for the United States.[38] Although cultural factors and patient or physician preference may play a role, as well as reimbursement policy decisions, survival associated with both therapy modalities is an important consideration in the treatment decision.

Studies comparing patient survival on HD and PD, however, have yielded conflicting results. Possible explanations for these inconsistent results include underlying differences in the populations studied (e.g., incident vs. prevalent patients, elderly vs. general population), differences in methodology used (e.g., intention-to-treat vs. as-treated), as well as unavailability of information on important confounders in several studies (e.g., presence and/or severity of co-morbid conditions). Although differences in measured clinical or demographic characteristics can be adjusted in multivariable regression analyses, confounding by unmeasured characteristics remains a threat to validity. It has been suggested that using information on the treatment center can be used to further reduce bias.[39,40] This can be conducted in several ways, such as through multivariable modeling, multilevel modeling, or including center information in exposure propensity scores.[41,42] Furthermore, the relative mortality risk of HD compared with PD patients may differ for various patient groups. In addition, the relative risks may change over time after the initiation of dialysis.[19-22]

In the Netherlands, a relatively high proportion of patients initiate renal replacement therapy (RRT) using PD. We conducted this study to compare mortality of incident HD and PD patients in the Netherlands, using Dutch registry data.

METHODS

Patients

We included all incident patients who started RRT between 1 January 1987 (start of prospective registration) and 31 December 2002 from the Dutch End Stage Renal Disease Registry (RENINE). We excluded patients younger than 18 years, patients who underwent RRT for less than 30 days, patients who had more than one episode of recovery of renal function, or who died directly following a period of renal recovery, patients who received a pre-emptive transplantation, patients who died during the first 90 days of RRT and patients from centers treating fewer than 20 dialysis patients or fewer than five PD patients. The outcome of interest was all-cause mortality, as registered by RENINE. The registry collects information on date and cause of death and verifies its information yearly with all centers.[4,43] From registry data, we also determined age and gender of patients. In the database, primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). We aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM), and a category for all other renal diagnoses (PRD-OTH). Furthermore, we used registry data on dialysis modality, year of start of dialysis, and the center at which dialysis was started.

Analysis

We adopted an intention-to-treat perspective and considered the dialysis modality on day 91 to be the definite modality. We left-censored survival time for the first 90 days and right-censored at first transplantation or 31 December 2002, whichever occurred first. We compared Kaplan-Meier survival curves of HD and PD patients, using the log-rank test.

To estimate the independent comparison between PD and HD mortality by controlling for observed potential confounders, we used a multivariable regression adjustment approach. The first step was to estimate univariable Cox proportional hazards models for all available variables. Age and year of start of dialysis were entered into the model as continuous variables and all other variables as categorical variables. All statistically significant variables ($P<0.05$) from the univariable analyses were put into a multivariable

Cox proportional hazards model. From the full multivariable model, we explored the significance of a quadratic term (age) and several two-way and three-way interaction terms. We tested for center effects by entering center as a categorical variable into the multivariable model.

In the final Cox model, we tested for violations of the proportional hazards assumption by testing for significance of time-dependent variables. As the proportionality assumption was violated for the main exposure variable, we applied time stratification, thus ensuring absence of time dependency within time strata. For all these analyses, we calculated hazard ratios (HRs) and 95% confidence intervals (CI) for PD relative to HD mortality within each time interval. In addition, we presented cumulative survival curves stratified by PD vs. HD. An HR reflects a relative survival difference for a period to which the HR pertains. Because the proportional hazards assumption was not satisfied, we calculated different HRs for different time periods. The long-term survival and life expectancy over the entire observation period are determined by the magnitude of the HRs and the duration of the period to which these ratios apply, in other words, by the cumulative effect of the different HRs. Absolute survival differences are therefore best reflected in differences in (the area under) the cumulative survival curves.

RESULTS

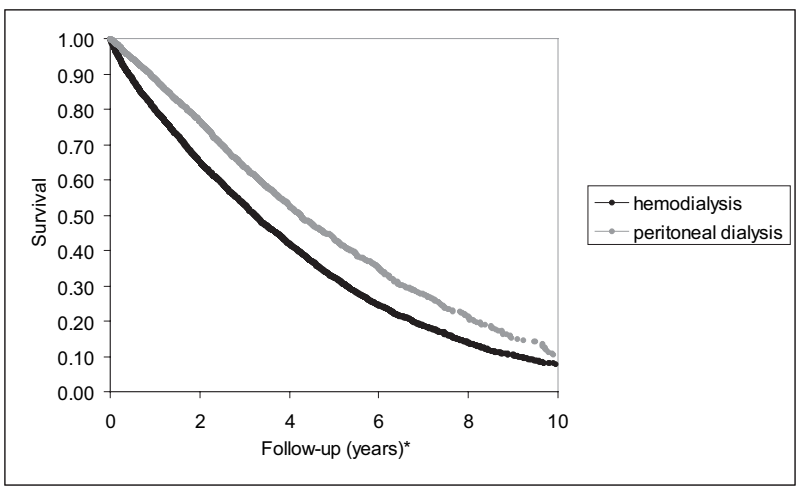
The RENINE Registry prospectively collected data of 20,687 patients who started RRT between 1 January 1987 and 31 December 2002. We discarded 2,157 patients who died during the first 90 days of RRT. Of the remaining patients, we excluded 517 patients because they were younger than 18 years and another 19 patients who had more than one episode of recovery of renal function or death directly following a period of renal recovery. Of the remaining patients, there were 699 who had received a pre-emptive transplantation before or at day 91. We excluded 625 patients from centers treating fewer than 20 dialysis patients or fewer than five PD patients and another 27 patients for whom center information was not available. As a result, our final sample included 16,643 patients from 47 centers. Mean age was 59 years (SD: 15.3) and 58.8% were male. Descriptive characteristics of patients are shown in Table 1. The Kaplan-Meier survival plot (Figure 1) showed a higher crude survival for PD compared with HD patients (log-rank test: $P<0.001$).

TABLE 1. Baseline characteristics of study cohort

	All patients	HD	PD	P-value
Number (%)	16,643	10,841 (65.1)	5,802 (34.9)	
Age (SD) (years)	59.0 (15.3)	61.8 (14.6)	53.6 (15.0)	<0.001
Female gender (%)	41.2	42.5	38.7	<0.001
Primary renal disease (%)				<0.001
GN	13.7	11.1	18.5	
HT	11.4	11.7	10.8	
RVD	8.7	9.8	6.6	
DM	15.2	14.9	16.0	
Other	51.0	52.5	48.1	
Year of first RRT (%)				<0.001
1987-1990	17.0	18.0	14.9	
1991-1994	23.5	23.2	24.0	
1995-1998	28.6	28.3	29.0	
1999-2002	31.0	30.5	32.0	
Years of follow-up (SD)	2.38 (2.14)	2.42 (2.24)	2.32 (1.95)	0.007

DM = diabetes mellitus, GN = glomerulonephritis, HD = hemodialysis, HT = hypertension, PD = peritoneal dialysis, RRT = renal replacement therapy, RVD = renovascular disease

FIGURE 1. Unadjusted survival of dialysis patients



Kaplan-Meier curves of survival of hemodialysis (black line) and peritoneal dialysis (grey line) patients, censored for transplantation (log-rank test: p<0.001).
* Follow-up censored for transplantation in years.

Multivariable regression analysis

In the univariable Cox model, dialysis modality was associated with survival: patients who initiated RRT using PD had a 30% lower mortality compared with HD patients (HR=0.70; 95% CI: 0.67-0.74; P<0.001). The coefficients of all other univariable models were also statistically significant, both in the overall population and in the HD and PD groups (see Table 2). The coefficient for the year of starting RRT was not significant in the total population, because its effect was in opposite directions for HD and PD patients. With increasing year of start of RRT, the relative risk of dying increased for HD patients and decreased for PD patients. Center was a significant univariable predictor of modality (P<0.001, data not shown).

TABLE 2. Univariable associations with mortality

	HD		PD		All patients	
	HR	**P-value**	**HR**	**P-value**	**HR**	**P-value**
Age (per year)	1.04	<0.001	1.06	<0.001	1.05	<0.001
Female vs. male gender	0.94	0.02	0.80	<0.001	0.91	<0.001
Primary renal disease vs. GN*						
HT	1.47	<0.001	2.15	<0.001	1.72	<0.001
RVD	2.35	<0.001	3.80	<0.001	2.86	<0.001
DM	2.11	<0.001	3.49	<0.001	2.55	<0.001
Other	1.38	<0.001	1.61	<0.001	1.53	<0.001
Year of first RRT (per year)	1.02	<0.001	0.99	<0.001	1.00	0.18
PD vs. HD	-		-		0.70	<0.001

* Compared with GN as reference group.
DM = diabetes mellitus, GN = glomerulonephritis, HD = hemodialysis, HR = hazard ratio, HT = hypertension, PD = peritoneal dialysis, RRT = renal replacement therapy, RVD = renovascular disease

The multivariable Cox model, adjusted for age, gender, primary renal disease, year of first RRT, and treatment center but without interaction terms revealed that mortality of PD patients and HD patients did not differ (HR=0.99; 95% CI: 0.94-1.05). Of the interaction variables tested in this multivariable model, however, four were statistically significant: age by modality (HD or PD) and diabetes as the primary cause of renal disease (PRD-DM) by modality, by age, and by gender (Table 3). An analysis using propensity scores was also undertaken and the results were virtually unchanged. Additional analyses using center size as a covariate yielded essentially identical results (not shown).

TABLE 3. Multivariable adjusted model

	HR	P-value
Age (per year)	1.05	<0.001
Female vs. male gender	0.87	<0.001
Primary renal disease vs. GN*		<0.001
HT	1.22	<0.001
RVD	1.68	<0.001
DM	5.65	<0.001
Other	1.31	<0.001
Year of first RRT (per year)	0.99	0.005
Dialysis center		<0.001
Peritoneal vs. hemodialysis	0.43	<0.001
Age x dialysis modality	1.01	<0.001
DM x dialysis modality	1.22	0.002
Age x DM	0.98	<0.001
Gender x DM	1.20	0.002

* Compared with GN as reference group.
DM = diabetes mellitus, GN = glomerulonephritis, HR = hazard ratio, HT = hypertension, RRT = renal replacement therapy, RVD = renovascular disease

Several interactions with time were statistically significant in the multivariable Cox model indicating violations of the proportionality assumption. We tested various time-stratification strategies. Finally, we stratified time into three periods: >3-6, >6-15, and beyond 15 months. For each of these periods, the relative mortality risk of PD compared with HD patients appeared constant over time. In order to illustrate the change in relative hazards over time and to account for the variables that were effect modifiers of the treatment variable (age, PRD-DM), we calculated HRs of PD compared with HD patients for representative values of these variables. We used four ages, 40, 50, 60, and 70 years, for detailed presentation (Table 4). For the eight groups defined by these values of age and the presence vs. absence of PRD-DM, the relative mortality risk of PD patients compared with HD patients increased over time, that is, the relative survival benefit diminished (Table 4). And for all time-strata, this relative PD survival benefit decreased with increased age and with the presence of PRD-DM. Among non-PRD-DM patients, the relative survival advantage associated with PD was highest for 40-year olds, although this relative advantage decreased over time, from an HR of 0.26 (95% CI: 0.17-0.41) in the time period of >3-6 months to an HR of 0.86 (95% CI: 0.74-1.00) in the period after 15 months. For 40- and 50-year-old patients with PRD-DM and for

TABLE 4. Associations between dialysis modality and mortality

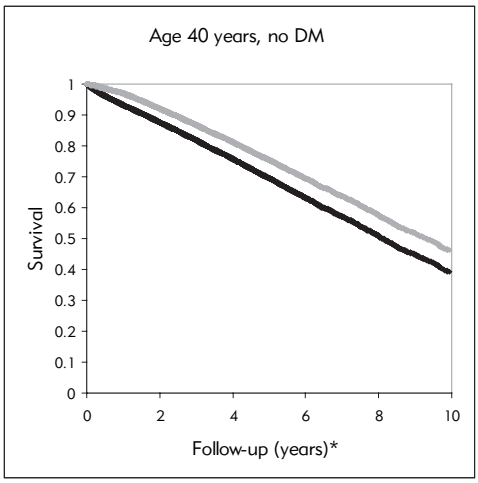
		Hazard ratios of peritoneal dialysis vs. hemodialysis (95% Confidence Intervals) *		
Age	**DM**	**>3-6 months**	**>6-15 months**	**>15 months**
40	No	0.26 (0.17-0.41)	0.51 (0.39-0.68)	0.86 (0.74-1.00)
40	Yes	0.40 (0.23-0.68)	0.59 (0.44-0.81)	1.06 (0.88-1.26)
50	No	0.35 (0.25-0.48)	0.62 (0.51-0.76)	0.95 (0.85-1.05)
50	Yes	0.53 (0.34-0.83)	0.72 (0.56-0.93)	1.17 (1.00-1.35)
60	No	0.46 (0.37-0.58)	0.75 (0.65-0.87)	1.05 (0.97-1.13)
60	Yes	0.71 (0.48-1.04)	0.87 (0.71-1.09)	1.29 (1.12-1.48)
70	No	0.62 (0.50-0.76)	0.92 (0.80-1.05)	1.16 (1.07-1.25)
70	Yes	0.95 (0.64-1.39)	1.07 (0.85-1.33)	1.42 (1.23-1.65)

* From models including age, gender, primary renal disease, year of start of RRT, center and the interaction terms age by modality, diabetes by modality, age by diabetes and gender by diabetes.
DM = diabetes as primary renal disease

50-, 60-, and 70-year-old patients without PRD-DM, the early relative survival advantage associated with PD disappeared over time. PD was even associated with worse relative survival after 15 months for 50-year-old PRD-DM patients (HR 1.17, 95% CI: 1.00-1.35) and 70-year-old patients without PRD-DM (HR 1.16, 95% CI: 1.07-1.25). Similarly, for 60- and 70-year-old patients with PRD-DM, PD was associated with a significantly worse relative survival (HR respectively 1.29, 95% CI 1.12-1.48 and 1.42, 95% CI 1.23-1.65) after 15 months, although there was no significant relative survival advantage for either modality up to 15 months.

To assess the impact of these HRs on actual cumulative survival, we constructed survival curves for these eight groups (Figure 2a-h). As can be deduced from these curves, the differences in absolute survival were similar as those with respect to the relative survival or HRs, with one exception. For 50-year-old patients without PRD-DM, we concluded from the HRs that the relative survival advantage disappeared over time, however, the cumulative survival benefit of PD remained over the entire observation period (Figure 2c).

FIGURE 2a-h. Adjusted survival curves of HD and PD patients



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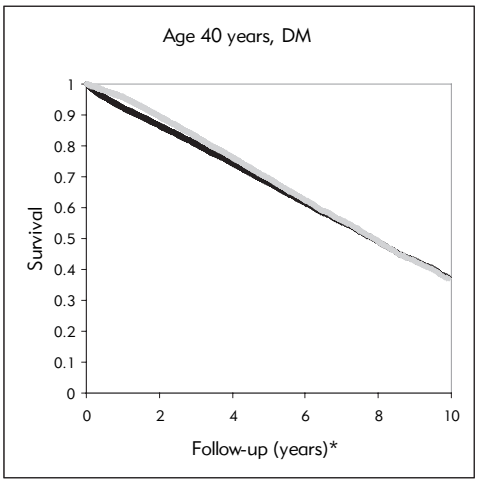

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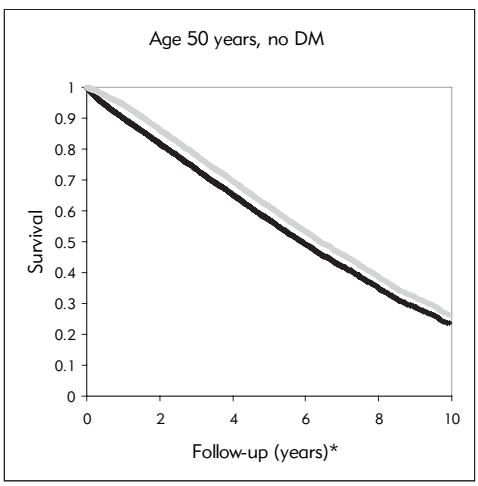

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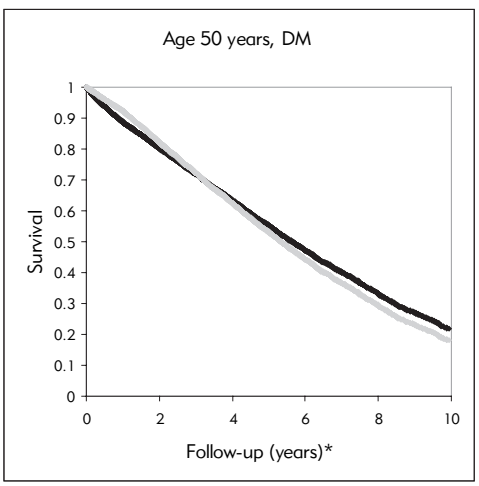

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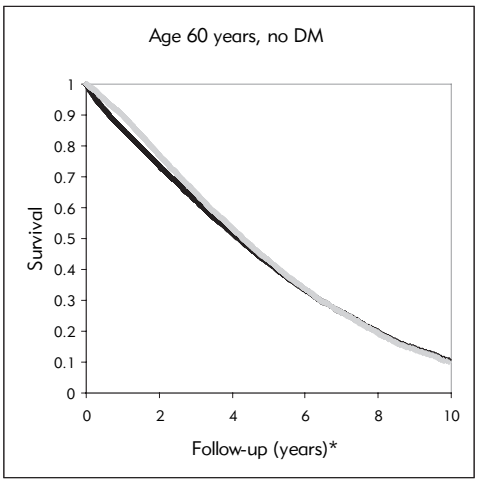

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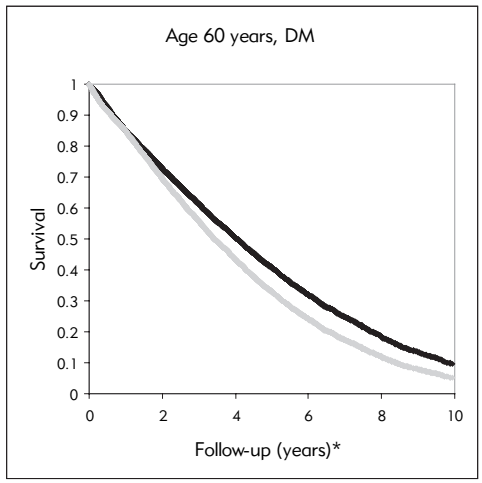

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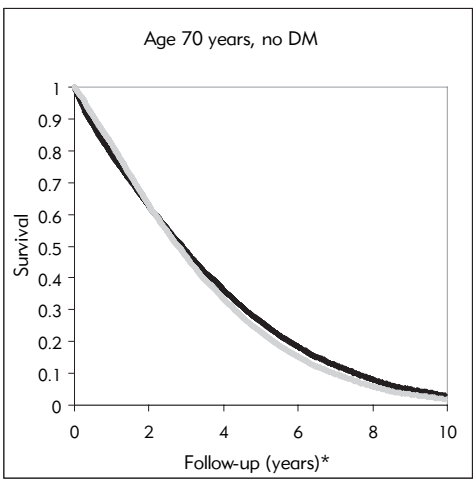

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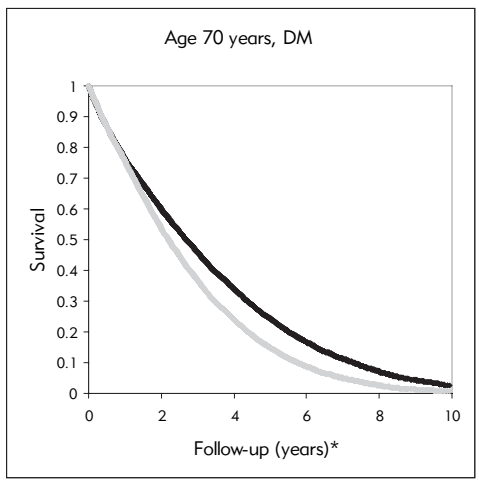


h

* Follow-up censored for transplantation in years.
Curves of survival of hemodialysis (black line) and peritoneal dialysis (grey line) patients, censored for transplantation, for various ages (yrs) and stratified by presence of diabetes mellitus (DM) being the primary renal disease.

DISCUSSION

In this comprehensive study of all patients who initiated chronic dialysis treatment between 1987 and 2002 in the Netherlands, unadjusted mortality of PD patients was 30% lower compared with HD patients. Multivariable adjustment for age, gender, primary renal disease, year of first RRT, and dialysis center, however, showed that the HR was not constant over time, but increased in favor of HD, with higher age, and in those whose primary renal disease was DM. In younger patients, PD was associated with superior survival in the first 15 months of RRT, independent of whether DM was the original renal disease. Among older patients, this association was only present for the first few months and only in those patients whose underlying renal disease was not DM. Independent of underlying renal disease, PD was associated with higher mortality after 15 months in patients older than 70 years of age. Examining the cumulative survival curves enables us to scrutinize the other aspect of this study, overall survival (Figure 2). For non-PRD-DM patients, PD was associated with a comparable (age 60 and 70) or better (age 40 and 50) overall survival compared with HD. Among PRD-DM patients, PD and HD showed equivalent survival among younger patients (age 40 and 50), but HD was associated with greater survival among older patients (age 60 and 70).

Our findings corroborate the existing literature on the decrease in relative survival of PD patients as compared with HD patients over time. Termorshuizen and colleagues[22] reported that mortality during the first two years was not different between HD and PD patients among participants of the NECOSAD study. However, they observed a higher relative mortality of PD patients after two years of treatment. Jaar and colleagues[44] came to similar conclusions in their recent study of 1,041 incident dialysis patients in the US. Fenton and colleagues[20] concluded that Canadian PD patients had a significantly higher survival than HD patients, the effect being largest for the first two years on dialysis. Heaf and colleagues[21] reported a survival advantage for Danish PD patients for the first 1-2 years, but after 2.5 years this association was reversed in patients with diabetes. Although these studies allow for different conclusions regarding the presence of an initial survival advantage for PD patients, the time trends in survival differences are similar; the relative mortality risk of PD patients has consistently been reported to increase over time. Differences regarding the initial survival advantage of PD during the first years of dialysis in these studies might be explained by different analytical approaches, prognostic factors available for study, and regional differences in patient population and dialysis practice.

The initial survival advantage of PD patients in our study might be explained by HD patients having higher co-morbidity at initiation of dialysis therapy.[18] If HD patients with the highest burden of co-morbidity die early resulting in healthier HD patients surviving, mortality rates of HD patients would then decrease over time. PD patients, who are generally healthier than HD patients initially, would develop higher mortality over time as they accumulate other co-morbidities. Some of these aforementioned studies did correct for co-morbidity, however, and still observed time trends similar to our study.[19-22] Alternatively, the higher dose of delivered dialysis for PD patients initially might account for the time trend in relative mortality. Collins and colleagues[19] reported, though, that initial delivered dose was not as different for HD and PD patients as had generally been believed. Finally, it has also been suggested that the short-term survival advantage of PD patients might be explained by better preservation of residual renal function in patients treated with PD as compared with patients treated with HD.[45] Residual kidney function has been shown to be an independent predictor of mortality for both HD[46] and PD[47] patients. As time progresses, residual kidney function declines and PD alone might not suffice to maintain adequate clearance. Therefore, some have advocated an Integrative Care Approach, starting RRT with PD and later switching to HD as residual renal function deteriorates.[21,48] To inform such an approach, it is important to consider both data on period-specific HRs and on cumulative survival over time. Even if one modality may be associated with greater mortality during later stages of RRT, the strategy may still be superior because of lower mortality during earlier time-periods, and vice versa.

In our study, we also found that the HR of PD compared with HD patients increased with age and in the presence of diabetes as primary renal disease. This effect modification had also previously been reported,[18,49-51] although contrasting findings were also described by Keshaviah and colleagues.[52] The latter group described a similar two-year survival for HD and PD patients, independent of age and diabetic status, when adjusting for co-morbidity, serum albumin, and dialysis dose. This controversy might be explained by differences in the covariate adjustment: Keshaviah included dialysis dose as a covariate, whereas the other studies did not. Jaar and colleagues[44] did find age to be an effect modifier, whereas diabetes was not. In their study, initial dialysis dose as well as cardiovascular morbidity was among the included covariates. However, with a cohort of just over 1000 patients, their statistical power was rather limited to detect any effect modification on prognostic main effects. Our study confirms the findings of Vonesh and colleagues[51] who analyzed 398,940 incident US dialysis patients from the

United States Renal Data System. These authors also reported effect modification by age and diabetes and found a similar time trend in relative survival of HD compared with PD patients in age- and diabetes-stratified subgroups.

Some limitations of our study deserve mention. The RENINE database does not include data on co-morbidity, but information on primary renal diagnosis is available. The most important co-morbid condition, diabetes, is likely well represented in the subgroup identified with diabetes as underlying renal disease, as diabetes and PRD-DM are likely to correlate strongly. Other factors that have been reported to affect dialysis mortality were also not available for study: ethnicity,[19,53] nutritional markers,[53-55] delivered therapy,[52] and transplant eligibility.[21]

Important factors, other than survival, in selecting dialysis modality for an individual patient would include HD and PD-associated quality of life and a patient's living arrangements and personal preference. Also the nephrologist's preference and the reimbursement system in a specific country are known to influence dialysis modality selection.[56,57] These aspects are beyond the scope of our study.

From our findings, we conclude that there is an initial survival advantage for PD patients compared with HD patients in the Netherlands. Over time, with advancing age, and in the presence of diabetes as primary disease, this relative survival advantage vanishes, and even reverses with time.

2.2

Predictors of access to the renal transplant waitlist, its influence on mortality and predictors of renal transplantation in the Netherlands

ABSTRACT

Objectives: To evaluate the predictors of waitlisting for renal transplantation (RTx) in patients undergoing dialysis and its influence on mortality, and to define the predictors of access to cadaveric RTx among patients waitlisted for RTx.

Methods: We merged data of 10,489 patients from the Dutch End Stage Renal Disease and Organ Transplant Registries for patients waitlisted for cadaveric RTx. Logistic regression was used to determine the predictors of waitlisting. Cox regression was used to estimate its association with mortality and access to cadaveric RTx.

Results: Waitlisted patients were younger, more likely to have glomerulonephritis as primary renal disease, to undergo peritoneal dialysis, and to have started dialysis in earlier years. In addition, dialysis center independently predicted waitlisting. The mortality of waitlisted patients was lower compared with non-waitlisted patients, with the hazard ratios (HR) increasing from 0.23 (95% CI 0.06 - 0.93) in the first half year of dialysis treatment to 0.59 (95% CI 0.42 - 0.83) after 4 years of dialysis treatment. Beyond 5 years on dialysis, being waitlisted was not associated with mortality. Among waitlisted patients, only primary renal disease and center were independent predictors of cadaveric RTx.

Conclusion: Waitlisting was predicted by age, primary renal disease, dialysis modality, year of start of dialysis, and dialysis center. Patients waitlisted for a transplant had a lower mortality compared with non-waitlisted patients, but this relative benefit declined with time since initiation of dialysis. Access to cadaveric RTx among waitlisted patients was associated with primary renal disease and center.

INTRODUCTION

Only selected patients on dialysis are waitlisted for a cadaveric renal transplantation (RTx). For example, older patients, those with a higher BMI, with co-morbidities such as congestive heart failure, lung disease or cancer, or with late referral to a nephrologist just prior to needing renal replacement therapy (RRT) have been shown to be less likely to be waitlisted.[23,24,58] Therefore, not surprisingly, mortality rates for patients waitlisted for RTx are considerably lower than for patients on dialysis who had not been waitlisted.[25]

Once waitlisted, different factors may influence access to transplantation. A higher rate of RTx has been reported for younger and Caucasian patients, men, patients with a higher income or education, and those with earlier and greater intensity of nephrologist care prior to RRT.[23,24] Conversely, patients with more co-morbidity, smokers and nursing home patients had lower rates of transplantation.[23] In addition, several studies indicated that peritoneal dialysis (PD) patients have better access to RTx than hemodialysis (HD) patients.[26,27] Recently, it was shown that the likelihood of receiving a RTx decreases with increasing degree of obesity.[59,60]

In the Netherlands, separate registries exist for RRT patients: the Dutch End Stage Renal Disease Registry (RENINE) contains patients on dialysis and RTx, whereas the Dutch Organ Transplant Registry (NOTR) collects detailed data on waitlisting and organ transplantation. The purpose of our study was to assess the predictors of waitlisting for cadaveric RTx among dialysis patients and to compare mortality of dialysis patients who are waitlisted with those not waitlisted. Additionally, we aimed to evaluate the predictors of cadaveric RTx in waitlisted dialysis patients in the Netherlands. Studying these questions became possible by merging data from the two Dutch registries.

METHODS

Patients

From RENINE, we studied all incident patients who initiated RRT between January 1st 1998 (start of prospective registration of waitlisting by NOTR) and December 31st 2006. We excluded patients younger than 18 years, patients who underwent RRT for less than 30 days, or those who had episodes of recovery of renal function. Furthermore, we excluded patients who received a pre-emptive or living-donor RTx, patients who died during the first 90 days of RRT and patients from centers treating fewer than 20 dialysis or fewer than 5 PD patients. In addition, we obtained waitlist information for all patients registered in NOTR during the same time-window. From both registries we only used data prior to the first RTx. Both RENINE and NOTR recoded Eurotransplant organ procurement numbers using the same encryption, and these pseudo-anonymized numbers were used to link the dialysis to the waitlist information.

The outcomes of interest were mortality and cadaveric RTx, as registered by RENINE. The registry collects information on dates of death and transplantation and verifies its information yearly with all centers.[4] From the RENINE data we also determined age and gender of patients. Primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). We aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM) and a category for all other renal diagnoses (PRD-OTH). Furthermore we used RENINE data on dialysis modality, year of start of dialysis, and the center at which dialysis was started. Dialysis modality was defined on day 91 of RRT. From NOTR, we assessed when patients were coded as 'transplantable' during their follow-up period, and only considered these to be waitlisted. In the analyses, all variables were entered into the models as categorical variables.

Analysis of predictors of waitlisting

We used logistic regression models to determine the predictors of waitlisting. We defined waitlisting as being listed as 'transplantable' on the wait list within the first year of dialysis treatment. In univariable analyses, we tested all baseline variables that were available from both databases and several interaction variables. The variables that

were statistically significant ($P<0.05$) were tested in a multivariable logistic regression model.

Analysis of dialysis mortality

For analyses of mortality, we left-censored survival time at 90 days after initiation of RRT and right-censored at transplantation and end of follow-up, whichever occurred first. We used univariable Cox proportional hazards models to study all available variables. Those that were significantly associated with mortality in the univariable analyses were then included in a multivariable Cox proportional hazards model. Additionally, we tested the multivariable model for interaction variables that were reported to be significant in our previous analyses of factors determining dialysis mortality[61] and for interactions between waitlist status and age, gender, PRD-DM, and dialysis modality. Since several variables in the multivariable model showed significant interactions with time, we stratified time into strata within which the proportional hazards assumption was satisfied. For each time stratum, we defined waitlisting as being transplantable on the wait list before the start of the time stratum.

Analysis of predictors of renal transplant access

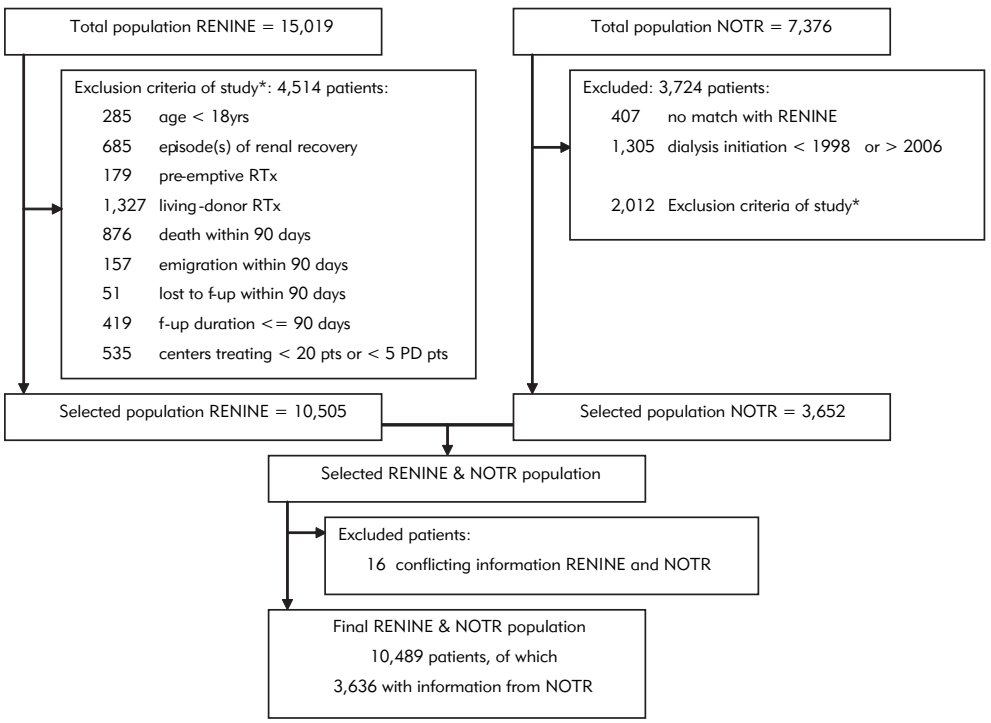
We assessed the predictors of cadaveric RTx access for the waitlisted dialysis population using Cox proportional hazards models. The waitlisted dialysis population was defined as those waitlisted and alive at 1 year of dialysis treatment. We computed survival time from the first day of being transplantable on the wait list, right-censoring at death and end of follow-up. We estimated univariable models for all available variables and entered all statistically significant variables into a multivariable Cox model. The final Cox model, containing all significant predictors was tested for violations of the proportional hazards assumption.

The multivariate study results are reported as odds ratios (ORs) and hazards ratios (HRs) with their respective 95% confidence intervals (CIs). All analyses were performed using SPSS 11.0.1 (SPSS Inc., Chicago, IL).

RESULTS

The RENINE Registry prospectively collected data of 15,019 patients who started RRT between January 1st 1998 and December 31st 2006. We excluded 4,514 patients according to the criteria listed in the Methods section, leaving 10,505 patients available for analysis (Figure 1). From NOTR, we received information for 7,376 patients. Of these, 1,914 patients were excluded. Reasons for exclusion are listed in Figure 1. When comparing the RENINE and NOTR databases after these exclusions, 16 patients had conflicting information and were also excluded from the analysis. As a result, our final sample included 10,489 patients from RENINE with information for 3,636 patients from NOTR (Figure 1). Two-hundred and ninety-one patients were waitlisted for a cadaveric renal transplant within the first 90 days of dialysis (Table 1). At 6 years after the start of dialysis, there were 511 patients on dialysis that had not died or received

FIGURE 1. Flow chart of exclusion of patients from RENINE and NOTR datasets



* Exclusion criteria of study as listed in the Methods section.
f-up = follow-up, NOTR = Dutch Organ Transplant Registry, PD = peritoneal dialysis, RENINE = Dutch End Stage Renal Disease Registry, RTx = renal transplantation

TABLE 1. Characteristics of non-waitlisted and waitlisted patients on day 91 and at 6 years after start of dialysis treatment

	on day 91 of RRT			at 6 yrs of RRT		
	not waitlisted	**waitlisted**	**P-value**	**not waitlisted**	**waitlisted**	**P-value**
number (%)	10,198 (97.2)	291 (2.8)		366 (71.6)	145 (28.4)	
age at start of RRT (yrs) (%)			<0.001			<0.001
<45	12.3	35.4		12.0	30.3	
45-60	22.6	41.9		18.3	51.7	
>=60	65.1	22.7		69.7	17.9	
female (%)	39.1	38.8	0.91	48.4	44.8	0.47
primary renal disease (%)			<0.001			0.17
GN	9.1	18.9		12.0	13.8	
HT	13.3	10.3		14.8	11.7	
RVD	12.0	2.1		8.2	2.8	
DM	19.4	12.4		12.6	12.4	
other	46.2	56.4		52.5	59.3	
peritoneal dialysis (%)	29.3	62.9	<0.001	34.7	42.8	0.09
year of start of RRT (SD)			0.44			0.29
1998-2000	29.0	30.9		94.3	91.7	
2001-2003	34.9	31.3		5.7	8.3	
2004-2006	36.1	37.8				

DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, RRT = renal replacement therapy, RVD = renovascular disease, yrs = years

a transplant, of whom 145 were waitlisted within the first 6 years of dialysis treatment (Table 1). Pronounced differences in the characteristics between waitlisted and non-waitlisted patients existed at 91 days after initiation of RRT: waitlisted patients were younger, more had started RRT using PD, and they were more likely to have PRD-GN and less likely to have PRD-DM and PRD-RVD. These differences, however, diminished over time (Table 1). At 6 years after first RRT, only age remained significantly different between waitlisted and non-waitlisted patients (supplemental material on patient characteristics for waitlisted and non-waitlisted patients for other time-strata between 91 days and 6 years are available upon request).

TABLE 2. Multivariable logistic regression model of the probability of being waitlisted

	OR	(95% CI)	P-value
age at start of RRT (years) (ref < 45)			<0.001*
45-60	0.76	(0.65-0.91)	0.002
>=60	0.14	(0.11-0.16)	<0.001
female	0.92	(0.80-1.07)	0.29
primary renal disease (ref=GN)			<0.001*
HT	0.48	(0.37-0.63)	<0.001
RVD	0.24	(0.16-0.36)	<0.001
DM	0.27	(0.21-0.36)	<0.001
other	0.64	(0.52-0.78)	<0.001
peritoneal dialysis (%)	2.17	(1.88-2.51)	<0.001
year of start of RRT (ref = 1998-2000)			0.07*
2001-2003	0.87	(0.74-1.02)	0.09
2004-2006	0.82	(0.68-0.98)	0.03
center of dialysis			<0.001*

* P-value from global Wald test of significance for inclusion of all categories of that variable.
95% CI = 95% confidence interval, DM = diabetes mellitus, GN = glomerulonephritis,
HT = hypertension, OR = odds ratio, ref = reference category, RRT = renal replacement therapy, RVD = renovascular disease

Independent predictors of being waitlisted for kidney transplantation at 1 year after onset of RRT are displayed in Table 2. Compared with patients below age 45, patients aged 45-60 years had a 24% (95% CI: 9%-35%) lower odds of being waitlisted, with patients aged 60 years or older experiencing a 86% (95% CI: 84%-89%) reduction in their odds of being waitlisted. Primary renal disease was also important: compared to patients with PRD-GN, patients with other underlying diseases had markedly reduced chances of being added to the waitlist (Table 2). Patients who used PD on day 91 of RRT had twice the likelihood of being waitlisted compared with HD patients, and there was significant heterogeneity in the likelihood of waitlisting among centers.

In our analyses of the association between waitlist status and mortality; age, gender, primary renal disease, dialysis modality, year of start of dialysis, and center of dialysis were significantly associated with the risk of death (not shown). Since several variables showed statistically significant interactions with time, we stratified time into seven strata within which all proportional hazards assumptions were satisfied. The number of patients at the beginning of each time-stratum (waitlisted and non-waitlisted), the

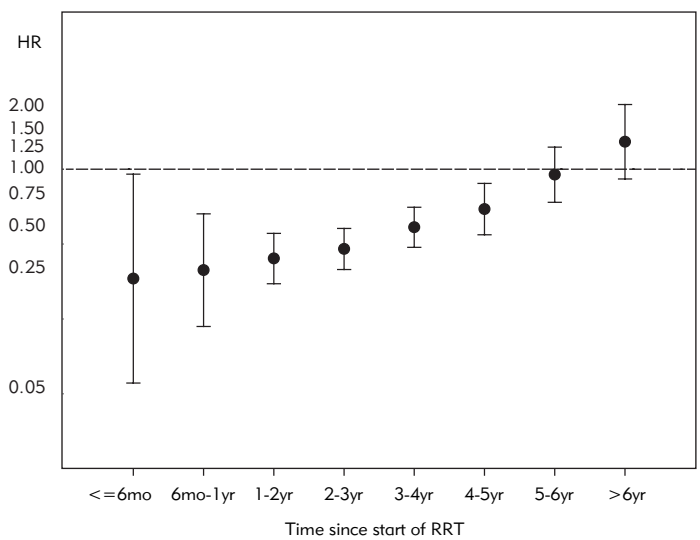
TABLE 3. Hazard ratios of waitlisted vs. non-waitlisted dialysis patient mortality

	n of patients at beginning of stratum	patients waitlisted		patients not waitlisted		HR	(95% CI)
		n	deaths (%)	n	deaths (%)		
<=6 months	10,489	291	0.7	10,198	5.7	0.23	(0.06-0.93)
6 months - 1 year	9,543	499	1.4	9,044	9.6	0.26	(0.12-0.55)
1-2 years	7,961	1,128	3.3	6,833	17.5	0.30	(0.22-0.42)
2-3 years	5,460	1,552	4.0	3,908	19.5	0.34	(0.26-0.45)
3-4 years	3,525	1,252	6.1	2,273	20.5	0.46	(0.35-0.60)
4-5 years	2,073	766	6.4	1,307	18.8	0.59	(0.42-0.83)
5-6 years	1,095	366	7.7	729	18.5	0.93	(0.64-1.34)
>6 years	511	145	18.6	366	26.2	1.44	(0.88-2.37)

95% CI = 95% confidence interval, HR = hazard ratio, n = number

proportion of patients that died within the time stratum, and the time-stratified HRs for mortality comparing waitlisted and non-waitlisted patients are shown in Table 3. During early time-periods, being waitlisted was associated with a markedly lower mortality risk (e.g., >70% during the first year of RRT). This relative mortality benefit of those who were waitlisted decreased (i.e., the HR increased) with increasing duration of RRT.

FIGURE 2. Hazard ratios (HRs) of mortality of waitlisted compared to non-waitlisted dialysis patients for all time-strata



mo = months, RRT = renal replacement therapy, yr = year

After 5 years of dialysis, there was no statistically significant relative survival benefit for waitlisted compared with non-waitlisted dialysis patients. The trend of this increasing HR over time is also depicted in Figure 2.

Patients receiving a cadaveric RTx were significantly younger, were more likely to be treated with PD and were more likely to have started dialysis in earlier years compared with those waitlisted that did not receive a cadaveric RTx (Table 4a). In multivariable analyses, only primary renal disease and center were significant predictors of access to transplantation. Analyses of time-dependent variables revealed that PRD-DM violated the proportional hazards assumption: in the first 3 years after waitlisting it was significantly associated with a higher chance of cadaveric RTx compared with PRD-GN (univariable HR: 2.22, 95% CI 1.55-3.19), and after 3 years, primary renal disease was not a significant predictor (Table 4b).

TABLE 4a. Characteristics of waitlisted patients that do not and do receive a cadaveric RTx

	total	no RTx	RTx	P-value
number (%)	1128 (100)	513 (45.5)	615 (54.5)	
age at waitlisting (yrs) (%)				<0.001
<45	32.5	26.3	37.7	
45-60	44.3	45.0	43.7	
>=60	23.1	28.7	18.5	
female (%)	37.7	40.7	35.1	0.05
primary renal disease (%)				0.36
GN	20.6	20.1	21.0	
HT	11.5	13.1	10.2	
RVD	3.0	3.5	2.6	
DM	11.1	11.9	10.4	
other	53.8	51.5	55.8	
peritoneal dialysis (%)	54.1	50.7	56.9	0.04
year of waitlisting (%)				<0.001
1998-2000	34.9	19.1	48.1	
2001-2003	38.0	32.7	42.4	
2004-2006	27.0	48.1	9.4	

DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, RRT = renal replacement therapy, RTx = cadaveric renal transplantation, RVD = renovascular disease

TABLE 4b. Univariate hazard ratios (HRs) for access to cadaveric renal transplantation (RTx)

	<= 3yrs of waitlisting			> 3yrs of waitlisting		
	HR	**(95% CI)**	**P-value**	**HR**	**(95% CI)**	**P-value**
primary renal disease (ref=GN)						
HT	1.14	(0.76-1.70)	0.53	0.95	(0.60-1.50)	0.83
RVD	1.54	(0.81-2.92)	0.18	1.47	(0.59-3.67)	0.41
DM	2.22	(1.55-3.19)	<0.001	0.66	(0.34-1.29)	0.23
other	1.08	(0.81-1.43)	0.60	0.97	(0.73-1.30)	0.86

95% CI = 95% confidence interval, DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, HR = hazard ratio, ref = reference catagory, RVD = renovascular disease, yrs = years

DISCUSSION

This is the first comprehensive study of access to the waitlist for cadaveric kidney transplantation and its impact on mortality in the Netherlands. This study was made possible by merging two distinct national registries, the Dutch End Stage Renal Disease registry RENINE and the Dutch Organ Transplant Registry NOTR. We found that age, primary renal disease, dialysis modality, vintage and dialysis center were independent predictors of access to the wait list. We confirmed reports from other countries that patients on the wait list had better survival than those not on the wait list. What had not been reported previously was our finding that this survival advantage of waitlisted patients diminished over time and was no longer present after 5 years of RRT. Access to cadaveric RTx was significantly predicted by primary renal disease within the first 3 years of dialysis treatment and by dialysis center.

The predictors of waitlisting we found in our study: age, primary renal disease, dialysis modality, and year of start of dialysis, have been described in the literature previously.[23,60,62-64] In addition to these predictors, others reported higher rates of waitlisting for males,[60,62,64] Caucasian patients,[60,64,65] patients of a higher social class[62] and patients with private insurance.[60] Lower rates of waitlisting were reported for smokers,[23] and patients with a several co-morbid conditions, such as congestive heart failure.[23,60] Furthermore, patients with a higher BMI,[58] or with late referral to a nephrologist just prior to needing RRT[24] have been shown to be less likely to be waitlisted.

In this large cohort of Dutch dialysis patients, we found that patients who had been waitlisted enjoyed significantly better survival compared to non-waitlisted patients. These findings are consistent with several other reports. In a Canadian population, crude mortality of non-waitlisted patients was estimated to be 4-fold higher than that of waitlisted patients.[30] Wolfe and colleagues[25] reported from a U.S. Renal Data System (USRDS) data sample of 228,552 patients that patients on dialysis that were waitlisted for transplantation had a substantially higher likelihood of survival. Their mortality was approximately 50% lower compared with all patients on dialysis for all subgroups by age, gender, ethnicity and cause of end-stage renal disease. This mortality risk reduction falls within the range of values we found for several time-strata. Others, however, have reported that waitlisting was not as predictive for mortality as generally assumed. Schold and colleagues[60] found a considerable overlap in risk-profile in waitlisted and non-waitlisted patients, resulting in lower survival among patients in the lowest survival quartile of waitlisted patients compared with patients in the upper survival quartile of non-waitlisted patients. Interestingly, we found that the rather marked survival benefit of being waitlisted during earlier time periods after onset of RRT decreased over time and even disappeared beyond 5 years of RRT. A similar observation has not been made previously. The most plausible explanation for our findings is the possibility that patients who receive a transplant are on average healthier, which leaves relatively sicker patients on the wait list. Furthermore, the detrimental effect of continued dialysis treatment of these waitlisted patients who do not receive a transplant may negatively affect their health. These patients' prognosis appears to become more similar to the prognosis of non-waitlisted patients.[28]

In our analyses of access to cadaveric RTx, PRD-DM was associated with a higher probability of transplantation within the first 3 years of dialysis and access differed significantly by dialysis center. After 3 years, primary disease was not associated with the access to RTx. The finding that patients with PRD-DM had a higher likelihood of RTx once waitlisted has not been reported in earlier studies. Others studies reported a similar access for patients with PRD-GN and PRD-DM.[62,64] A possible explanation for our findings could be that the difference in prognosis between waitlisted and non-waitlisted patients is larger for PRD-DM patients than for the other types of primary disease. Dialysis patients with PRD-DM that do get waitlisted may have such a good prognosis that they are more likely to get transplanted. When comparing the characteristics of patients across the different types of primary disease, no significant differences were found (data not shown). However, unmeasured differences, such as in co-morbidity

might be responsible for our findings. After 3 years, primary disease was not a significant predictor of RTx; this might be due to faster progress of morbidity in patients with PRD-DM compared with patients with PRD-GN, rendering prognostically more comparable patient populations over time.

Dialysis modality was not a significant predictor of access to RTx in our analyses. Although Chalem and colleagues[26] did report that PD patients had a higher access to cadaveric RTx in a univariable analysis, this effect disappeared in the multivariable analysis. Independent predictors included age, year of waitlist registration, blood group, HLA alleles frequency and peak panel reactive antibody (PRA) level. Oniscu and colleagues[62] reported age, primary renal disease, transplant center and year of waitlist registration as independent predictors. A low serum albumin,[60] co-morbid disease[66] and obesity[59,60] have also been shown to negatively impact access to RTx. Furthermore, sociodemographic variables such as non-caucasian ethnicity,[60,65-67] lower education,[68] employment status,[66] or income,[67,68] as well as poorer insurance status,[60,69] and nursing home residency[23] were reported to be associated with a lower access to RTx. In addition, patients that were referred to a nephrologist more than 1 year prior to start of RRT and with a higher number of pre-dialysis nephrologist visits were more likely to get transplanted.[24] We did not find gender to be associated with access to cadaveric RTx. Jindal and colleagues[70] reviewed the literature on gender differences in access to and outcome of RTx, and living RTx donation. Many studies found that women have poorer access to both living-donor and cadaveric RTx, even after correcting for potential confounders. Proposed explanations include higher immunization among, in particular, multiparous women, less social support among women with renal disease and perhaps a less assertive attitude among women in their interaction with health-care providers.

We found remarkably fewer predictors of access to cadaveric RTx in the waitlisted population, compared with the number of predictors of being waitlisted. From this finding, we infer that the waitlisting procedure may select more prognostically comparable patients for access to RTx. This finding has also been described by Oniscu and colleagues[62] using data from the Scottish Renal Registry.

Center of dialysis was a significant predictor in all three analyses. The influence of center on access to RTx has been described previously.[62] Also, other forms of center variability in RTx rates have been reported in the literature. Axelrod and colleagues[71] reported that compared with residents from urban areas, patients living in rural areas or

small towns had lower rates of waitlisting and transplantation. Ashby and colleagues[72] described a large geographical variation in access to kidney transplantation. A possible explanation for this center effect would be that university hospitals generally treat patients with a worse prognosis compared with smaller hospitals. Worse prognostic factors would lead to increased mortality, a lower probability of waitlisting and a lower access to renal transplantation. Additionally, it has been suggested that center characteristics, size, organizational aspects and attitudes of health care staff towards transplantation may be of influence.[62]

Some limitations of our work deserve mention. First, our databases lacked a number of possible predictors of the outcomes studied. We were unable to assess race or ethnicity, which has been shown to influence waitlisting for[23] and access to RTx[73] and dialysis mortality.[19,53] In addition, we had no information on the other socio-demographic, clinical and immunological factors that have been described as determinants of access to the wait list and to RTx, as discussed previously. Secondly, we only analyzed the predictors of waitlisting at 1 year, as a representative point in time. Strengths of this study include availability of data from an entire country, and over a long period of time, as well as a detailed analysis with particular attention to changes of important associations over time.

In conclusion, we confirmed that several factors that had been defined as predictors of waitlisting in other countries are also operational in the Netherlands: age, primary renal disease, dialysis modality, year of starting dialysis, and center of dialysis. We also confirmed that waitlisted dialysis patients had a considerably better survival compared with non-waitlisted patients, but were the first to describe that this relative benefit decreased with increasing dialysis duration. Access to RTx in the waitlisted population was determined by primary renal disease within the first 3 years and by center of dialysis, but not by other studied factors. Thus, the process of waitlisting appears to be effective in selecting appropriate patients for cadaveric RTx.

2.3

Live donor nephrectomy and return to work: does the operative technique matter?

ABSTRACT

Objective: Several studies report an earlier return to work after minimal invasive kidney donation compared to open donor nephrectomy. However, this variation in outcome might be influenced by other factors than the surgical technique used, such as the advice given by the physician regarding return to work. In this study, we compare the absence from work after open (ODN), laparoscopic (LDN), and hand-assisted donor nephrectomy (HA) performed in the Netherlands, in relation to the advice given.

Methods: Questionnaires containing questions about return to work or return to daily activities were sent to 78 donors from three hospitals. In the HA and ODN hospitals, advice on full return to work was 3 months. In contrast, advice given in the LDN hospital was 6 weeks.

Results: After LDN, donors resumed their work after 6 weeks, 5 weeks faster compared to ODN ($P=0.002$) and HA ($P<0.001$). Complete return to work occurred 9 weeks sooner in the LDN group compared to the ODN and HA groups (both $P<0.001$). In the unemployed group, there was no significant difference in length until full return to daily activities.

Conclusion: Return to work is influenced by the advice on return to work given by the physician as well as the morbidity associated with the surgical approach.

INTRODUCTION

The number of available postmortal kidneys remains stable and is insufficient to match the number of organs required to reduce the wait list for kidney transplantation. Living (un)related donation represents a large potential supply of organs and, as a consequence, has the potential to reduce the shortage. The discomfort associated with open donor nephrectomy (ODN), however, may deter potential living donors from volunteering. Laparoscopic donor nephrectomy (LDN) represents an alternative to the conventional open method and is associated with less morbidity, shorter length of stay, and earlier return to work.[74-77] However, this technique is associated with a long learning curve, discouraging transplant surgeons from applying this technique. The hand-assisted (HA) technique was introduced to make the laparoscopic procedure easier and faster to master, thus resulting in more widespread acceptance by surgeons and increased availability to donors. It is believed that morbidity of the hand-assisted technique is comparable to that of LDN since both techniques result in equivalent incisions. Unfortunately, LDN and HA are associated with increased costs induced by the use of disposable instruments and increased operating time compared to ODN.[78,79] However, a shorter hospital stay and earlier return to work can compensate these costs.

Studies reporting on convalescence period after kidney donation are mainly performed in the United States, where health care insurance and employment structures are very different from those in the Netherlands. Also, it is questionable to take return to work as an indirect measurement of the invasiveness of the procedure. Indeed, the advice given by the physician might influence return to work more than the morbidity related to the surgical approach. The aim of this study was to evaluate the duration of absence from work for LDN, HA, and ODN in relation to the attitude and advice of the supportive care team.

METHODS

Patient selection

Three hospitals in the Netherlands, all with extensive operative experience in the field of live kidney donation, supplied a list of patients who had donated a kidney in the period from 25 January 2000 through 1 October 2001. The list contained information such as operating date, date of birth, gender, and addresses. Data on the LDN were provided by the Erasmus Medical Center (EMC), those of the HA group by the University Hospital Amsterdam (AMC), and those of the ODN group by the University Hospital Nijmegen (St Radboud). A letter accompanying the questionnaire explained the donor's participation was on a voluntary basis and would not have any consequences for follow-up and treatment. Questionnaires were sent to 25 donors who were operated in the EMC, 29 donors who were operated in the St Radboud, and 24 donors who were operated in the AMC. The questionnaire contained questions about employment, full- or part-time work, return to work (partly or completely back to preoperative hours), and, when unemployed, full resumption of normal activities. Time to return to work was defined at two moments: on the first day of resuming work after a sick-leave period (return to work) and when donors resumed work according to their preoperative hours (full return to work).

Follow-up of the donors in St Radboud and AMC was mainly done by a nephrologist. In the EMC, the surgeon performed the follow-up at 3 weeks and 3 months, after which the donors where referred to a nephrologist for annual follow-up. Both St Radboud and AMC informed donors the expected duration until return to normal activities or work would be 3 months. The EMC informed donors they where expected to resume normal activities or work after 6 weeks. However, in all three centers the decision to go back to work was left to the donor.

Operating technique

Open donor nephrectomy

The patient is placed in a full lateral decubitus position by flexing the operating table, gaining maximum access between the iliac crest and the ribs. The method used in this study consists of an extra-peritoneal approach, with a flank incision just above or below the twelfth rib, cutting the muscles, without resection of the rib. Gerota's fascia is

opened and the kidney is mobilized to get access to the renal vessels. After clamping of the renal vessels as close to the aorta and caval vein as possible, these structures and the ureter are cut. The organ is removed through the incision and is placed in a basin filled with cold preservation fluid. A needle is placed in the artery, and the kidney is flushed with a 4°C preservation solution until the venous effluent is clear and the kidney is discolored.

Laparoscopic (transperitoneal) donor nephrectomy

The patient is positioned on the operating table similar to the open approach allowing a conversion to lumbotomy, if necessary. After a subumbilical open introduction of a 10-mm Hasson trocar, pneumoperitoneum is established by insufflation of carbon dioxide with an abdominal pressure of 12 mmHg. A 10-mm 30° video endoscope is inserted and the abdomen is inspected. Under direct vision, a 10-mm trocar and three to four 5mm trocars are placed and instruments can be introduced. A 5-mm endo-babcock clamp is used for retraction of the liver or spleen. Retraction is secured by grasping the lateral abdominal wall. The hepatic or splenic flexure of the colon is mobilized using a 5-mm curved ultrasonic device (Ultracision, Ethicon, Sommersville, NJ, USA) and retracted medially, exposing the kidney. Gerota's fascia is opened and the renal vein and ureter are identified and dissected. The anterior and posterior aspects of the kidney are both freed as well as the upper pole from adjacent attachments and structures. At this point, the kidney is allowed to fall medially and the renal artery, which is identified behind the renal vein, is dissected toward the aorta. The vessels are encircled with a rubber vessel loop to enable gentle traction and correct positioning of the stapling device. Dissection of the ureter, including the periureteral tissue and the ureteral arterial branch, is carried on to the crossing with the iliac artery. The left gonadal, lumbar, and adrenal veins are clipped and divided. The adrenal gland is released from the medial superior aspect of the renal capsule using the ultrasonic device. Preparations are then made for extraction of the kidney by making a Pfannenstiel incision of about 5 cm. Through this incision, an extraction device (Endocatch, US Surgical, Norwalk, CT, USA) is inserted. After administration of 5000 U of heparin, the ureter is clipped and divided. The renal vein and artery are divided using a linear vascular stapler (EndoGIA 30, US Surgical). Anticoagulation is then reversed with protamine. The kidney is placed in a specimen bag, brought out through the 5-cm incision, and flushed with cold preservation fluid.

After closure of the incision, pneumoperitoneum is reestablished and the abdomen is inspected. After complete hemostasis, the trocars are removed and the incisions are closed.

Hand-assisted donor nephrectomy
The procedure is performed as previously described in an article by Bemelman and colleagues.[80] A Pfannenstiel incision of approximately 7.5-8 cm is made correlating with the size of the surgeon's glove. This incision is used to mobilize the cecum or sigmoid and the distal ureter. Subsequently, the hand port is installed (Omniport, Advanced Surgical Concepts, Co., Wicklow, Ireland), and the left hand is inserted. A pneumoperitoneum of 12 mmHg is established. Two 10- to 11-mm trocars are introduced, respectively, subumbillically and epigastric. The operation is further conducted in the same order as the laparoscopic procedure. After dissecting and dividing of the ureter and the vessels, the kidney is removed with the aid of the hand-assisted device and perfused with cold preservation fluid.

Statistical analysis

Statistical analysis was performed using the SPSS 9.0 (SPSS Inc., Chicago, IL, USA) statistical software package. Comparisons of continuous variables between laparoscopic, hand-assisted, and open donor nephrectomy were performed using the Mann-Whitney-U test. Categorical data were reported as absolute number of patients and/or percentage of the group studied and were compared using the chi-square test. Correlation of age with return to work for each group was determined using the Spearman correlation coefficient. A P-value of <0.05 was considered to be statistically significant.

RESULTS

Of the 78 questionnaires that were sent to living kidney donors, 73 were returned (94%) and all were analyzed. The analyzed LDN group consisted of 25 donors, the HA group of 22 donors, and the ODN group of 26 donors.

Demographic data are listed in Table 1. There were no significant differences between the three groups for gender, employment and the type of employment (full- or part-time). Employed donors in the HA group were generally younger compared to the ODN

TABLE 1. Demographic variables[a]

	Open donor nephrectomy (ODN)	Laparoscopic donor nephrectomy (LDN)	Hand-assisted donor nephrectomy (HA)
	n=26	n=25	n=22
Gender			
Men	15 (58%)	12 (48%)	9 (41%)
Women	11 (42%)	13 (52%)	13 (59%)
Employed			
Yes	15 (58%)	19 (76%)	14 (64%)
No	11 (42%)	6 (24%)	8 (36%)
Employment			
Full-time	12 (80%)	11 (58%)	9 (64%)
Part-time	3 (20%)	8 (42%)	5 (36%)
Age (Years)			
Total group	52 (37-74)	46 (25-65)[b]	38 (25-63)[c]
Employed group	48 (37-58)[d]	45 (25-62)[e]	34 (25-47)
Unemployed group	65 (48-74)	54 (25-65)[f]	52 (36-63)[g]

a Data given are number of patients (percentage) or median (range).
b P=0.01 vs. ODN.
c P<0.001 vs. ODN.
d P<0.001 vs. HA.
e P=0.013 vs. HA.
f P=0.034 vs. ODN.
g P=0.004 vs. ODN.

and LDN groups (P<0.001, respectively P=0.013). In the unemployed group, ODN donors were generally older than LDN and HA (P=0.034, respectively P=0.004).

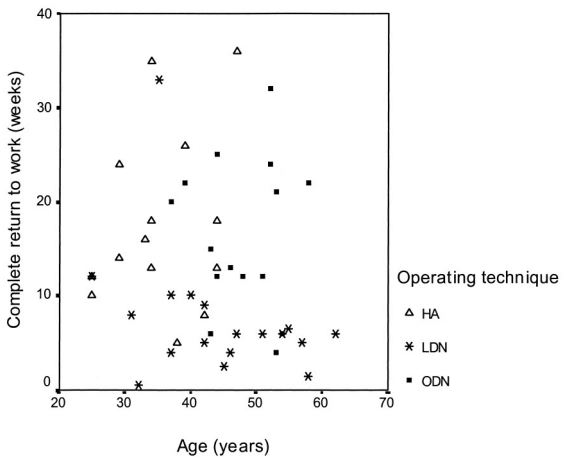
As shown in Table 2, return to work, either partly or completely back to preoperative hours, was accomplished 6 weeks after LDN. This was significantly shorter than ODN and HA, which were, respectively, 12 and 10 weeks. Also, full return to work (100% of preoperative hours) was significantly shorter in the LDN in contrast to ODN and HA. ODN did not differ from HA for either outcome. There was no significant correlation of age with time until complete (100% of preoperative hours) return to work for either group (all P>0.15, Fig. 1). The same applied to 'partly' return to work. In the unemployed group, time to full return to daily activities similar to preoperative activities was comparable for all three groups.

TABLE 2. Employment and absence from work[a]

	Open donor nephrectomy (ODN)	Laparoscopic donor nephrectomy (LDN)	Hand-assisted donor nephrectomy (HA)
Employed	n=15	n=19	n=14
Return to work[b] (weeks)	12.0 (3-22)*	6.0 (0.5-25)	10.0 (5-21)**
Return to work[c] (weeks)	15.0(4-32)**	6.0 (0.5-33)	15.0 (5-36)**
Unemployed	n=11	n=6	n=8
Full recovery (weeks)	4.3 (0-13)	4.5 (3-10)	5.2 (0-8)

* P=0.002 vs. LDN.
** P<0.001 vs. LDN.
a Data given are median (range).
b Partly or completely back to pre-operative hours.
c Completely back to pre-operative hours.

FIGURE 1. Graph showing correlation of age with return to work after LDN (stars), ODN (closed squares), and HD (open triangles)



DISCUSSION

Since the number of postmortal kidneys falls short of the number required by the patients waiting for a kidney transplant, living donation represents a large supply of organs. However, the altruistic, healthy donor is exposed to morbidity associated with the donor nephrectomy, which may deter potential donors from donating. A long conva-

lescence period and absence from work may also be an important disincentive to the potential donor. Studies show a reduced discomfort and faster convalescence of the donor after laparoscopic or hand-assisted donor nephrectomy.[74-77,81,82] Questions remain as to whether correlation of the surgical technique with the earlier convalescence is valid or whether the convalescence is mainly caused by the socioeconomic behavior of the donor.

Several American studies show a return to work after 2.3 to 3.9 weeks in the LDN group compared with 5.3 to 7.4 weeks in the ODN group.[75,76,81] In another report, donors returned to work after 3.5 weeks after HA compared to 4.1 weeks after ODN.[82] In our study, absence from work is considerably longer for all groups compared to American studies. This might be caused by the difference in social and insurance structures. In the Netherlands, donors receive paid sick leave from work, so there is no stimulus to restart work as quickly as possible. Also, advice from physicians regarding return to work may be different from that given in the United States. A Swedish study, comparing ODN and LDN, showed a duration of sick leave of 6 weeks in the laparoscopic group compared with 7 weeks in the open group. Time away from work of our LDN group is comparable with that of the LDN group from the Swedish study. However, we have found a much longer absence for the open group. When comparing absence from work of the HA group from our study and that of an American study, we find a (mean) difference of more than 3 months (3.5 vs. 17.7 weeks).[82] The age of both groups is comparable (37 vs. 38 years) and does not explain this discrepancy. The dissimilarity could be a result of a difference in social and economical structures of the United States and the Netherlands. Also, hand-assisted donors, in this study, are informed prior to operation that they will probably not work for 3 months. It seems the donors comply with this advice.

Although the hand-assisted procedure was introduced as an operating technique accompanied by the same benefits as LDN, in this study, the HA group differs significantly with regard to absence from work compared to the LDN group. Wolf and colleagues[83] showed a comparable morbidity after hand-assisted and laparoscopic nephrectomy. This indicates that the difference found in return to work between the LDN and HA group is probably caused by the difference in advice prior to operation. The donors of the LDN group were informed they probably would not work for 6 weeks, contrary to the HA group who where told they would be absent for 3 months.

Contrary to the literature,[84] donors of the HA group refrained from work as long as the donors from the ODN group. The comparable variables in time away from work for HA and ODN group suggests a corresponding morbidity for both operating techniques. However, this is unlikely since the incision of the HA is much smaller and the abdominal wall muscles are not divided. A reason for the similar results of HA and ODN could be that both groups received the same advice from their physicians related to the expected duration of sick leave (based on their own experience).

We have found no difference in duration until full recovery in the unemployed group. This indicates donor recovery periods are similar for all groups, but return to work is dependent on the advice given by the caretakers.

This study demonstrates that in a well-defined population there is a great variance in return to work after a live donor nephrectomy. The question remains if this variation in outcome is caused by the morbidity related to the surgical approach or a difference in the advice given to the donor with regard to return to work. Considering the comparable morbidity after HA and LDN, the difference in return to work may be a reflection of attitude and expectation of the physician more than the actual recovery period of the donor. It is remarkable that the actual duration of sick leave of all groups correlates with the advice given by the physician. Secondly, it is important to note that recovery is similar in the nonemployed group.

In conclusion, this study shows that the approach and the advice of the physician to the donor regarding the moment of resumption of work has a great influence on the convalescence period and, in particular, the actual return to work. In order to perceive return to work as an indirect measure of the invasiveness of the procedure, all donors should receive similar advice. It is important to realize that advice and stimulation from the physician on return to work influences the outcome. All studies comparing morbidity and convalescence period of surgical techniques should define a methodological standardization with regard to this advice given to the donors. Only then can we determine if a more rapid convalescence is caused by a socioeconomic policy or the surgical technique used.

3

Quality of life of patients on renal replacement therapy

3.1

Quality of life assessed with the Medical Outcomes Study Short Form 36-Item Health Survey of patients on renal replacement therapy: a systematic review and meta-analysis

ABSTRACT

Objective: The Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) is the most widely used generic instrument to estimate quality of life of patients on renal replacement therapy. Purpose of this study was to summarize and compare the published literature on quality of life of hemodialysis (HD), peritoneal dialysis (PD), and renal transplant (RTx) patients.

Methods: We used random-effects regression analyses to compare the SF-36 scores across treatment groups and adjusted this comparison for age and prevalence of diabetes using random-effects meta-regression analyses.

Results: We found 52 articles that met the inclusion criteria, reporting quality of life of 36,582 patients. The unadjusted scores of all SF-36 health dimensions were not significantly different between HD and PD patients, but the scores of RTx patients were higher than those of dialysis patients, except for the dimensions Mental Health and Bodily Pain. Point differences between dialysis and RTx patients varied from 2 to 32. With adjustment for age and diabetes, the differences became smaller (point difference 2-22). The significance of the differences of both dialysis groups compared with RTx recipients disappeared for the dimensions Vitality and Social Functioning. The significance of the differences between HD and RTx patients disappeared on the dimensions Physical Functioning, Role Physical, and Bodily Pain.

Conclusion: We conclude that dialysis patients have a lower quality of life than RTx patients, but this difference can partly be explained by differences in age and prevalence of diabetes.

INTRODUCTION

Because survival among patients with end-stage renal disease (ESRD) is improving, health-related quality of life is becoming more important as an outcome measure in the evaluation of the various renal replacement therapies (RRTs) and other therapeutic interventions for these patients. Moreover, it has been argued that quality of life of patients on RRT can predict their future morbidity and mortality.[85-88] In general, measurement of health-related quality of life is becoming more important; not only as an outcome measure in chronic disease but also as an adjustment factor in economic evaluations.

Reflecting the increasing interest, the body of literature on quality of life among patients on RRT has expanded rapidly in recent years. Of the RRTs, renal transplantation (RTx) is generally accepted as the preferred treatment for ESRD. As early as the 1980s, Evans and colleagues[33] reported that quality of life is higher among RTx recipients compared with dialysis patients. Other authors, however, reported that this might be explained by pre-existing differences between patients selected for the different forms of RRT,[34] including differences in age, sex, ethnicity, primary renal disease, and co-morbidity. This study however, included only a small number of peritoneal dialysis (PD) and RTx patients. Studies on the difference in health-related quality of life of hemodialysis (HD) compared with that of PD patients remain controversial. Some studies show a higher quality of life for PD patients as compared with hospital HD patients,[33,35] whereas others found similar physical quality of life for PD and HD patients, but higher mental quality of life for PD patients.[36] Thus, considerable uncertainty remains as to the differences in quality of life of HD and PD patients and as to the differences in quality of life of dialysis patients and RTx patients when adjusted for covariates.

When confronted with such a large body of literature with disparate results it can be helpful to perform a systematic review and meta-analysis, adjusting for covariates where possible. Previously, Cameron and colleagues[34] performed a meta-analysis of the literature on quality of life associated with RRTs. Nevertheless, this study reviewed the literature on emotional distress and/or psychological well-being measures and did not include measures of health-related quality of life.[34] The Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) is the most widely used generic quality-of-life assessment instrument to estimate quality of life of patients with ESRD.[89] It has shown to be valid,[90] sensitive to treatment changes,[91] and to be accepted by ESRD patients.[92]

The purpose of our study was therefore to summarize the published literature on the SF-36 as a measure of health-related quality of life of patients receiving HD, PD, and RTx. Furthermore, our aim was to compare the SF-36 scores across treatment groups adjusted for age and prevalence of diabetes as co-morbidity.

METHODS

Study retrieval

An English literature search was performed using MEDLINE (United States National Library of Medicine, Bethesda, MD, USA) and PsycINFO (Web SPIRS, Silver Platter, New York, NY, USA). All articles from peer-reviewed journals, published before June 2005 were considered for inclusion. Additional studies were identified through the bibliographies of the articles. Studies were included if they met the following criteria: 1) they reported all SF-36 dimension scores; 2) they included at least one of the forms of RRT specified as HD, PD or RTx; 3) data were collected prospectively; and 4) the sample size was at least 10 patients per treatment group. Articles were excluded if the data were provided by proxies. We also excluded articles on quality of life of combined pancreas-kidney transplant recipients. Of articles with similar or overlapping researchers or articles from the same center, we evaluated their independence by determining when, where and how many subjects were included. If more than one published article reported data from the same subjects, the most recent article was selected, unless its sample was smaller or less information on covariates was reported.

SF-36

The SF-36 consists of eight dimensions, generating a profile of health-related quality of life.[93] 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 are transformed into a score between zero and hundred for each dimension. Higher scores indicate better health.

Data extraction

A standardized data sheet was used to collect the data from the studies. Data were extracted by one reader (Y.S.L.) and independently verified by two others (J.L.B., M.H.H.). Discrepancies were resolved by discussion. Readers were not blinded to information about the authors, author affiliation, and journal name, because this has been shown to be unnecessary.[94] The extracted study characteristics included publication year, country and center of authors and patients, number of patients included, demographic and clinical patient characteristics and the eight SF-36 dimension scores. If discrepancies in numbers existed between text and tables, we extracted the number reported in the table. If SF-36 scores had to be read from a graph, we rounded off to the nearest 0.5 points. If the study reported quality of life at multiple time-points, we chose one time-point closest to the mean time on therapy for the treatment group. For studies evaluating interventions, such as immunosuppressive regimens or exercise programs, we selected the baseline time-point to minimize the effect of interventions on the mean quality-of-life estimates, unless the intervention started at the initiation of the RRT. If the time of interview in relation to time on treatment was not reported we chose the time-point for which sample size and age were reported and if this information was available for all time-points we chose the time-point for which most demographic or clinical information was available.

If treatment groups were split up according to covariates, we preferred to use data of the total group, if reported. If, however, more demographic or clinical information was available for the split groups we included these groups as separate entries into the meta-analysis.

Data synthesis and analysis

We explored the data, testing for homogeneity of the variables age, sex, diabetes, time on RRT, and SF-36 dimension scores within the three treatment groups separately. After, we calculated pooled weighted means and 95% confidence intervals for these variables using random-effects models, also for the three treatment groups separately. Random-effects models weigh the outcomes of the study according to the within-trial as well as the between-trial variance.[95] We tested for statistically significant differences between the groups, using Students' t-tests and chi-square tests. In a random-effects meta-regression analysis[96,97] we corrected the differences in SF-36 scores between the

treatment groups for the covariates age and co-morbidity (diabetes mellitus), for the subgroup of studies for which this information was available. These covariates have been reported to be independent predictors of quality of life among RRT patients. We also performed a subanalysis of all studies reporting time on RRT to evaluate its effect on differences in SF-36 scores between the treatment groups. To account for multiple testing, we considered a P-value<0.01 to reflect statistical significance for all statistical tests and models. For the analyses we used SAS 8.02 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Our literature search resulted in 192 articles. Of these articles we excluded 35 on the basis of the abstract: 2 were excluded because they concerned a thesis or book, 5 because they were review articles, 11 because quality of life of a different patient group was reported, 7 because quality of life of renal donors was reported, 2 because patients had predialysis renal insufficiency, 3 because quality of life of caregivers was reported, 2 because the sample included less than 10 patients, and 3 because no mean SF-36 scores were reported. Of the remaining 157 articles, we excluded 105 on the basis of the full text, for the following reasons: other quality-of-life measurement techniques were used (n=2), sample size was not reported (n=4) or less than 10 patients were analyzed (n=1), mean SF-36 scores were not reported for all eight dimensions (n=66), patients with predialysis renal insufficiency were included (n=3), scores among combined groups were reported (e.g., HD and PD patients, or HD, PD, and RTx patients; n=12), and plausible overlap with another included article (n=17). Exclusion of these studies ensured included studies to be of good quality and all included studies were of at least level 2b evidence according to the Oxford Center for Evidence-Based Medicine classification.[98] One intervention study was initiated directly after RTx[99] and did not report absolute scores at a well-defined follow-up point, therefore we used the baseline measurements from this study.

In our meta-analysis, we included 52 studies, that reported on the quality of life of 92 groups of patients on RRT measured with the SF-36;[36,85,92,99-147] quality of life was reported for 44 HD groups (30,372 patients), 20 PD patient groups (3,262 patients), and 28 RTx groups (2,948 patients) (Tables of SF-36 scores and selected study and patient characteristics for all groups from the individual studies are reported in the appendix and are available online at

http://www.ispor.org/valueinhealth_index.asp). Tests for homogeneity were statistically significant for all variables, meaning that the null hypothesis of homogeneity was rejected. Therefore, using random-effects rather than fixed-effects models appears to be justified. Mean age, computed using random-effects models, was not significantly different for HD (55.8 years) compared with PD (52.9 years) (P=0.085) patients but RTx recipients (mean age=43.7 years) were significantly younger than dialysis patients (P<0.001) (Table 1). The majority of patients were male and there were no statistically significant differences in sex distribution among the three treatment groups (P>0.039). Prevalence of diabetes was 24% among HD, 17% among PD, and 7% among RTx patients, with a significant difference for the HD to RTx patient comparison (P<0.001). This prevalence might be lower than that reported by the United States Renal Data System, because most studies are from other countries than the United States and in general, prevalence of diabetes is known to be lower in Europe and Asia. The mean treatment time was 44.1 months for HD patients, 24.3 months for PD, and 63.8 months for RTx recipients. Comparing all treatment groups, PD and RTx patients had a significantly different mean time on treatment (P=0.001).

In general, SF-36-dimension scores were significantly lower for HD and PD compared with RTx patients (Fig. 1) (P<0.01), except for the Mental Health dimension for which PD scores were not significantly different from scores of RTx recipients (P=0.019). Scores of HD compared with PD patients were not statistically significantly different (P>0.055).

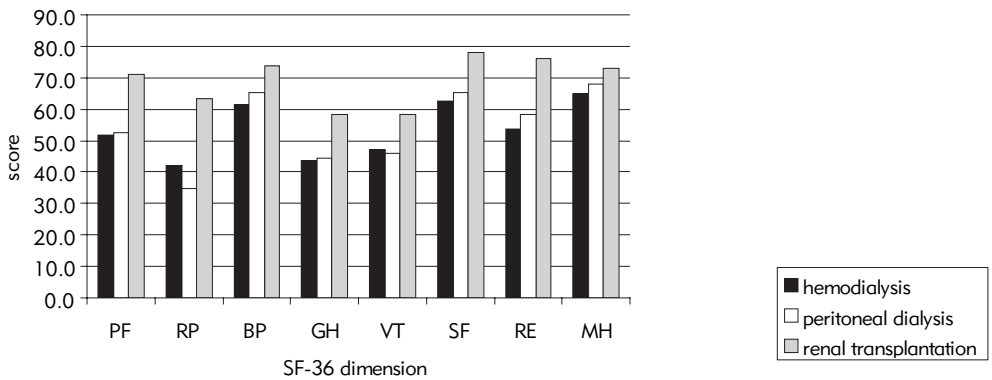
TABLE 1. Demographic and clinical characteristics of renal replacement therapy patients

	HD			PD			RTx		
	n	**Mean***	**95% CI**	**n**	**Mean***	**95% CI**	**n**	**Mean***	**95% CI**
Mean age (years)	43	55.8	(53.9-57.7)	20	52.9	(50.1-55.7)	27	43.7	(41.3-46.0)
Proportion male	37	0.55	(0.52-0.58)	18	0.55	(0.50-0.59)	17	0.61	(0.57-0.65)
Proportion with diabetes	24	0.24	(0.18-0.30)	14	0.17	(0.11-0.26)	9	0.07	(0.04-0.12)
Mean time on treatment (months)	32	44.1	(32.9-55.3)	12	24.3	(6.1-42.5)	21	63.8	(50.1-77.6)

*Mean based on random-effects model.
CI = confidence interval, HD = hemodialysis, n = number of groups, PD = peritoneal dialysis, RTx = renal transplantation

We found 23 studies that reported the percentage of patients with diabetes mellitus in 47 patient groups.[36,101,102,104-106,110-113,117,120,124,126,127,131,133,136,138,141-143,146] The random-effects means of the SF-36 scores computed from these studies (Table 2) were very similar to those computed from all studies (Fig. 1). Significance of the differences between treatment groups was also similar, except for the Bodily Pain dimension (no significant

FIGURE 1. SF-36 scores from all articles: random-effects-model means



BP = Bodily Pain, GH = General Health perceptions, MH = Mental Health, PF = Physical Functioning, RE = Role limitations due to Emotional functioning, RP = Role limitations due to Physical functioning, SF = Social Functioning, VT = Vitality

TABLE 2. SF-36 scores from articles that reported the percentage of patients with diabetes (n=23 studies)

	HD		PD		RTx		P-value*		
	Mean†	95% CI	Mean†	95% CI	Mean†	95% CI	HD vs. PD	HD vs. RTx	PD vs. RTx
PF	51.5	(46.7-56.2)	53.6	(47.2-60.0)	74.8	(67.1-82.5)	0.594	<0.001	<0.001
RP	45.1	(39.8-50.4)	34.1	(26.9-41.4)	66.3	(57.5-75.0)	0.017	0.001	<0.001
BP	60.2	(57.2-63.2)	66.1	(62.0-70.2)	74.0	(69.1-78.9)	0.025	<0.001	0.016
GH	42.4	(40.2-44.5)	45.5	(42.6-48.5)	57.9	(54.5-61.4)	0.087	<0.001	<0.001
VT	47.8	(44.8-50.8)	46.1	(42.0-50.2)	58.6	(53.7-63.4)	0.504	<0.001	<0.001
SF	61.7	(57.4-66.1)	65.5	(59.7-71.3)	79.1	(72.1-86.2)	0.304	<0.001	0.005
RE	51.5	(47.0-56.0)	55.3	(49.0-61.7)	73.9	(66.4-81.4)	0.325	<0.001	<0.001
MH	63.7	(60.9-66.5)	67.2	(63.4-71.0)	69.5	(64.9-74.1)	0.147	0.034	0.435

* Conclusions as to significance of difference from the confidence intervals are slightly different than from the P-value due to the fact that the distributions of the scores are flat and not entirely normal.
† Mean based on random-effects model.
BP = Bodily Pain, CI = Confidence Interval, GH = General Health perceptions, HD = hemodialysis, MH = Mental Health, PD = peritoneal dialysis, PF = Physical Functioning, RE = Role limitations due to Emotional functioning, RP = Role limitations due to Physical functioning, RTx = renal transplantation, SF = Social Functioning, VT = Vitality

TABLE 3. SF-36 scores from articles that reported the percentage of patients with diabetes adjusted for age and diabetes

	HD		PD		RTx		P-value*		
	Mean†	95% CI	Mean†	95% CI	Mean†	95% CI	HD vs. PD	HD vs. RTx	PD vs. RTx
PF	55.4	(50.1-60.7)	54.4	(48.3-60.5)	69.4	(60.6-78.2)	0.801	0.017	0.007
RP	49.9	(44.2-55.5)	34.2	(27.7-40.6)	56.4	(47.1-65.8)	<0.001	0.283	<0.001
BP	63.3	(59.9-66.7)	66.7	(62.9-70.6)	69.5	(64.1-75.0)	0.163	0.087	0.404
GH	43.5	(40.8-46.1)	45.8	(42.3-49.0)	56.4	(52.1-60.6)	0.230	<0.001	<0.001
VT	50.1	(47.2-53.1)	45.7	(42.3-49.0)	51.7	(46.9-56.5)	0.042	0.630	0.047
SF	64.2	(59.0-69.4)	66.1	(60.4-71.9)	76.3	(67.9-84.8)	0.610	0.032	0.051
RE	51.8	(46.4-57.3)	55.0	(48.6-61.4)	71.9	(62.8-81.0)	0.432	0.001	0.004
MH	64.0	(60.5-67.5)	67.2	(63.3-71.1)	69.0	(63.3-74.7)	0.203	0.186	0.616

* Conclusions as to significance of difference from the confidence intervals are slightly different than from the P-value due to the fact that the distributions of the scores are flat and not entirely normal.
† Mean based on random-effects model.
BP = Bodily Pain, CI = confidence interval, GH = General Health perceptions, HD = hemodialysis, MH = Mental Health, PD = peritoneal dialysis, PF = Physical Functioning, RE = Role limitations due to Emotional functioning, RP = Role limitations due to Physical functioning, RTx = renal transplantation, SF = Social Functioning, VT = Vitality

difference in score between PD and RTx patients) and the Mental Health dimension (no significant difference between HD and RTx patients). The point differences of the scores of the dialysis groups compared with the RTx group varied from 2 to 32.

In random-effects meta-regression analyses, we corrected for age and diabetes. The covariates did not attain statistical significance in many of the regression models. Only in the regression models estimating the Role Physical score and the Vitality score, the age covariate was associated with a P-value lower than 0.01. From the regression analyses and the mean age (52.9 years) and proportion with diabetes (0.16) in the total population we computed adjusted scores (see Table 3). Compared with the unadjusted scores, the adjusted scores were higher for HD patients and lower for RTx recipients. The adjusted scores of PD patients were similar to the unadjusted scores. Thus, in general, the differences between the groups became smaller. This is also reflected in the point differences of the adjusted scores of the dialysis groups compared with the RTx group, which varied from 2 to 22 (unadjusted: 2-32). After adjustment, the significance of the differences of both dialysis groups compared with RTx recipients disappeared for the Vitality dimension and the Social Functioning dimension. In addition, the significance of the differences between HD and RTx patients disappeared on the Physical Functioning,

the Role Physical, and the Bodily Pain dimensions. The non-significantly lower score of PD as compared with HD patients on the Role Physical dimension became statistically significant. In random-effects meta-regression analyses including time on replacement therapy, this variable did not show any effect on existing differences in SF-36 scores between the three treatment groups. In the subgroup of studies that reported age and diabetes as well as time on therapy, it did have an independent effect on the significance of three PD versus RTx comparisons. But in a meta-regression model adjusted for age and diabetes as well as time on RRT, the additional effect of time on therapy only persisted for one PD versus RTx comparison. Because we did not want to include too many covariates and because the additional effect of time on RRT was negligible, it was not included as a covariate in the full meta-regression model.

DISCUSSION

The present meta-analysis corroborates the consensus that health-related quality of life differs across the different forms of RRT. Except for the Mental Health dimension, health-related quality of life as measured by the SF-36 was higher among RTx patients than among dialysis patients. SF-36 scores among HD patients compared with PD patients were not statistically significantly different. Nevertheless, meta-regression analyses revealed that some of the differences in scores between dialysis patients and RTx recipients could be partly explained by differences in age and presence of diabetes between these treatment groups.

Changes in SF-36 scores after adjustment were more pronounced for HD and RTx patients as compared with PD patients, since the average mean age and prevalence of diabetes in PD patients was closer to the average mean age and prevalence of diabetes across all treatment groups. This may explain why the differences between scores of PD patients and RTx patients disappeared with adjustment for only two dimensions, whereas with adjustment, the differences in scores disappeared in five dimensions for HD compared with RTx patients.

Wu and colleagues[147] report both unadjusted SF-36 scores and scores adjusted for age, sex, race, education, albumin, creatinine, hematocrit, and co-morbidity score for HD and PD patients after 1 year of dialysis treatment. Unadjusted scores of PD patients were significantly higher for the Bodily Pain dimension and lower for the Vi-

tality dimension. After adjustment, the difference in Vitality disappeared, but the difference in Bodily Pain remained. Nevertheless, all differences were borderline significant (P-value between 0.03 and 0.05). Merkus and colleagues[124] showed that a significantly higher unadjusted quality of life of PD patients as measured on four dimensions of the SF-36 only persisted for the Mental Health dimension after adjustment.

From their study among HD, PD, and RTx patients and patients receiving conservative therapy, Baiardi and colleagues[101] conclude that treatment method and age independently influenced quality of life. Dimensions most affected were Physical Functioning, Bodily Pain, General Health, and Vitality. Scores for the four dimensions corrected for mean age and hemoglobin level showed that for the Physical Functioning and Bodily Pain dimensions, patients receiving conservative treatment and RTx patients had better results than those on dialysis. Similar to our results, compared with their unadjusted scores the adjusted scores of HD patients were in general higher and the adjusted scores of RTx patients were lower. Adjusted scores of PD patients were only slightly higher than unadjusted scores. In general, differences across the treatment groups became smaller. Adjusted differences in quality of life between dialysis and RTx patients might be smaller than generally thought because RTx patients commonly have a long history including dialysis, which affects their quality of life.

In a meta-analysis of emotional distress and psychological well-being of HD, PD, and RTx patients, Cameron and colleagues[34] reported comparable differences in quality of life. The authors did not formally adjust for covariates influencing these differences, but did report differences in covariates among the treatment modalities. They concluded that because RTx patients are generally younger, healthier, better educated, and more likely to be employed, it cannot be ruled out that differences in emotional distress and psychological well-being are partly a result of differences in case mix.

To be able to assess real differences in quality of life among RRT patients, Cameron and colleagues[34] suggested a prospective repeated-measures experimental design in which the same cohort of patients can be assessed repeatedly and at clinically significant milestones, such as when a patient switches to a different treatment modality. Nevertheless, such switches are usually induced by changes in demographic or clinical variables, so analysis of data from such a study should still be adjusted for case-mix variables. Another solution the authors suggested was to limit research participants to

those patients for whom any form of RRT would be equally suitable. Results, however, would not be generalizable to the entire patient population. This problem is also relevant to our meta-regression analyses, because we used the average mean age and proportion with diabetes across all treatment groups to calculate adjusted scores. Adjusted scores should therefore not be interpreted as actual scores. More interesting is the direction of the change of the scores after adjustment and the significance of the differences of adjusted scores among the treatment groups.

There are several limitations to our study that should be mentioned. First, the results of meta-analyses always rely on completeness of available published literature. Thus, they are known to be influenced by publication bias. Nevertheless, ours is a study of mostly noncomparative studies and from the comparative studies that we included only absolute measures were extracted. So if publication bias should have affected our study, its effect can be assumed to be very small.

Second, we would have wanted to adjust for all possible case-mix differences that might influence reported health-related quality of life. Age, sex, ethnicity, socioeconomic status, education, employment, and income are considered to be independent demographic predictors of quality of life.[148] Additionally, several disease-associated factors such as primary renal disease, treatment history, anemia and co-morbid disease are also known to be associated with quality of life.[148] Unfortunately, not all these covariates were consistently published in the studies and the number of studies was too small to be able to correct for many case-mix differences. Therefore, we decided to only adjust for case mix in a subset of studies and for a limited number of covariates. But even if more studies reporting all these covariates would have been available, caution is required in selecting covariates for the regression analysis. Covariates need to be prespecified to avoid data dredging.[97] Furthermore, results are easier to interpret when the covariate has a high variability across studies compared with within studies. But still, interpretation of meta-regression analyses using patient covariates is not always straightforward because of the fact that the relationship of the outcome with patient averages across trials may not be the same as the relationship of the outcome across patients within trials. This phenomenon is also referred to as aggregation bias or the ecologic fallacy.[97]

Lambert and colleagues[149] compared a meta-regression analysis using mean patient covariates to an analysis with individual patient-level data. They found that although

the estimates from the meta-regression analysis were not biased, there was a greater variation for the meta-regression estimates than for the estimates from the analysis on the individual patient-level data. They concluded that to investigate whether patient characteristics are related to treatment, a meta-analysis of summary data might not be apt and that an individual-patient-level data analysis will generally be necessary to uncover such relationships. We did, however, find significant changes with adjustment.

From this meta-analysis we conclude that HD and PD patients tend to have a lower quality of life than RTx recipients. Quality of life seems comparable for HD and PD patients. Adjusting the SF-36 scores for mean age and prevalence of diabetes in a meta-regression analysis showed that some differences in scores between dialysis and RTx patients can be partly explained by unequal patient selection for the different RRT modalities. This implies that although quality of life of dialysis patients is worse than that of RTx recipients, the difference between these groups might not be as big as generally thought. This is important in choosing an appropriate therapy for an individual patient. In targeting interventions aimed at improving quality of life, factors independently associated with quality of life, such as co-morbidity, should also be taken into account.

3.2

Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis

ABSTRACT

Objective: Various utility measures have been used to assess preference-based quality of life of patients with end-stage renal disease (ESRD). The purposes of this study were to summarize the literature on utilities of hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (RTx) patients, to compare utilities between these patient groups, and to obtain estimates for quality-of-life adjustment in economic analyses.

Methods: We searched the English literature for studies that reported visual analogue scale (VAS), time trade-off (TTO), standard gamble (SG), EuroQol-5D (EQ-5D), and health utilities index (HUI) values of ESRD patients. We extracted patient characteristics and utilities and calculated mean utilities and 95% confidence intervals (CIs) for categories defined by utility measure and treatment modality using random-effects models.

Results: We identified 27 articles that met the inclusion criteria. VAS articles were too heterogeneous to summarize quantitatively and we found only one study reporting HUI values. Thus, we summarized utilities from TTO, SG, and EQ-5D studies. Mean TTO and EQ-5D-index values were lower for dialysis compared to RTx patients, though not statistically significant for TTO values (TTO values: HD 0.61, 95% CI 0.54-0.68; PD 0.73, 95% CI 0.61-0.85; RTx 0.78, 95% CI 0.63-0.93; EQ-5D-index values: HD 0.56, 95% CI 0.49-0.62; PD 0.58, 95% CI 0.50-0.67; RTx 0.81, 95% CI 0.72-0.90). Mean HD versus PD associated TTO, EQ-5D-index and EQ-VAS values were not statistically significantly different.

Conclusion: RTx patients tended to have a higher utility than dialysis patients. Among HD and PD patients, there were no statistically significant differences in utility.

INTRODUCTION

Health-related quality of life is becoming increasingly important as an outcome measure, especially in chronic diseases. It can be assessed with both general and disease-specific instruments. General instruments allow for comparisons of quality of life associated with different diseases. Many methods are currently available, and two types can be distinguished: health-profile measures and preference-based methods. Health-profile measures assess health status on a number of domains, such as physical, emotional, or social impairments. An example of such a measure is the Medical Outcomes Study Short Form 36-Item Health Survey (SF-36). Preference-based methods assign a single index value to health-related quality of life. This value is expressed on a ratio scale and length of life is used as the metric for measuring the subject's preference for the quality of life in a given health state. Thus, quality of life is a quantitative measure of the strength of a person's preference for an outcome, also defined as a person's utility associated with the outcome. Examples include time trade-off (TTO) and standard gamble (SG) methods. Some health-profile measures allow for the calculation of a utility, using a tariff or set of preference weights. Such tariffs have been estimated by deriving general population utilities for all possible health states that may result from a health-profile method.[31] The valuations of those health states have been estimated using preference-based methods. Utilities can be used in economic evaluations to adjust expected life years for quality of life.[31]

End-stage renal disease (ESRD) is an example of a chronic disease for which quality of life is an important outcome measure. First, patients with ESRD generally have a diminished quality of life compared to the general population. Second, it has been shown that quality of life is a predictor of future morbidity and mortality for this patient population.[85-88] ESRD entails the need for renal replacement therapy (RRT). Differences in quality of life associated with the alternative forms of RRT have been reported in the literature. When assessing studies using preference-based methods, renal transplantation (RTx) is associated with a higher quality of life than either hemodialysis (HD) or peritoneal dialysis (PD).[150-153] Nevertheless, other authors suggested that this might be due to pre-existing different characteristics of patients selected for the alternative forms of RRT, such as age, sex, ethnicity, primary renal disease, and co-morbidity.[34] Studies comparing the utilities of HD and PD patients remain controversial. Some studies show a higher quality of life for PD patients as compared to HD patients,[152,154] whereas others found similar utilities for PD and HD patients.[121,150,155-157]

To adjust for quality of life in economic analyses in ESRD patients, summary estimates from meta-analyses would be helpful. The systematic review and meta-analysis we performed previously on health-related quality of life of these patients only included studies using the SF-36,[158] a health-profile measure that cannot be used to adjust for quality of life in economic studies. Thus, the aims of the present study were to review and summarize the literature on preference-based quality of life of patients on RRT, to obtain mean utilities that can be used to adjust life expectancy in cost-effectiveness analyses, and to compare mean utilities of HD, PD, and RTx patients.

METHODS

Study retrieval

An English literature search was performed using Medline and PsycLIT. All articles from peer-reviewed journals, published before September 2006, were considered for inclusion. Additional studies were identified through the bibliographies of the articles that were found through this search. Studies were included if they met the following criteria: 1) they reported absolute utilities using the visual analogue scale (VAS), TTO, or SG method or utilities derived from the EuroQol-5D (EQ-5D) or health utilities index (HUI) questionnaires; 2) they included at least one of the forms of RRT specified as HD, PD, or RTx; 3) data were collected prospectively; and 4) the sample size was at least 10 patients per treatment group. Articles were excluded if the data were provided by proxies. We also excluded studies on quality of life of combined pancreas-kidney transplant recipients. Of articles with similar or overlapping researchers or articles from the same center, we contacted the authors for additional information and if this was not possible, evaluated their independence by determining when, where, and how many subjects were included. If more than one published article reported data from the same subjects, the most recent was selected, unless its sample was smaller or less information on covariates was reported.

Utility measures

The VAS is usually a 100 mm scale, ranging from 0 to 100, on which the respondent has to mark his valuation of his health status. The rating scale (RS) is the analogous question using a verbal rating on a scale from, for example, 0 to 100. It can be an-

chored in different ways: 0 can reflect the lowest possible quality of life, worst possible health status, or death, while 100 can reflect the highest possible quality of life, normal or perfect health.

The TTO approach was originally developed by Torrance and colleagues[159] and tested with respect to reliability and validity in ESRD patients by Churchill and colleagues.[150] It involves asking a patient to think about his kidney disease for the past 2 to 3 weeks and then choose between two hypothetical options: either remaining in his current health state for the patient-specific life expectancy or to trade off a number of years to live in full health. The number of years to be traded off is varied between 0 and the total life expectancy and the question is iterated until the patient is indifferent between the two options. The utility is then calculated by dividing the number of years that the patient would not be willing to trade by the total life expectancy at the point of indifference.

The SG method, derived from expected utility theory, requires the respondent to make a decision between either staying in his current health state or undergoing a hypothetical therapy.[160] This therapy has two possible outcomes: 1) there is a chance of immediate death; 2) if the patient survives he will be cured and will live in full health. The chance of death associated with this hypothetical therapy is varied in an iterative manner until the patient is indifferent between staying in his current health state and undergoing the hypothetical therapy. The utility is calculated as one minus the probability of death at the point of indifference.

The EQ-5D is a generic multiattribute utility that was developed by the EuroQol group.[161] It is self-administered and comprises two parts. The first part, the EQ-5D profile, consists of five items: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three levels of functioning: no problem, some problems, and extreme problems. Tariffs from several countries are available to compute a utility, the EQ-5D-index value, from an EQ-5D profile combination. The tariff based on the UK population sample values is most commonly used.[162] The second part of the questionnaire is the EQ-VAS, rating health from 0 (worst imaginable health state) to 100 (best imaginable health state).

The HUI is a multiattribute utility that describes almost one million health states, classified on different domains.[163] The most recent version is the HUI3, which classifies a health state on eight domains: ambulation, dexterity, cognition, emotion, pain and dis-

comfort, vision, hearing, and speech. For the health states, utilities have been derived from a reference population using a combination of SG and RS values. This derivation was accomplished, using a multiattribute model which assumes that choices in which one domain or attribute is varied do not depend on the level of another domain. Preferences for a certain number of states were elicited and the utilities for the other states were derived using this model.

Data extraction

A standardized data sheet was used to collect the data from the studies. Data were independently extracted by two readers (Y.S.L., J.L.B.) and discrepancies were resolved by discussion. Readers were not blinded to information about the authors, author affiliation, and journal name, because this has been shown to be unnecessary.[94] The extracted study characteristics included publication year, country and center of authors and patients, number of patients included, demographic and clinical patient characteristics and utilities. If discrepancies in numbers existed between text and tables, we extracted the number reported in the table. If utilities had to be read from a graph, we rounded off to the nearest 0.01 point on a 0-1 point scale.

From studies assessing quality of life after RTx at multiple time points, we extracted the utility at the time point closest to 12 months after transplantation, because this reliably reflects quality of life of RTx patients. From studies evaluating interventions, we extracted the utility at the baseline time-point to minimize the effect of the intervention on the mean quality-of-life estimate. If treatment groups were split up according to covariates, we preferred to use data of the total group, if reported. If total group data were not available, however, we included the groups as separate entries into the meta-analysis.

Data synthesis and analysis

We categorized the data according to both utility measure and treatment modality (HD, PD, and RTx). Per category, we assessed the number of studies, patient groups, and patients. We analyzed the data quantitatively for categories comprising at least three patient groups for which a mean utility was reported. If the standard deviation (SD) was not reported, we imputed the mean SD of the category. To be able to assess differences in patient characteristics, we also intended to summarize patient and clinical characteristics. As only age and sex were reported in most studies, we had to restrict

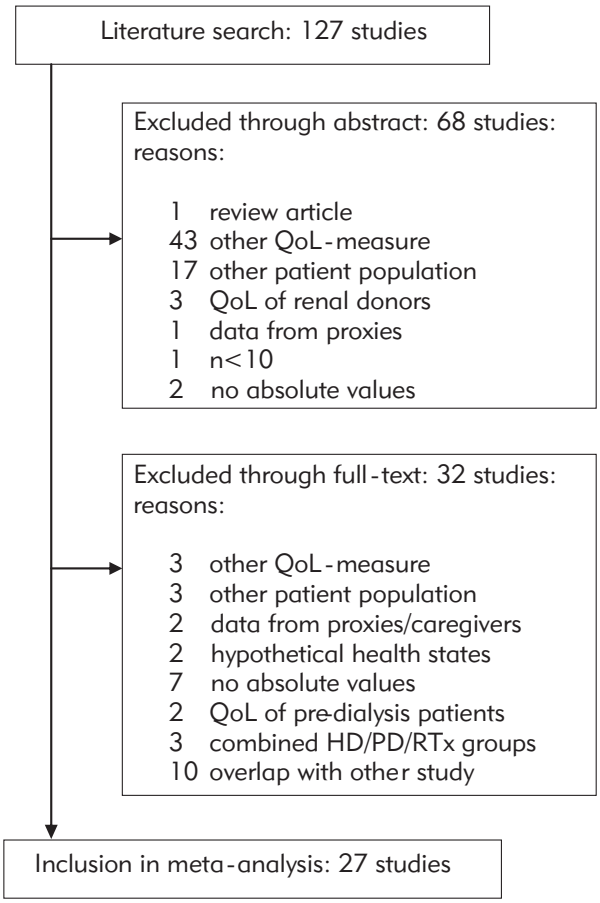
our analyses to these variables; those studies not reporting age and sex were left out of the calculation of mean age and sex. For studies reporting only the mean but not a SD, the mean SD from the other studies was imputed. Quantitative analyses of the variables utility, age, and sex were thus performed. We tested for between-study homogeneity of the variables within each category, using the Q-statistic to provide descriptive information of between-study variation.[95] Because the tests for homogeneity have a low power, the acceptance of the null-hypothesis of homogeneity provides no firm evidence of the absence of between-study variation.[95] Therefore, we used random-effects models to calculate pooled weighted means and 95% confidence intervals (CIs) for all variables, also per category defined by utility measure and treatment modality. Random-effects models weigh the outcomes of the study according to the within-study as well as the between-study variance.[95] In order to perform the analyses in the SAS 8.02 statistical program (SAS Institute Inc., Cary, NC, USA), we transformed the sex variable (proportion male) onto a logit-scale, assuming linearity of the logit. We tested for statistically significant differences between HD, PD, and RTx groups, using Student's t-tests. In addition, we compared mean age and sex among the treatment groups.

RESULTS

Our search identified 127 studies, of which we excluded 68 on the basis of the abstract and 32 on the basis of the full text. Reasons for exclusion are depicted in Figure 1. Exclusion of these studies ensured included studies to be of good quality. The remaining 27 studies that we included in our meta-analysis were of at least level 2b evidence according to the Oxford Center for Evidence-Based Medicine classification.[98] Quality of life was assessed with a single measure in most studies: three studies used a VAS,[116,154,164] eight studies the TTO,[151,156,165-170] one study the SG,[171] and nine studies the EQ-5D.[121,152,153,157,172-176] In addition, there were six studies that used several utility measures: one used a VAS, the TTO, and SG;[177] two used the TTO, SG, and EQ-5D;[109,155] one used a VAS and the TTO;[150] one used the TTO and SG;[178] and one used the TTO and HUI3.[179] Tables 1-5 show, per category defined by utility measure and treatment modality, the patient groups (sample size, mean age, proportion males, and mean and SD of utilities) that were included from these studies.

For several categories, quantitative analyses were not performed. First of all, the groups in the VAS/HD category (Table 1) were reported in four articles, of which one article

FIGURE 1. Flow chart literature search



Flow chart depicting the literature search, number and reason of excluded articles and number of included articles. HD = hemodialysis, n= sample size, PD = peritoneal dialysis, QoL = quality of life, RTx = renal transplantation

scaled VAS from worst possible to best possible health, one from death to perfect health, one from lowest to highest quality of life, and one did not report the anchors. As scaling varied so much, meta-analysis was considered not to be meaningful in this category. The HD group for which VAS was scaled from worst to best possible health was added to the analysis of the EQ-VAS values. Furthermore, there were not enough groups to calculate means for the categories VAS/PD, VAS/RTx, SG/PD, SG/RTx, and EQ-VAS/RTx. Lastly, there was only one patient group for which a HUI value was reported (Table 5). Thus, meta-analyses were performed for TTO utilities (HD, PD, and RTx patients), SG utilities (HD patients), EQ-5Dindex utilities (HD, PD and RTx patients),

and EQ-VAS utilities (HD and PD patients). Mean age and sex were also computed for these categories, except for the TTO/RTx category, because not enough data were available. Tests for homogeneity were statistically significant for the utility, age, and sex variables in most categories, indicating the presence of between-study heterogeneity. Exceptions were VAS value in the EQ-5D/HD category; age, index value, and VAS value in the EQ-5D/PD category; age in the TTO/PD category; and TTO value in the TTO/RTx category.

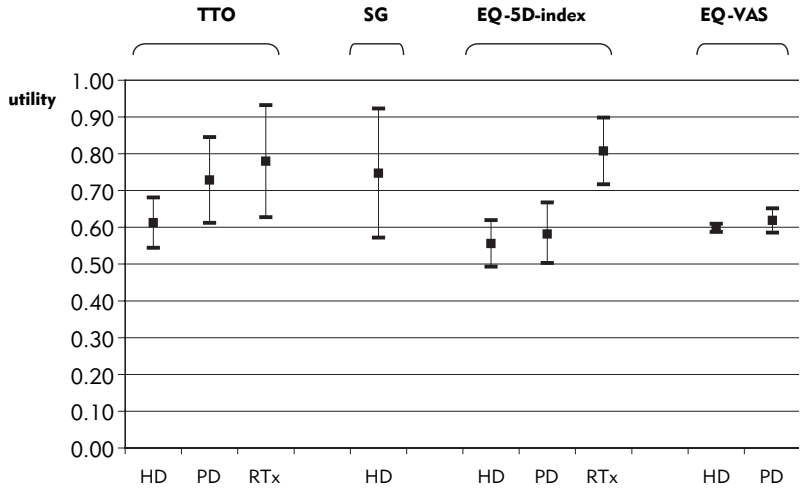
TABLE 1. Mean age, proportion of males, and utilities (mean, SD): VAS articles

Author	Publication year	n	Age (years)	Proportion male	VAS (mean)	VAS (SD)
HD						
Churchill, et al.[150]	1987	38	NA	NA	0.77	NA
Churchill, et al.[150]	1987	36	NA	NA	0.75	NA
Hays, et al.*[116]	1994	165	53	0.48	0.59	0.20
Hornberger, et al.[177]	1992	58	53	0.59	0.69	0.15
Wolcott, et al.*[154]	1988	33	47.4	0.70	0.73	NA
PD						
Churchill, et al.[150]	1987	24	NA	NA	0.79	NA
Wolcott, et al.[154]	1988	33	46.2	0.70	0.86	NA
RTx						
Churchill, et al.[150]	1987	73	NA	NA	0.86	NA
Forsberg et al.#[164]	1999	32	47	0.84	0.80†	NA

*Hays 1994 and Wolcott 1988: both were conducted in California, there is no information to assess whether or not some patients were included in both studies.
#Forsberg: we chose to report the global QoL VAS (i.s.o. the global health VAS), which is more comparable to the VAS used in the other study in transplant patients (Churchill 1987: VAS of lowest vs. highest quality).
†Median.
No meta-analyses were performed because HD-studies were too heterogeneous with respect to anchoring of the VAS and there were too few PD and RTx groups.
HD = hemodialysis, n = sample size, NA = not available, PD = peritoneal dialysis, RTx = renal transplantation, SD = standard deviation, VAS = visual analogue scale

Random-effects-model means and 95% CIs for utilities are shown in Tables 2-4 and Figure 2. In addition, P-values of the treatment modality comparisons are shown in Figure 2. Quality of life was most extensively studied in HD patients, in comparison to the other treatment groups. The mean utilities of dialysis patients were statistically significantly lower than the mean utility of RTx patients, when comparing EQ-5D-index values (HD 0.56, 95% CI 0.49-0.62; PD 0.58, 95% CI 0.50-0.67; RTx 0.81, 95% CI 0.72-0.90). The mean TTO values of HD, PD, and RTx patients were not statistically

FIGURE 2. Random-effects-model means (95% confidence intervals (CIs)) of utilities



P-values	TTO	SG	EQ-5D-index	EQ-VAS
HD vs. PD	0.087	NA	0.631	0.230
HD vs. RTx	0.051	NA	0.001	NA
PD vs. RTx	0.567	NA	0.010	NA

Random-effects-model means (black squares) and 95% confidence intervals (whiskers) of utilities per utility measure category, for hemodialysis (HD), peritoneal dialysis (PD) and renal transplant (RTx) patients.
EQ-5D = EuroQol-5D, NA = not available, SG = standard gamble, TTO = time trade-off, VAS = visual analogue scale

TABLE 2. Mean age, proportion of males, and utilities (mean, SD): TTO articles

Author	Publication year	n	Age (years)	Proportion male	TTO† (mean)	TTO (SD)
HD						
Bass, et al.[156]	2004	109	NA	0.40	0.69	0.53
Canadian EPO Study Group[165]	1990	40	48	0.63	0.42	NA
Canadian EPO Study Group[165]	1990	40	44	0.48	0.52	NA
Canadian EPO Study Group[165]	1990	38	43	0.68	0.49	NA
Churchill, et al.[166]	1991	47	60	0.68	0.44	0.28
de Wit, et al.[155]	2002	69	60	0.52	0.89	0.17
Harris, et al.[167]	1991	30	NA	0.60	0.49	0.33
Heidenheim, et al.*[179]	2003	15	48.8	0.64	0.70	0.27
Hornberger, et al.[177]	1992	58	53	0.59	0.71	0.23

Kontodimopoulos, et al.[178]	2006	504	57.1	0.61	0.73	0.32
Molzahn, et al.#[151]	1997	52	48.2	0.66	0.39	0.32
Molzahn, et al.#[151]	1997	37	48.9	0.66	0.61	0.29
Sesso, et al.[169]	1996	47	44.1	0.79	0.65	0.27
Sesso, et al.[169]	1996	54	41.6	0.46	0.65	0.27
Sesso, et al.[170]	1997	53	46	0.60	0.67	0.31
Sesso, et al.[170]	1997	60	51.1	0.63	0.71	0.31
REM mean			49.7	0.61	0.61	
(95% CI)			(46.5 – 52.9)	(0.55 – 0.66)	(0.54 – 0.68)	
PD						
Bass, et al.[156]	2004	57	NA	0.33	0.74	0.50
Bass, et al.[156]	2004	22	NA	0.32	0.70	0.55
Churchill, et al.[150]	1987	31	NA	NA	0.56	0.29
de Wit, et al.[109]	2001	59	56	0.69	0.86	0.23
de Wit, et al.[109]	2001	37	55	0.49	0.93	0.14
Molzahn, et al.#[151]	1997	30	47.9	0.66	0.53	0.28
REM mean			53.1	0.50	0.73	
(95% CI)			(46.2 – 60.0)	(0.39 – 0.61)	(0.61 – 0.85)	
RTx						
Churchill, et al.[150]	1987	79	NA	NA	0.84	0.24
Laupacis, et al.[168]	1996	132	NA	NA	0.74	NA
Molzahn, et al.#[151]	1997	96	42.08	0.66	0.76	0.25
REM mean					0.78	
(95% CI)					(0.63 – 0.93)	

† 40% of utility-means (from 4 of the 14 studies) were derived by iterative elicitation (the other values were derived by a single question or did not report elicitation method).
*Heidenheim 2003: demographics were reported in another paper: Lindsay et al 2003.[186]
#Molzahn 1997: proportion male was only available for total sample of RRT patients, not per treatment modality group.
CI = confidence interval, HD = hemodialysis, n = sample size, NA = not available, PD = peritoneal dialysis, REM mean = Random-effects-model mean, RTx = renal transplantation, SD = standard deviation, TTO = time trade-off

significantly different, although the utility of HD patients tended to be lower than the value of PD and RTx patients. Random-effects-model means for HD and PD patients were compared for TTO, EQ-5D-index, and EQ-VAS studies. For both EQ-5D-index and EQ-VAS values, the means of HD and PD patients were similar. For the TTO studies, mean quality of life was not significantly different, although it tended to be higher among PD patients (0.73, 95% CI 0.61-0.85) than among HD patients (0.61, 95% CI 0.54-0.68).

TABLE 3. Mean age, proportion of males, and utilities (mean, SD): SG articles

Author	Publication year	n	Age (year)	Proportion male	SG* (mean)	SG (SD)
HD						
de Wit, et al.[155]	2002	69	60	0.52	0.86	0.19
Hornberger, et al.[177]	1992	58	53	0.59	0.62	NA
Kontodimopoulos, et al.[178]	2006	504	57.1	0.61	0.91	0.13
McFarlane, et al.[171]	2003	19	50.1	0.68	0.77	0.23
McFarlane, et al.[171]	2003	24	47.2	0.75	0.53	0.35
REM mean			53.6	0.63	0.75	
(95% CI)			(47.9 – 59.3)	(0.53 – 0.73)	(0.57 – 0.92)	
PD						
de Wit, et al.[109]	2001	59	56	0.69	0.81	0.24
de Wit, et al.[109]	2001	37	55	0.49	0.74	0.24

* 86% of utility-means (from 4 of the 5 studies) were derived by iterative elicitation (the value from the other study was derived by a single question).
No meta-analysis was performed for PD patients, because there were too few PD groups.
CI = confidence interval, HD = hemodialysis, n = sample size, NA = not available, PD = peritoneal dialysis, REM mean = Random-effects-model mean, SD = standard deviation, SG = standard gamble

TABLE 4. Mean age, proportion of males, and utilities (mean, SD): EQ-5D articles

Author	Publication year	n	Age (year)	Proportion male	EQ-5D-index (mean)	EQ-5D-index (SD)	EQ-VAS (mean)	EQ-VAS (SD)
HD								
de Wit, et al.[155]	2002	69	60	0.52	NA	NA	0.60	0.18
Lee, et al.*[153]	2005	99	63.0	0.61	0.44	0.32	NA	NA
Manns, et al.[121]	2003	151	62.2	0.58	0.62	NA	0.60	NA
Roderick, et al.*[176]	2005	269	56.6	0.61	0.60	0.28	0.60	0.18
Roderick, et al.*[176]	2005	314	62.5	0.63	0.60	0.31	0.59	0.20
Sennfalt, et al.#[152]	2002	27	62.2	NA	0.44	0.08	NA	NA
Wasserfallen, et al.[157]	2004	455	64	0.63	0.62	0.30	0.60	0.18
REM mean			60.4¶	0.58¶	0.56		0.60¶	
(95% CI)			(57.7 – 63.0)	(0.53 – 0.63)	(0.49 – 0.62)		(0.59 – 0.61)	
PD								
de Wit, et al.[109]	2001	59	56	0.69	NA	NA	0.61	0.20

de Wit, et al.[109]	2001	37	55	0.49	NA	NA	0.61	0.20
Lee, et al.[153]	2005	74	58.7	0.51	0.53	0.34	NA	NA
Manns, et al.[121]	2003	41	56.1	0.49	0.56	NA	0.65	NA
Sennfalt, et al.#[152]	2002	27	62.2	NA	0.65	0.15	NA	NA
Wasserfallen, et al.[157]	2004	50	60	0.55	0.58	0.32	0.61	0.19
REM mean			57.9	0.55	0.58		0.62	
(95% CI)			(54.4 – 61.4)	(0.49 – 0.61)	(0.50 – 0.67)		(0.59 – 0.65)	
RTx								
Cleemput, et al.†[174]	2003	29	52.6	0.65	0.73**	NA	NA	NA
Greiner et al.‡[172]	2001	58	48	0.55	0.86	NA	NA	NA
Lee, et al.[153]	2005	209	52.8	0.60	0.71	0.27	NA	NA
Moons, et al.[175]	2003	350	52	0.60	0.80**	NA	0.75**	NA
Polsky, et al.§[173]	2001	65	50	0.65	NA	NA	0.82	0.21
Polsky, et al.§[173]	2001	70	45	0.53	NA	NA	0.84	0.23
Sennfalt, et al.#[152]	2002	27	61.7	NA	0.86	0.13		
REM mean			51.4	0.60	0.81			
(95% CI)			(48.5 – 54.3)	(0.54 – 0.64)	(0.72 – 0.90)			

* Lee 2005 & Roderick 2005: included patients from the Cardiff University Hospital, there is no information to assess whether or not some patients were included in both studies.
# Sennfalt 2002: it is not clear whether values are EQ-5D-index or EQ-VAS values, and if they are index-values, the algorithm used is not stated (Dolan paper was not cited).
¶ Includes Hays et al. 1994.
† Cleemput 2003: there is no overlap with the study by Moons et al (information obtained from author). EQ-5D-index-value is from the 12-month time-point. Demographics were reported for the total sample of patients on the transplant wait list at baseline.
** Medians, not included in the meta-analyses.
‡ Greiner 2001: EQ-5D-index-value is from the 12-month time-point. Demographics were reported for baseline sample only, information on age was not reported in the paper, but was obtained through the author.
§ Polsky 2001: EQ-VAS-values are from the 12-month time-point, demographics were reported for the baseline sample only, however.
No meta-analysis was performed for the EQ-VAS value of RTx-patients, because there were too few RTx groups.
CI = confidence interval, EQ-5D = EuroQol-5D, HD = hemodialysis, n = sample size, NA = not available, PD = peritoneal dialysis, REM mean = Random-effects-model mean, RTx = renal transplantation, SD = standard deviation

TABLE 5. Mean age, proportion of males, and utilities (mean, SD): HUI articles

Author	Publication year	n	Age (year)	Proportion male	HUI (mean)	HUI (SD)
HD						
Heidenheim et al.[179]	2003	15	48.8	0.64	0.79	0.18

HD = hemodialysis, HUI = health utilities index, n = sample size, SD = standard deviation

Means for age and sex computed using random-effects models are also shown in Table 2-4. For EQ-5D studies, mean age was computed for all three treatment modalities and RTx patients were significantly younger (51.4 years, 95% CI 48.5-54.3) than HD (60.4 years, 95% CI 57.7-63.0) or PD (57.9 years, 95% CI 54.4-61.4) patients. For HD and PD patients, mean age was also comparable in TTO studies. Sex was also comparable among treatment groups, with the proportion of males varying from 0.50 (95% CI 0.39-0.61) in the TTO/PD category to 0.63 (95% CI 0.53-0.73) in the SG/HD category.

DISCUSSION

From this systematic review and meta-analysis, we conclude that the comparisons of utilities of the alternative forms of RRT resulted in mostly non-significant differences, although quality of life tended to be highest for RTx and lowest for HD patients. For the EQ-5D utilities, RTx patients did have significantly higher quality of life than dialysis patients. There was no statistically significant difference in utilities between HD and PD patients, although when measured with the TTO, PD patients tended to have a higher quality of life. Among the alternative forms of RRT, utilities were most frequently studied in HD patients.

A superior quality of life for RTx compared to dialysis patients has been described previously in meta-analyses. Cameron and colleagues[34] reported less emotional distress and more psychological well-being for RTx patients compared to dialysis patients. We found, in a meta-regression analysis of SF-36 scores among RRT patients, that dialysis patients had a lower quality of life than RTx patients, but that this difference was in part explained by differences in age and prevalence of diabetes.[158] In the present meta-analysis, we also found that RTx patients were younger, which might partly explain our findings. In studies that directly compared utilities of RTx and dialysis patients, however, RTx patients were found to have a higher quality of life, even when correcting for covariates known to influence quality of life such as age, sex, marital status, renal diagnosis, and morbidity.[151,153]

The EQ-5D-index values of the US general population were recently reported by Hanmer and colleagues.[180] Compared to these published values, dialysis patients have a markedly lower quality of life, whereas RTx patients have a comparable quality of life

(i.e., general population values for females and males: 0.79 and 0.82 in the age group of 50-59 years; and 0.75 and 0.79 in the age group of 60-69 years).

In our study, we found few statistically significant differences between treatment groups. The lack of statistically significant differences might be explained by the wide CIs. These wide CIs, calculated with random-effects models, reflect the incorporation of within-study as well as between-study variances. Variation between the studies existed, for example, in elicitation techniques, and patient populations. Heterogeneity in patient populations is due to numerous reasons: several demographic and clinical variables are known to influence of quality of life. One might argue that studies showed too much variation to perform meta-analyses. With our analyses, however, we accounted for variation in different ways, depending on the type of variation. With respect to differences in elicitation techniques of the TTO and SG, studies showed that results are similar using an interviewer-based technique or an article-based technique.[181,182] Therefore, combining results from studies using different elicitation techniques seems justified. As for variation in patient populations: because the aim of our study was to obtain summary estimates for adjustment of quality of life in economic evaluations that should be generalizable to the entire population, we feel that summarizing utility estimates over all patients included in our study is appropriate. This is in line with what has been suggested by Laird and Mosteller,[95] which is if the purpose of the meta-analysis is to study a broad issue, then summarizing the information about that variation, using a random-effects model, is an important contribution.

Several limitations to our study deserve mention. First, the reliability of meta-analyses always depends on the completeness of published studies and may therefore be subject to publication bias. As the studies included in our meta-analysis were mostly noncomparative, this bias should be relatively small. Second, the number of studies per category was small for most categories, especially for PD and RTx patients.

In addition, we would have wanted to make a recommendation as to which utility measure to choose for adjustment in economic analyses. Nevertheless, the number of studies that used more than one measurement method was too limited. De Wit and colleagues[183] suggest that from the societal perspective, general public values should be used because these represent aggregate values of people without specific interest in particular health states. The Panel on Cost-Effectiveness in Health and Medicine also recommended the use of methods that allow patients' values of health profiles to be

converted to utilities using a tariff based on utilities of the general public for the health profiles,[184] such as the EQ-5D index and the HUI. In our meta-analysis, we found that EQ-5D-index values were available in the literature for HD, PD, and RTx patients.

Although it is generally accepted that quality of life is an important parameter in economic analysis, the operationalization of the concept is still under debate. As has already been described in the 80s by Mulley,[185] there are many pitfalls in quality-of-life assessment. Mulley argues that defining 'health' is difficult and can be influenced by a large number of variables and that different disciplines - economy or psychology - hold different views of how to establish health outcomes. Most importantly, Mulley discusses how utility measurement has shown incongruities. Not only do the results vary by utility measure, but also the timing of measurement is important because utility changes over the course of life, and shows a response shift during disease progression in chronic diseases. Therefore, utility assessment should be tailored to the purpose of the measurement. For economic analyses, the goal is to maximize quality-adjusted life years and therefore, to establish a consensus view of the preference for the various health outcomes. Thus, aggregating across ratings from different populations seems justified.

In conclusion, our meta-analysis of utilities of patients on RRT shows that RTx patients tended to have a higher quality of life compared to dialysis patients, but are also younger. There was no statistically significant difference between HD and PD patients' mean utilities. The results from this meta-analysis can be used to adjust life expectancy for quality of life in cost-effectiveness studies of programs for ESRD patients.

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4

Decision analytic studies of interventions in renal replacement therapy: patients and donors

4.1

Living renal donors: optimizing the imaging strategy - decision- and cost-effectiveness analysis.

ABSTRACT

Objective: To determine the most cost-effective strategy for preoperative imaging performed in potential living renal donors.

Methods: In a decision-analytic model, the societal cost effectiveness of digital subtraction angiography (DSA), gadolinium-enhanced magnetic resonance (MR) angiography, contrast material- enhanced spiral computed tomographic (CT) angiography, and combinations of these imaging techniques was evaluated. Outcome measures included lifetime cost, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios. A base-case analysis was performed with a 40-year-old female donor and a 40-year-old female recipient.

Results: For the donor, MR angiography (24.05 QALYs and $9,000) dominated all strategies except for MR angiography with CT angiography, which had an incremental ratio of $245,000 per QALY. For the recipient, DSA and DSA with MR angiography yielded similar results (10.46 QALYs and $179,000) and dominated all other strategies. When results for donor and recipient were combined, DSA dominated all other strategies (34.51 QALYs and $188,000). If DSA was associated with a 99% specificity or less for detection of renal disease, MR angiography with CT angiography was superior (34.47 QALYs and $190,000).

Conclusion: For preoperative imaging in a potential renal donor, DSA is the most cost-effective strategy if it has a specificity greater than 99% for detection of renal disease; otherwise, MR angiography with CT angiography is the most cost-effective strategy.

INTRODUCTION

Before a potential living renal donor donates a kidney, he or she undergoes an extensive work-up that includes an interview, physical examination, laboratory tests, and ultrasonography (US). A detailed radiological examination of the kidneys concludes this work-up.[187-192] The purpose of the radiological examination is to determine the number, location, and length of the renal arteries and to detect anomalies or diseases of the renal vasculature. In addition, it is used to screen for renal disease that may have escaped detection during an earlier examination.[187,191-194] The transplantation team uses this information to decide whether or not it is safe for the potential donor to undergo removal of one kidney. Furthermore, the team can decide which kidney to use, on the basis of findings in regard to the renal vasculature and on the basis of the presence of abnormalities.[195-198]

At present, imaging at Erasmus MC Rotterdam, the Netherlands, includes intra-arterial digital subtraction angiography (DSA) for the examination of the renal arteries, and immediately after, urography is performed for screening the urinary system. DSA with urography is known to be an accurate method, but it requires catheterization, the use of iodine-containing contrast material, and exposure of the patient to ionizing radiation.[199,200] Furthermore, DSA is an expensive technique,[201] and with the current strategy, only limited information about the venous anatomy is obtained. This information could be important, especially if nephrectomy is performed laparoscopically.

To overcome the drawbacks of the presently used imaging, other techniques have been proposed to replace it. Researchers in a number of studies have assessed the accuracy and feasibility of alternative techniques, such as gadolinium-enhanced magnetic resonance (MR) angiography[194,202-205] or computed tomographic (CT) angiography.[206-213] These techniques can depict both the arterial and venous vasculature and the collecting system and parenchyma. MR angiography accurately depicts the anatomy of the vasculature, but mild forms of fibromuscular dysplasia may be missed.[194] CT angiography has capabilities similar to those of MR angiography, but CT angiography has a higher resolution than does MR angiography and is, furthermore, technically more robust. The disadvantages of CT angiography, however, are that the patient is exposed to ionizing radiation and that iodinated contrast material is needed. Nonetheless, both MR angiography and CT angiography are less expensive than DSA.[205]

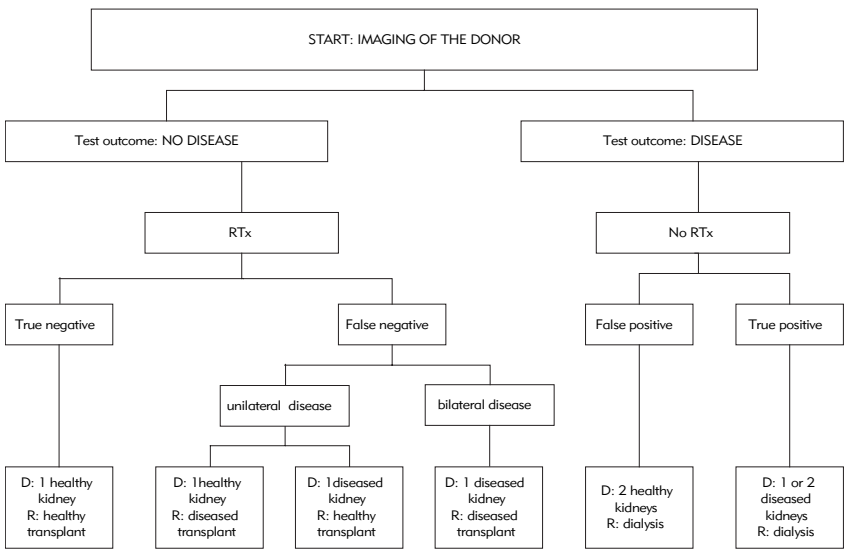
To our knowledge, only two studies were conducted in which CT angiography and gadolinium-enhanced MR angiography were compared.[214,215] In these studies, however, the techniques were compared in regard to the depiction of only arterial and venous anatomy. Furthermore, the currently used imaging strategies vary among centers at which transplantation is performed.[189] This variation in the use of imaging strategies indicates the prevailing uncertainty as to what the optimal strategy is and, thus, emphasizes the need for further investigation of those that are available. Thus, the purpose of our study was to determine the most cost-effective strategy for preoperative imaging performed in potential living renal donors.

METHODS

Model

A decision model comparing various strategies used for screening potential renal donors was developed from the societal perspective to evaluate the morbidity, mortality, and costs to both renal donors and renal recipients.[31] The strategies we considered (Table 1) were DSA with urography (i.e., the current strategy), MR angiography, spiral CT angiography, and combinations of these imaging techniques.

FIGURE 1. Schematic representation of the structure of the model



D = donor, R = recipient, RTx = renal transplantation

TABLE 1. Abbreviations of strategies

DSA*	Current imaging strategy, DSA, with urography, was performed
MR angiography†	Performed with enhancement with gadolinium-based contrast material
Spiral CT angiography†	Performed with contrast enhancement
DSA with MR angiography‡	Current imaging strategy, performed first, and MR angiography were performed during one visit
MR angiography, DSA†,‡	If results of MR angiography were inconclusive, the current imaging strategy was performed during a second visit
MR angiography with CT angiography§	MR angiography, performed first, and CT angiography were performed during one visit
No test, always transplantation||	No test, and transplantation was always performed
No test, no transplantation||	No test, and transplantation was not performed

* Standard of reference for detection of renal disease; we assumed DSA does not fail technically.
† If the donor has any contraindication to MR angiography (e.g. claustrophobia, metal implants), or if MR angiography or CT angiography failed technically, the donor underwent the current imaging strategy.
‡ If both MR angiography and DSA are performed but MR angiography failed technically, results of only DSA were considered.
§ If MR angiography was contraindicated, only CT angiography was performed and when the latter failed technically, DSA was performed. When both MR angiography and CT angiography were performed, but one failed technically, we assumed that the transplantation team relied on the results of the successful imaging strategy. If both tests failed, DSA was performed.
|| Reference strategy.

To compare these imaging strategies, we modeled the prevalence of vascular anomalies and kidney disease, the probability of detection of anomalies and disease, and long-term outcomes. We (Y.S.L., K.V., M.G.M.H.) developed a Markov process model to estimate the quality-adjusted life expectancy and lifetime cost for both renal donors and recipients. Figure 1 shows a schematic representation of the decision model. The model starts with imaging performed in the donor, when the donor has already undergone the first phases of the work-up, which included the interview, physical examination, laboratory tests, and US.

A diagnosis of renal disease was determined when an abnormality in the renovascular system, the kidney, or the collecting system and distal urinary tract was seen on the image. Renovascular anomalies and abnormalities that do not have a major effect on the prognosis of the patient, such as unilateral cysts, calculi, and parenchymatous lesions, were excluded from our determination of the diagnosis of renal disease. If imaging findings suggested renal disease, no transplantation was performed. However,

because of inaccuracy, renal disease may not have been present, which constituted a missed opportunity. If imaging findings did not reveal renal disease, transplantation was performed, with its associated morbidity and mortality for both donor and recipient. If unilateral renal disease was not detected during imaging performed in the donor, the donor may have one diseased kidney after transplantation, or the recipient may receive a diseased transplant. In the case of bilateral renal disease, both the donor and the recipient have a diseased kidney after transplantation.

With the model, we considered that the presence of renovascular anomalies (i.e., multiple renal arteries or veins, early arterial branching) influences the choice of which kidney to transplant and increases the duration of the surgery, which results in higher costs.

Furthermore, we also considered that a donor with renal disease diagnosed during the radiological examination will be treated and may need dialysis later in life. A donor who has one diseased kidney after transplantation and a recipient who receives a diseased kidney will develop clinical renal disease at a later point in life and may require dialysis. A potential recipient whose donor received - correctly or incorrectly - a diagnosis of renal disease will continue to receive treatment with dialysis. A recipient, whose transplant fails, returns to dialysis.

Data sources and assumptions

Background information

A systematic review of the literature pertaining to living renal donor transplantation was performed. The search strategy we used to retrieve the literature-based information was as follows: living donors AND kidney NOT cadaver NOT developing countries NOT DNA NOT Histocompatibility testing NOT reoperation NOT Kidney/*histology NOT Kidney Calculi/*etiology NOT liver NOT drug therapy NOT pancreas transplantation NOT antibodies. Additional data were obtained from our own clinical data and from the Dutch statistics. We (Y.S.L., M.C.J.M.K.) performed a cost analysis for the local setting. Tables 2-4 present the parameters of the model, with the values used in the base-case analysis and the ranges over which these values were varied in the sensitivity analyses. (More detail on the computation of the test characteristics, probabilities, and costs is reported in the appendix.)

Tests and test characteristics of the various strategies

Published reports were reviewed by the first author (Y.S.L.) concerning DSA performed with a low-osmolar contrast agent administered through intra-arterial injection into the femoral artery, MR angiography performed with an intravenously administered gadolinium-based contrast agent, or CT angiography performed with an intravenously administered low-osmolar contrast agent. Studies of researchers were included in this review if they reported sensitivity and specificity for renal disease or renal anomalies.

TABLE 2. Estimates for model variables: characteristics of imaging examinations

Variable	Baseline value	Range	Source
DSA			
Se for renal disease (%)	100	82-100	*
Sp for renal disease (%)	100	95-100	*
Se for renal anomalies (%)	82	75-91	200,201
Complications (%)	1.7	0.5-3	221,222
Mortality (%)	0.033	0.029-0.162	221,222
Technical failures (%)	0	NA	EO
MR angiography			
Se for renal disease (%)	93	90-100	217
Sp for renal disease (%)	90	88-100	217
Se for renal anomalies (%)	82	71-100	203,205
Complications (%)	0	0-0.031	†
Mortality (%)	0	0-0.0009	†
Not suitable for MR angiography (%)	6.7	3-10	‡
Technical failures (%)	2.5	1-4	204,205
CT angiography			
Se for renal disease (%)	95	90-100	208,216
Sp for renal disease (%)	98	97-100	208,216
Se for renal anomalies (%)	83	65-99	209,210,212,213
Complications (%)	0.031	0.002-0.062	223
Mortality (%)	0.0009	0.0003-0.0026	223
Technical failures (%)	1.9	0.5-3.5	207
DSA with MR angiography			
Se for renal disease (%)	100	82-100	§
Sp for renal disease (%)	100	95-100	§
Se for renal anomalies (%)	82	82-95	‖
Complications (%)	1.7	0.5-3	¶

Mortality (%)	0.033	0.029-0.162	**
Not suitable for MR angiography (%)	6.7	3-10	‡
Technical failures (%)	2.5	1-4	204,205
MR angiography, DSA if MR angiography results inconclusive			
Se of MR angiography for renal disease (%)	95	90-99	††
Sp of MR angiography for renal disease (%)	95	90-99	††
Se of MR angiography for renal anomalies (%)	82	82-95	‡‡
Complications when only MR angiography is performed (%)	0	0-0.031	†
Mortality when only MR angiography is performed (%)	0	0-0.0009	†
Not suitable for MR angiography (%)	6.7	3-10	‡
Technical failures of MR angiography (%)	2.5	1-4	204,205
Inconclusive results of MR angiography (%)	30	10-50	§§
Se of DSA with MR angiography for renal disease (%)	100	82-100	||||
Sp of DSA with MR angiography for renal disease (%)	100	95-100	||||
Se of DSA with MR angiography for renal anomalies (%)	82	82-95	||||
Complications (%)	1.7	0.5-3	¶
Mortality (%)	0.033	0.029-0.162	**
MR angiography with CT angiography¶¶			
Se for renal disease (%)	100***	NA†††	208,216,217
Sp for renal disease (%)	100***	NA†††	208,216,217
Se for renal anomalies (%)‡‡‡	83	65-99	209,210,212,213
Complications (%)	0.031	0.002-0.062	¶
Mortality (%)	0.0009	0.0003-0.0026	**
Not suitable for MR angiography (%)	6.7	3-10	‡

* DSA was assumed to be the reference standard.
† It was assumed that MR angiography did not involve any risks.
‡ Paul Nederkoorn, MD, written communication, August 2000.
§ The sensitivity and specificity of DSA were used.
|| The sensitivity of for the detection of anomalies with MR angiography was used; however since MR angiography can depict venous anomalies, the sensitivity for detection of anomalies with this strategy was expected to be higher than that of DSA. Therefore a sensitivity analysis was performed using the baseline estimate as the lower value and an estimated value of 95% as the upper value.
¶ Complication rates of the combination strategies were computed by summing the complication rates of each strategy.
** Mortality rates of the combination strategies were computed as follows: mortality of first imaging examination performed + (1 - mortality of first imaging examination performed) * mortality of the second imaging examination performed.
†† No data were available. Estimates were made determined on the basis of the assumption that these values were higher than those of the characteristics of MR angiography.
‡‡ The sensitivity of MR angiography was used.
§§ Because of inconclusive results of MR angiography, DSA was performed.
|||| The values of the characteristics (baseline and sensitivity analysis estimates) of DSA with MR angiography were used.
¶¶ Data are those that apply when both MR angiography and CT angiography were technically successful.
*** Technically, these figures were between 99 and 100%, but when rounded, they were 100%.
††† Values of characteristics of MR angiography and CT angiography were varied separately. Because the same variables were used with MR angiography with CT angiography, the values of the characteristics of this strategy were also varied over a plausible range.
‡‡‡ The sensitivity for depiction of anomalies of CT angiography was used.
EO = expert opinion, NA = not available, Se = sensitivity, Sp = specificity

We considered the currently used strategy (i.e., DSA with urography) as the reference standard for detection of renal disease and surgery as the reference standard for detection of renovascular anomalies. Even though the sensitivity and specificity of DSA for detection of renal disease are probably not 100%, DSA is at present the best possible reference standard since disease cannot be detected during surgery. For detection of anomalies, we considered surgery as the reference standard. A disadvantage of choosing surgery as the reference standard is, however, that only one of the two kidneys is seen during surgery, which is most likely the one with the least complicated anatomy.

TABLE 3. Estimates for model variables: prevalences and risks

Variable	Baseline value	Range	Source
PREVALENCES AMONG DONORS			
Renal anomalies (%)*	44.7	41.5-49.4	200,210,220
Unilateral anomalies (% of all anomalies)	75	70-79	218-220
Venous anomalies (% of all anomalies)	25	15-35	210
Renal disease (%)	6.3	3.2-10.6	200,210,220, PS
Unilateral disease (% of all diseases)	80	70-90	220
DONOR RISKS			
Operation			
Morbidity (% of complications)	14	5-20	224
Mortality (%)	0.03	0.00-0.05	224,244,245
Long-term			
Relative risk of mortality compared with that of general population	1	0.39-1.5	226
Dialysis-free survival if renal disease was present	15	10-20	†
Proportion of donors developing ESRD in whom disease was not detected (%)	25	0-100	‡
Proportion of donors developing ESRD in whom disease was detected (%)	5.3	0-10	EO
RECIPIENT RISKS			
Operation			
Morbidity (% of complications)	33	10-50	EO
Mortality (%)	1	0.5-3	EO
Long-term			
Relative risk of mortality of RTx recipient compared with that of general population			
1 year after transplantation	9.7	7.5-35.5	29,227-229

3 years after transplantation	3.6	NA	29,227-229
5 years after transplantation	5.0	4.8-8.7	29,227-229
Relative risk of mortality of patient receiving CAPD compared with that of general population	14	11-16	20
Relative risk of mortality of patient receiving HD compared with that of general population	21	18-24	20
Proportion of patients receiving CAPD among total of those receiving dialysis (%)	28	10-50	230
Graft failure rate after transplantation			
1 year	0.072	0.020-0.092	227-229,231,232
3 years	0.050	0.026-0.044	227-229,231,232
5 years	0.034	0.039-0.048	227-229,231,232

* Renal anomalies consist of multiple renal arteries, early arterial branching, and multiple renal veins.
† Dialysis-free survival for a donor was assumed to be 15 years.
‡ Since the probability that dialysis was needed in donors with undetected disease was unknown, it was assumed to be 25% and it was varied over a wide range.
CAPD = continuous ambulatory peritoneal dialysis, EO = expert opinion, ESRD = end-stage renal disease, HD = hemodialysis, NA = not available, PS = present study, RTx = renal transplantation

We (Y.S.L., M.G.M.H.) estimated the sensitivity and specificity for detecting renal disease and the sensitivity for detecting anomalies associated with gadolinium-enhanced MR angiography and contrast-enhanced spiral CT angiography on the basis of data from published studies.[203,205,216,217] The specificity for detection of anomalies was not used, because false-positive test results have no consequences since costs are incurred only if anomalies are present. Imaging characteristics are presented in Table 2.

Prevalence of anomalies and kidney disease

On the basis of data from large studies in regard to the preoperative examination of renal donors,[200,210,218-220] we (Y.S.L., M.G.M.H.) estimated the prevalence of renal anomalies and renal disease in potential living renal donors (Table 3).

Donor risks

We (Y.S.L., M.G.M.H.) estimated the morbidity and mortality associated with various strategies[221-223] and the morbidity associated with laparoscopic nephrectomy[224] on the basis of data from the literature. Since a reliable estimate for mortality associated with laparoscopic donor nephrectomy was not available, it was assumed to be the mortality associated with open nephrectomy.[191] Long-term survival among renal donors was estimated on the basis of Dutch mortality statistics,[225] since on the basis of data in the

literature, we determined that this is the same as or better than the survival of the general population.[226]

If, however, a renal donor has a diseased kidney after transplantation, and this diseased kidney has escaped detection during the diagnostic work-up, we assumed a 25% chance that the donor would need renal replacement therapy after 15 years. If a donor receives a diagnosis of renal disease during the work-up, the donor is treated for the disease. On the basis of our own clinical data, we estimated that 5% (one in 19) of these donors who receive a diagnosis of disease and are treated would require dialysis after 15 years because of untreatable or recurrent disease. The survival rate for a donor who requires dialysis after 15 years was assumed to be the same as that of the general population for the first 15 years and to be the same as that of patients receiving dialysis after this period. Data regarding donor risks are presented in Table 3.

Recipient risks

Morbidity associated with renal implantation was estimated on the basis of our own clinical data. We (Y.S.L., J.N.M.I.) estimated surgical mortality to be 1%. Relative risks of mortality for recipients of a renal transplant[29,227-229] and for patients receiving both CAPD and hemodialysis[20] compared with the mortality of the general Dutch population[225] were computed on the basis of data from the literature.[20,29,227-229] To determine a relative risk of mortality for dialysis, the relative risks of CAPD and hemodialysis were averaged according to the prevalences of both methods among patients receiving dialysis in the Netherlands.[230] We also computed transplant failure rates on the basis of data from the literature in regard to graft survival.[227-229,231,232] We assumed that recipients who received a diseased transplant had a survival rate that was the same as that of recipients of a non-diseased transplant for the first 10 years, and we assumed that they would need dialysis after this period. Table 3 includes the data on recipient risks.

Quality weights

Because renal donors are healthy individuals, their quality-of-life estimate was considered to be 1. However, for donors who need dialysis after 15 years, the estimate was assumed to be 1 for the first 15 years and the same as the estimate for patients receiving dialysis after this period. The quality-of-life estimates for transplant recipients and patients receiving dialysis were obtained from the literature (Table 4).[150,233] We assumed that the quality weight of a recipient who received a diseased transplant was the same

TABLE 4. Estimates for model variables: quality-of-life and cost estimates

Variable	Baseline value	Range	Source
QUALITY-OF-LIFE ESTIMATES			
Donor	1	0.9-1	*
RTx recipient†	0.84	0.84-0.94	150,233
CAPD patient†	0.56	0.56-0.79	150,233
HD patient†	0.43	0.43-0.63	150,233
COST ESTIMATES FOR YEAR 2000 ($)			
Cost of mortality	2,337	1,168-3,505	‡
Imaging tests			
Current work-up (DSA, with urography)	478	393-648	PS
MR angiography	509	362-656	PS
CT angiography	252	182-325	PS
Test complications§	681	340-1,021	PS
Transplantation			
Donor nephrectomy	6,628	6,131-7,126	PS
Extra costs per operation when anomalies were present and detected during imaging||	96	48-165	PS
Extra costs per operation when anomalies are present but not detected during imaging||	239	121-411	PS
Complications of donor nephrectomy¶	1,701	1,021-2,382	PS
Recipient implantation	6,962	6465-7460	PS
Cost of complications of recipient implantation**	3,402	1,701-5,104	PS
Costs per year of life			
Donor who has donated	91	62-162	††
Patient receiving CAPD	27,499	18,243-36,395	56,235
Patient receiving HD	43,866	30,329-57,556	235
Renal transplant recipient, first year after transplantation	4,173	1,492-6,029	235, EO
Renal transplant recipient, subsequent years after transplantation	3,112	1,398-5,935	235, EO

* Donors were assumed to be in perfect health.
† Quality estimates were obtained from the patient populations, using the time trade-off technique.
‡ It was assumed that mortality resulted in 2 days of hospitalization in the intensive care unit prior to death.
§ It was assumed that complications required 2 days of hospitalization.
|| Costs were computed by considering the prevalences of unilateral and bilateral disease.
¶ It was assumed that complications required 5 days of hospitalization.
** It was assumed that complications required 10 days of hospitalization.
†† It was assumed that donor check-up costs were similar to costs of a visit to an outpatient clinic of a university hospital.
CAPD =continuous ambulatory peritoneal dialysis, EO = expert opinion, HD = hemodialysis, PS = present study, RTx = renal transplantation

as the quality weight of a transplant recipient for the first 10 years and the same as the quality weight associated with dialysis after this period.

Costs

To compute costs of imaging and transplantation, the Dutch guidelines for computing costs in health care were used.[234] Costs were determined from the societal perspective and included both medical and non-medical costs (Table 4).

Direct medical costs included costs for personnel, materials, equipment, supporting departments, housing and overhead, and hospitalization and consultations. For the computations, we obtained data from the Departments of Radiology and Surgery and the Finance Department of our center. For the computation of equipment costs, we used the annuitization method, with a discount rate of 3%.[31] Costs for hospitalization and consultations were computed by using prices from the Dutch guidelines and data from our center.

Furthermore, we (Y.S.L., M.C.J.M.K.) computed direct non-medical costs of the imaging strategies and of surgery of both donor and recipient, which included travel expenses and time costs. On the basis of the Dutch guidelines, travel expenses were calculated as travel distance multiplied by a fixed cost per kilometer. Time costs were computed by using the estimated time required to undergo the imaging and the surgery and the average sex- and age-specific wage rates.[184] We obtained wage rates from the Central Bureau of Statistics, Voorburg/Heerlen, the Netherlands.

We assumed that annual direct medical costs for a donor after transplantation were the same as the costs of an outpatient visit.[234] Annual direct medical costs of receiving a renal transplant and yearly costs of CAPD and hemodialysis were computed on the basis of data from the literature.[56,235] For the annual direct non-medical costs, we computed travel expenses and time costs in the same manner as we computed these costs for the imaging and the surgery. All costs were standardized to Dutch guilders for the year 2000 and subsequently were converted to U.S. dollars for the year 2000 (exchange rate: 10,000 Dutch guilders = $4,186 = 4,545 euros).

Indirect costs were not considered in the computation of costs. Production loss for a donor does not occur because the general health of a donor was assumed to be the same before and after donation. For the recipient, production loss was assumed to be

negligible, since recipients' pre- and post-transplantation employment rates did not differ significantly.[236]

Analyses

The lifetime costs and quality-adjusted life years (QALYs) gained were calculated for each strategy. First, these data were calculated for the donor and recipient separately, and subsequently, the total lifetime cost and total QALYs were calculated for each strategy for donor and recipient combined. Both QALYs and costs were discounted at 3% (range, 0%-10%) per year. On the basis of costs and QALYs for donor and recipient considered separately, we computed incremental cost-effectiveness ratios. To enable decision making for both donor and recipient combined, we summed the costs for the recipient and donor, summed their respective QALYs, and calculated the corresponding incremental cost-effectiveness ratios.

Strategies that were dominated or extended dominated were eliminated from further consideration. A strategy was considered to be dominated by another strategy if costs were higher, whereas QALYs were lower than they were for the other strategy. A strategy was considered to be extended dominated by another strategy if it had a higher incremental cost-effectiveness ratio and lower QALYs. A strategy that was both more costly and more effective was considered to be cost effective if its incremental cost-effectiveness ratio did not exceed the threshold of society's willingness to pay for gaining 1 QALY (R).[237] A recently published article indicated that R was $25,000 - $400,000.[238]

Since the purchasing power of $1 in the United States was about the same as that of 1 Dutch guilder in the Netherlands in the year 2000, we used an R of 100,000 Dutch guilders ($41,000) as our baseline estimate and varied R from 25,000 to 400,000 Dutch guilders ($10,000 - $168,000) in our sensitivity analyses. All analyses were performed with statistical software (DATA 3.5.7; TreeAge Software, Williamstown, MA). A base-case analysis was performed with a 40-year-old female donor and a 40-year-old female recipient. We performed one-way sensitivity analyses to test if our baseline results were sensitive to varying all estimates over plausible ranges. In addition, we performed several two-way sensitivity analyses.

RESULTS

Base-case analysis

The lifetime costs, QALYs, and incremental cost-effectiveness ratios in regard to the donor and recipient considered separately are shown in Table 5 for our base-case analysis. With respect to the donor, QALYs differed very little among the imaging strategies. The 'no test, no transplantation' reference strategy dominated all other strategies, but since the donor desires to donate his or her kidney, we assumed this strategy would not be

TABLE 5. QALYs, cost and incremental cost-effectiveness ratios

Strategy*	QALYs†	Cost ($)	Incremental Cost-Effectiveness ratio ($ per QALY)‡
Donor			
No test, always transplantation	23.98	11,100	(Reference)
DSA	24.05	9,600	Dominated
DSA with MR angiography	24.05	9,900	Dominated
MR angiography	24.05	9,000	§
MR angiography, DSA	24.05	9,500	Dominated
CT angiography	24.06	9,300	Extended dominated
MR angiography with CT angiography	24.06	9,800	245,000
No test, no transplantation	24.07	1,200	(Reference)
Recipient			
No test, no transplantation	5.16	425,000	(Reference)
MR angiography	9.99	200,000	Dominated
MR angiography, DSA	10.29	186,000	Dominated
CT angiography	10.36	183,000	Dominated
MR angiography with CT angiography	10.42	180,000	Dominated
DSA	10.46	179,000	§
DSA with MR angiography	10.46	179,000	§
No test, always transplantation	10.62	165,000	(Reference)

* Strategies are listed according to increasing QALYs.
† QALYs were rounded off and may falsely seem similar.
‡ Computed without considering the 'No test, no transplantation' strategy and the 'No test, always transplantation' strategy.
§ Strategy associated with lowest cost, used as a reference strategy to compute incremental cost-effectiveness ratios.
QALY = quality-adjusted life year

an option for the donor. The 'no test, no transplantation' strategy is presented for comparison purposes only. Of the strategies, MR angiography was associated with the lowest cost. MR angiography with CT angiography yielded more QALYs but at $245,000 per QALY. In regard to the recipient, the QALYs varied more among the strategies, and the costs were much higher. From the recipient's perspective, the 'no test, always transplantation' strategy dominated all other strategies, but it would be unethical not to test donors at all (this strategy is also presented for comparison purposes only). Of the strategies, DSA and DSA with MR angiography dominated all other strategies. Costs and QALYs for these strategies were the same, since additionally performing MR angiography would affect only donor costs of the imaging and the surgery.

Summation of costs and QALYs of donor and recipient and computation of incremental cost-effectiveness ratios (Table 6) showed that DSA (34.51 QALYs and $188,000) dominated all other strategies.

Sensitivity analyses

The results of application of the model were not sensitive to varying parameters over a plausible range except for two of the one-way sensitivity analyses. In one analysis, in which specificity of DSA was 99% or less, MR angiography with CT angiography was the most cost effective from the combined perspective of donor and recipient (34.47 QALYs and $190,000). In another analysis, the model proved to be sensitive to the specificity of CT angiography for detection of renal disease: if specificity was 100%, CT angiography would be the most cost-effective strategy (34.52 QALYs and $187,000).

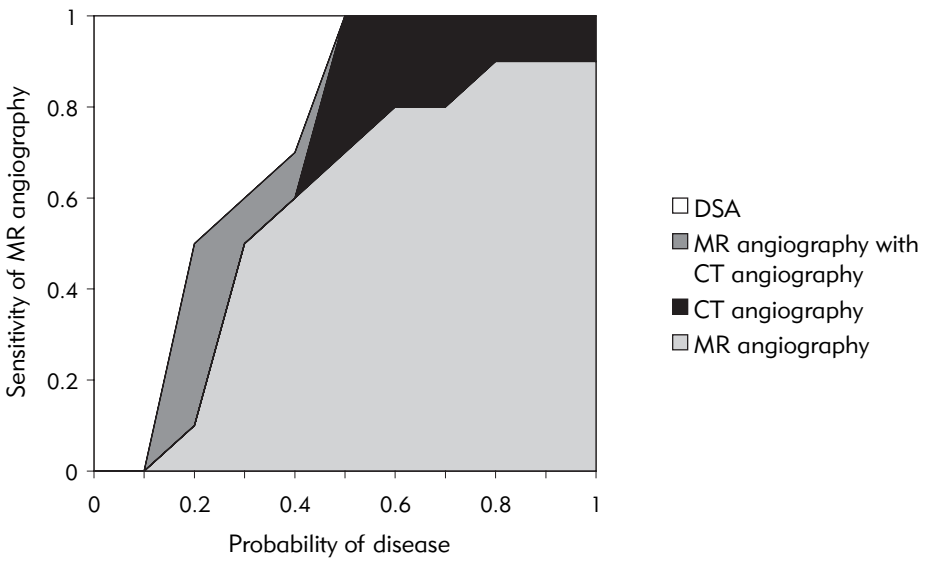
In two-way sensitivity analyses, we varied both the prevalence of disease and sensitivity or specificity of MR angiography or CT angiography for detection of renal disease. The analysis for the optimal decision from the combined perspective of donor and recipient, when sensitivity of MR angiography and prevalence of disease were varied, is shown in Figure 2. At low prevalences of disease, DSA is the most cost effective. When prevalence is slightly higher, MR angiography with CT angiography is superior. Contrary to what we would have expected, at high prevalence of disease, MR angiography is the most cost effective when its sensitivity for detection of renal disease is low, and CT angiography is the most cost effective when sensitivity of MR angiography for disease is high.

TABLE 6. Cost, QALYs, and incremental cost-effectiveness ratios for donor and recipient combined

Strategy*	QALYs	Cost ($)†	Incremental Cost-Effectiveness ratio ($ per QALY)‡
No test, no transplantation	29.23	426,000	(Reference)
MR angiography	34.04	209,000	Dominated
MR angiography, DSA	34.35	196,000	Dominated
CT angiography	34.42	192,000	Dominated
MR angiography with CT angiography	34.48	190,000	Dominated
DSA	34.51	188,000	§
DSA with MR angiography	34.51	189,000	Dominated
No test, always transplantation	34.60	176,000	(Reference)

* Strategies are listed according to increasing QALYs. See for abbreviations of strategy-names Table 1.
† Numbers are based on data from the base-case analysis and therefore may differ from those of the sensitivity analysis.
‡ Computed without considering the 'No test, no transplantation' strategy and the 'No test, always transplantation' strategy.
§ Strategy associated with lowest cost was used as a reference strategy to compute incremental cost-effectiveness ratios.
QALY = quality-adjusted life year

FIGURE 2. Two-way sensitivity analysis varying prevalence of disease and sensitivity of MR angiography (light grey area) for detection of disease from the combined perspective of donor and recipient

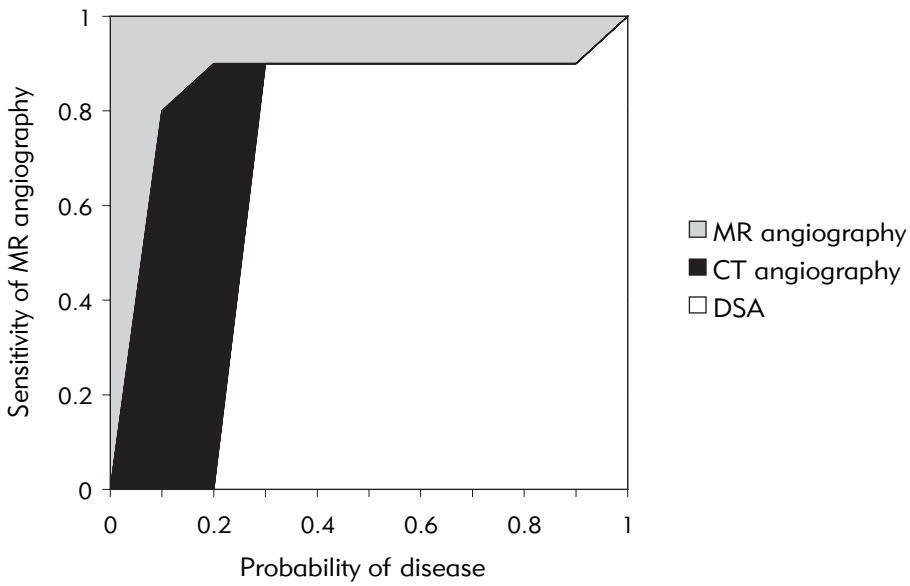


On the x-axis, prevalence of renal disease is represented and on the y-axis, sensitivity of MR angiography for detection of renal disease is represented. Both were varied between 0 and 100%. The areas in the plot represent the ranges over which a certain strategy is most cost effective from the combined perspective of donor and recipient, when the 'No test, always transplantation strategy' was left out of the analysis. At low prevalence of disease, DSA (white area) was the most cost effective. MR angiography with CT angiography (dark grey area) was superior if the prevalence was slightly higher. For high prevalence of disease, either CT angiography (black area) or MR angiography was superior depending on the sensitivity of MR angiography.

When both prevalence of disease and the sensitivity of MR angiography are varied in determining the most cost-effective strategy from the perspective of the donor (Figure 3), MR angiography is most cost effective at low prevalence of disease. When prevalence is slightly higher, CT angiography is superior, and if prevalence of disease is high, DSA is most cost effective. However, if the sensitivity of MR angiography is high, MR angiography is superior (unless the prevalence of disease is 100%).

Age was also varied from 25 to 75 years for both donor and recipient in a two-way sensitivity analysis. The DSA strategy was most cost effective over the entire age range.

FIGURE 3. Two-way sensitivity analysis varying prevalence of disease and sensitivity of MR angiography (grey area) for detection of disease from the perspective of the donor only



On the x-axis, prevalence of renal disease is represented and on the y-axis, sensitivity of MR angiography for detection of renal disease is represented. Both were varied between 0 and 100%. The areas in the plot represent the ranges over which a certain strategy is most cost effective from the perspective of the donor, when the 'No test, no transplantation strategy' was left out of the analysis. MR angiography was superior if it was associated with a high sensitivity. For the combination of a low prevalence of disease and low-to-moderate sensitivity of MR angiography, CT angiography (black area) was superior. In all other cases DSA (white area) was superior.

DISCUSSION

The objective of our study was to identify the most cost-effective strategy for the preoperative evaluation of living, related, potential renal donors. On the basis of a decision- and cost-effectiveness analysis, we conclude that from the perspective of the donor, MR angiography is the most cost-effective strategy, whereas from the combined perspective of donor and recipient, DSA is the most cost-effective strategy. If, however, specificity of DSA for the detection of renal disease is 99% or less, MR angiography with CT angiography is most cost effective from the combined perspective of donor and recipient.

Several general limitations to our study should be mentioned. First, the model was based on multiple data sources. Second, much of the information used in this study was obtained from the literature and, thus, may be subject to publication bias. Furthermore, generalizability is limited because cost data were obtained from only our own center. In addition, imaging protocols for each of the techniques, characteristics of both the donor and recipient population, and expertise may vary among transplantation centers.

Limitations more specifically related to our model included limited availability of data. No literature data were available concerning survival with renal disease. Pozniak and colleagues[210] argued that fibromuscular dysplasia is relatively stable in patients older than 40 years and that most donors are approximately 40 years of age. However, arterial stenosis is known to progress. Thus, we took into account the possibility that donors would need dialysis after a number of years and varied the estimates over a wide range to assess possible changes in results. Also, few data have been published that can be used to quantify the quality of life of renal donors. On the basis of the available qualitative literature,[239] we assumed the donors were perfectly healthy. Further research into the quality of life of renal donors is necessary, however, because preserving the quality of life of the donor is a high priority.

Information concerning the test characteristics of the imaging strategies for detection of renal disease is also lacking. Most studies report characteristics for detection of arterial anomalies, such as multiple renal arteries and early arterial branching. These anomalies, however, only influence the costs of the surgery that the donor undergoes because the length of the surgery is increased. More important for the radiological examination are the sensitivity and specificity with respect to detection of renal disease, since these influence both costs and QALYs in regard to both donor and recipient. Therefore, re-

searchers in future studies should focus on test characteristics of imaging strategies for the detection of renal disease rather than on test characteristics for the detection of renal anomalies.

Several technical implications of our analyses can be mentioned. First, some of our results were counterintuitive but, on reflection, could be explained and helped us obtain insight into how various factors could and should contribute to the decision. For example, counter to our intuition, we found that DSA is the most cost-effective option at low prevalence of disease (Figure 2). This can be explained by the fact that, at low prevalence of disease, specificity is more influential. A high transplantation rate is more cost effective from the combined perspective of both donor and recipient because of the benefits to the recipient. Because false-positive results imply no transplantation, a high specificity is required, and DSA has the greatest specificity of 100%. At higher prevalence of disease, sensitivity becomes more important, and for the transplantation rate to be high, a high false-negative rate (implying transplantation), and thus low sensitivity, is required. This explains why MR angiography is the most cost-effective option when prevalence of disease is high and sensitivity for detection of disease is low.

With consideration of only the donor's results (Figure 3), it can be seen that the counterintuitive results from the combined perspective are indeed caused by the benefit to the recipient (both in terms of QALY gains and cost savings) through a higher transplantation rate.

Second, a one-way sensitivity analysis showed that CT angiography is most cost effective if its specificity is 100%. Since results in studies in the literature are contradictory as to the ability of CT angiography to depict or exclude fibromuscular dysplasia,[210,213,216,240-242] one can argue that a specificity of 100% will not be attainable. However, researchers in all studies used single-detector row spiral CT angiographic equipment, and one might argue that with multi-detector row spiral CT angiography, a higher specificity of CT angiography could be determined. Even if 100% specificity can be determined, the harmful effects of radiation exposure should also be considered.

Furthermore, although some authors advocate the use of MR angiography in addition to DSA to depict venous anomalies, the addition of MR angiography to the imaging strategy cannot be cost effective, because the additional costs that result from having to deal with anomalies during the surgery are less than the cost of MR angiography.

However, in our analysis we did not take into account the confidence of the surgeon who performed the transplantation. One would expect that having imaging data prior to surgery would enhance the surgeon's confidence. Quantification of this increased confidence could translate into an increase in the surgeon's quality of life. If an analysis is performed from the societal perspective, this should also be considered. We believed, however, that including the surgeon's quality of life would be extending the analysis too far.

Finally, in the analyses, the 'no test, always transplantation' reference strategy appeared to be the most cost effective option for the combined perspective of the donor and the recipient. As has been stated, however, performing no test at all in donors would be unethical, since the transplantation team relies on the findings on the images in planning and performing the surgery[214] and because the team should not compromise its care for the safety of the donors.[213]

In the analysis of the clinical implications of our results, we should emphasize the importance of the perspective used. If costs and effectiveness of only the donor were considered, MR angiography would be best because it is associated with a lower transplantation rate. To optimize the recipient's outcome, it would be best if the donor underwent DSA or DSA with MR angiography. When the combined perspective of donor and recipient was considered, DSA was the most cost effective. The outcomes of the recipient may outweigh those of the donor in this combined result, because, for the recipient, the difference in QALYs gained varies more among the strategies.

The choice of how to combine the outcomes of two subjects, in this case, the donor and the recipient, is not as straightforward as it may seem. According to Hippocrates's principle of 'first do no harm', we may believe that the donor's survival and quality of life should weigh more in the overall analysis. According to the utility theory applied in the context of cost-effectiveness analysis of health care, all QALYs are considered the same, regardless of who benefits from the gained QALYs.[184] In accordance with this theory, we valued a QALY of a donor the same as a QALY of the recipient. It may, however, be argued, that a QALY of the donor should be weighed more heavily than a QALY of the recipient, because the donor gives up QALYs for the benefit of the recipient. Such an argument would be based on the notion that 'losses loom larger than gains'.[243] Altruistic motives of the donor were not considered in this model, since the desire to donate is extremely difficult, if not impossible, to quantify.

In conclusion, for the preoperative radiological examination performed in potential living renal donors, DSA is the most cost-effective strategy when it is considered as the reference standard, but if the specificity of DSA for the detection of disease is 99% or less, which is probable, MR angiography with CT angiography is the most cost-effective strategy.

4.2

Quantifying the benefit of early living-donor renal transplantation with a simulation model of the Dutch renal replacement therapy population

ABSTRACT

Objectives: In patients requiring renal replacement therapy (RRT), early living-donor renal transplantation improves patient- and graft-survival compared with possible cadaveric renal transplantation, but the magnitude of the survival gain remains unknown. Our objective was to quantify the survival benefit of early living-donor transplantation compared with dialysis with possible cadaveric transplantation for patients starting RRT of different ages and genders with varying primary renal diseases, and to estimate the population benefit from increasing the early transplantation rate.

Methods: We developed a computer-simulation model using data from the Dutch End Stage Renal Disease Registry and published data, modeling a life-time time horizon from the perspective of patients starting RRT. We compared two strategies: *Early living-donor renal transplantation* (RTx) (pre-emptive or within 90 days of dialysis initiation) and *Dialysis* (with possible cadaveric renal transplantation when available). Outcome measures were increase in life expectancy (LE) and quality-adjusted life expectancy (QALE).

Results: LE (QALE) benefits of the *Early living-donor renal transplantation* compared with the *Dialysis* strategy for 40-yr-old patients ranged from 7.5 – 9.9 LYs (6.7 – 8.8 QALYs) depending on the primary renal disease. For 70-yr-old patients the benefit was 4.3 – 6.0 LYs (4.3 – 6.0 QALYs). Increasing the early living-donor RTx rate from currently 5.8% to 22.2% (the highest in Europe) would increase average LE of RRT patients by 1.2 LYs and increase LE for annual incident cases in the Netherlands by over 1,800 LYs.

Conclusions: Efforts to increase the early living-donor RTx rate should focus on younger patients and could potentially result in a substantial increase in LE for patients starting RRT.

INTRODUCTION

The number of years spent on renal dialysis prior to renal transplantation (RTx) has been shown to be negatively correlated with renal graft and patient survival, both in cadaveric as well as in living-donor transplant recipients.[3,246,247] Several studies have shown a patient or graft survival benefit of pre-emptive transplantation[247-252] and therefore, timely, preferably pre-emptive renal transplantation has been advocated for patients nearing end-stage renal disease.[247-250] In countries participating in the Eurotransplant organ procurement system, waiting time for a cadaveric transplant cannot be accrued before starting renal replacement therapy (RRT). Therefore, pre-emptive transplantation can only be performed when a living donor is available. Moreover, graft survival of a living-donor transplant has been shown to be significantly better than for cadaveric donor transplants.[3]

Although living donors are exposed to an operative risk, they are reported to have a long-term survival comparable to or even better than the normal population[253] and an end-stage renal disease (ESRD) incidence as low as 0.5% after 40 years of donation.[254] In spite of these low risks for the living donor, patients requiring RRT have been shown to be reluctant to accept a transplant from a living donor because of lack of knowledge regarding the long-term consequences associated with dialysis and with living-donor transplantation.[255]

It is difficult to inform patients about these risks using data from the current literature. Studies comparing the survival of patients following a pre-emptive renal transplant from a living donor with the survival of patients following a cadaveric renal transplant do not properly reflect the trade-off, because they do not account for the uncertainty whether a patient starting dialysis will actually receive a cadaveric transplant. Therefore, from such studies, the true benefit of pre-emptive living-donor transplantation compared with dialysis and possible cadaveric transplantation for a patient that is about to start RRT cannot be estimated. Moreover, the observational studies performed to compare pre-emptive transplantation with post-dialysis transplantation reported relative mortality rates,[247-249] rather than life-expectancy (LE) benefits.

Therefore, we used a computer-simulation model to quantify the LE benefit of early living-donor renal transplantation compared with dialysis while waiting for possible cadaveric renal transplantation for patients starting RRT of different ages and gender,

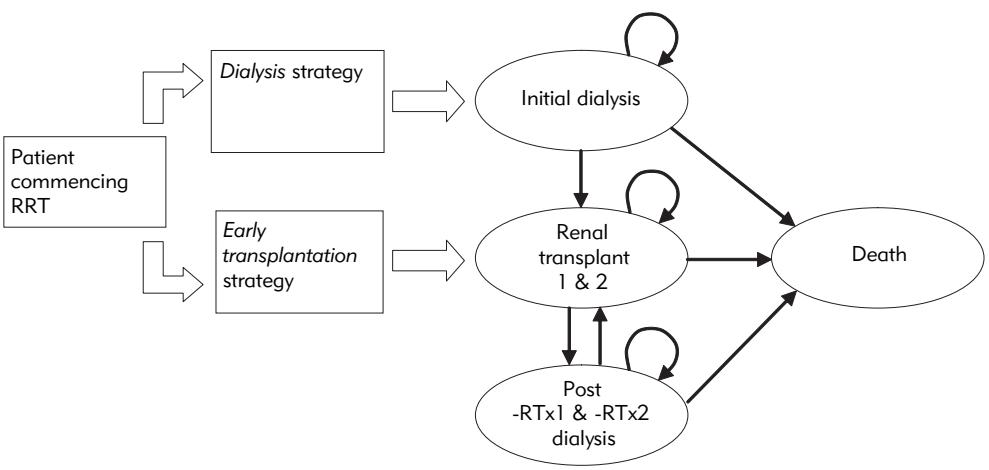
with varying primary renal diseases. Secondly, we estimated the population benefit that could be accrued from increasing the early transplantation rate in the Netherlands.

METHODS

Model

We developed a state-transition model to estimate the LE of patients commencing RRT, comprising 4 states: 1) hemodialysis (HD), 2) peritoneal dialysis (PD), 3) RTx and 4) death. Two treatment strategies were evaluated for these patients. In the first strategy, *Dialysis*, patients start dialysis therapy, with the chance of being waitlisted and of receiving a renal transplant from a cadaveric donor. Dialysis therapy is subdivided into HD and PD; subsequent switches were not modeled explicitly but were reflected in the source data. If patients receive a renal transplant, graft failure may occur and patients return to HD or PD. Patients can receive a maximum of two renal transplants. The second strategy, *Early transplantation*, patients receive a pre-emptive or early renal transplant (within the first 90 days of dialysis) from a living donor. If the transplant fails, patients will be treated with HD or PD. Patients may receive a cadaveric transplant at a later stage. A schematic overview of the model is presented in Figure 1.

FIGURE 1. Schematic overview of the simulation model



RRT = renal replacement therapy, RTx = renal transplantation

We used a Markov process model, with a cycle length of three months. State-transition rates, dependent on patient covariates were estimated from Cox models and transformed into 3-monthly transition probabilities. We estimated the Cox models for death and for transitions to other treatments for three treatment periods: initial dialysis, transplantation and post-transplant dialysis. Patient history in terms of type of previous dialysis modality and previous transplants was tracked using additional health states. Outcome measures were LE and quality-adjusted life expectancy (QALE) from the perspective of the patients receiving RRT. In this methods section we discuss our main data sources and assumptions; more detailed information on the construction of the model is reported in the technical appendix.

Data sources and assumptions

Patient sample

We used a sample of 15,435 patients from the Dutch End Stage Renal Disease Registry, RENINE, who started RRT between January 1st 1987 and December 31st 2002. Registry data included age, gender, primary renal disease, year of start of RRT, dialysis center, date and type of transplantation (living-donor or cadaveric), transplantation center and date of death. In RENINE, primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). We aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM) and a category for all other renal diagnoses (PRD-OTH).

Initial dialysis models

Both initial dialysis Cox models (mortality and rate of transplantation) were left-truncated for the first 90 days. Because several variables had a significant interaction with time, we estimated initial dialysis mortality using a time-stratified Cox-proportional hazards regression model censoring at transplantation or the end of follow-up. The transplantation rate for initial dialysis patients was also estimated with a time-stratified Cox-proportional hazards model, but censoring at death or at the end of follow-up, at the age of 78 years or at a maximum dialysis time of 13 years because no patient was transplanted beyond that age or dialysis duration. Although we did not have information on transplantability for all dialysis patients, such information was available for another subset of RENINE data. Based on this sample, we estimated the hazard ratios (HRs) of transplantable patients compared with the entire

initial dialysis population for both mortality and transplantation rates and used these HRs as relative risks to adjust the mortality and transplantation rates obtained from the initial dialysis models.

Transplant models (first and second transplant)

RTx patient mortality and graft failure for first and second transplants were modeled from patients in the dialysis mortality model that were transplanted before December 31st 2002 (4,699 first and second transplants), and from patients that received an early transplant (772 first and second transplants). This resulted in a total of 5,471 transplants. Three Cox-models were constructed for patient mortality, graft failure and return to HD, and graft failure and return to PD. The transplant mortality analysis was censored for graft failure and graft failure analyses were censored for patient death and for graft failure with transition to the other dialysis modality.

Post-transplant dialysis models

Post-transplant dialysis mortality was based on the data of patients included in the transplant models that returned to dialysis after failure of a first (n=893) or a second renal transplant (n=102). In the Cox model, patients were censored at transplantation or at the end of follow-up. The rate of receiving a second transplant was modeled on the sample that returned to dialysis after failure of a first renal transplant (n=893). Patients were censored at death or at the end of follow-up.

Extrapolating survival data beyond observed follow-up time

We extrapolated our survival data beyond the observed follow-up time to allow for a lifetime time-horizon by fitting weighted quadratic regression functions on the baseline cumulative hazard over time for each Cox model.

Quality of life

For estimates of utilities of HD, PD, and RTx patients, we used EuroQoL EQ-5D estimates from a recently published from systematic review of the literature,[256] in accordance with recommendations from the Panel on Cost-Effectiveness in Health and Medicine to prefer values from an indirect method.[184] The means and standard deviations (SDs) were 0.5560 (0.0283) for HD, 0.5817 (0.0385) for PD and 0.8077 (0.0407) for RTx patients. To account for short-term disutilities from procedures, we deducted the duration of procedure-related hospitalization, i.e., assumed a quality of life of 0 for those days. The duration of hospitalization was based on expert opinion (J.F.M.W.) for

HD shunt and PD catheter implantation and on data from the Dutch Organ Transplant Registry for cadaveric and living RTx.[257]

Uncertainty and variability

We performed second-order Monte Carlo simulations to account for parameter-uncertainty. Parameter uncertainty of transition probabilities was accounted for by estimating the Cox-proportional hazards models on 1,000 bootstrap samples of the RENINE patient sample, and estimating a weighted quadratic regression model on the baseline cumulative survival of each of the 1,000 Cox models. Bootstrapping was performed separately for the three different treatment periods (R, version 2.5.1, The R Foundation for Statistical Computing, Vienna, Austria). For the uncertainty in quality of life estimates, we fitted beta distributions on the means and SDs of the EQ-5D values that we obtained from our meta-analysis.

Analyses

We calculated LE, expressed in life years (LYs) and QALE, expressed in quality-adjusted life years (QALYs) for the two strategies for patients commencing RRT. We assessed the outcome measures for different scenarios defined by age (40, 50, 60, or 70 years), gender, and primary renal disease. The LEs associated with both strategies were compared with that of the Dutch general population[258] based on general population mortality rates in 1996, the mean year of start of dialysis in our cohort. The model was developed and analyzed in TreeAge Pro Suite 2007 (TreeAge software, Inc., Williamstown, MA).

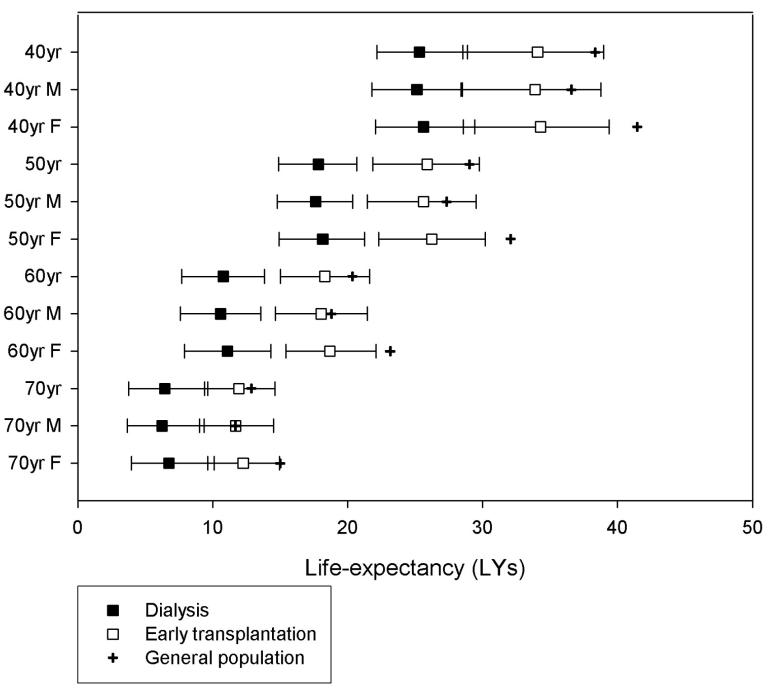
Based on the incidence of RRT-patients and the percentages of early transplantation and dialysis as initial RRT modalities on day 91 in the Netherlands in 2005,[2] we calculated the absolute number of incident early transplantation patients and incident dialysis patients. We estimated mean LEs associated with the *Early transplantation* and *Dialysis* strategies for the mean age and gender distribution of the incident 2005 cohort and multiplied these estimated LEs with the incidence rates and numbers for early transplantation and dialysis to obtain an estimated average LE for an individual patient as well as for the entire incident cohort. We repeated this calculation, assuming the highest early transplantation rate reported in incident patients among ERA-EDTA affiliated countries[2] and calculated the benefit of increasing the early trans-

plantation rate to this higher rate for both a potential patient as well as for the Dutch population.

RESULTS

The estimated LEs and 95% CIs associated with the *Dialysis* and *Early transplantation* strategies for the scenarios defined by patient age and gender are shown in Figure 2. The LE associated with the *Early transplantation* strategy was higher than the LE associated with the *Dialysis* strategy. The LEs for the *Dialysis* and for the *Early transplantation* strategies respectively, decreased from 25.3 and 34.1 LYs for a 40-yr-old patient to 6.5 and 11.9 LYs for a 70-yr-old patient. For all ages, LE was higher for women versus men. When comparing the two strategies, the survival benefit of *Early transplantation* compared with *Dialysis* decreased with age, from 8.7 LYs for 40-yr-old and 8.0 LYs for 50-yr-old patients to 7.5 for 60-yr-old and 5.5 LYs for 70-yr-old patients.

FIGURE 2. Life-expectancies and 95% confidence intervals for the *Dialysis* and *Early transplantation* strategies and general population life expectancy by age and gender

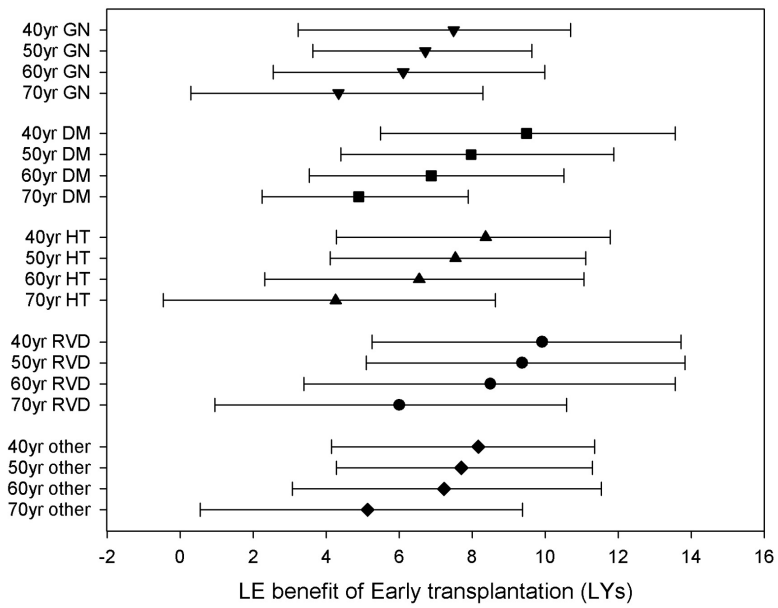


F = female, LYs = life years, M = male, yr = year

Figure 2 also denotes the LE of the Dutch general population according to age and gender in the year 1996 (the mean year of start of dialysis in our analyses). When compared with identically aged individuals from the general population, the need for dialysis reduced life expectancy substantially, ranging from a loss of 13.0 LYs for 40-yr-old patients to 6.4 LYs for 70-yr-old patients. Substituting *Early transplantation* also resulted in a diminished LE compared with the general population. The difference also decreased with increasing age, but the general population estimates fell within the confidence intervals of the *Early transplantation* LE-estimates. For both strategies, the loss of LE compared with the general population was higher for women than for men.

Early transplantation increased LE (Figure 3) from 7.5 to 9.9 LYs for 40-yr-old patients and from 4.3 to 6.0 LYs for 70-yr-old patients, and there were no significant differences among the PRD categories. The decrease in survival benefit of *Early transplantation* with age, found for the entire population, was similar for all disease categories.

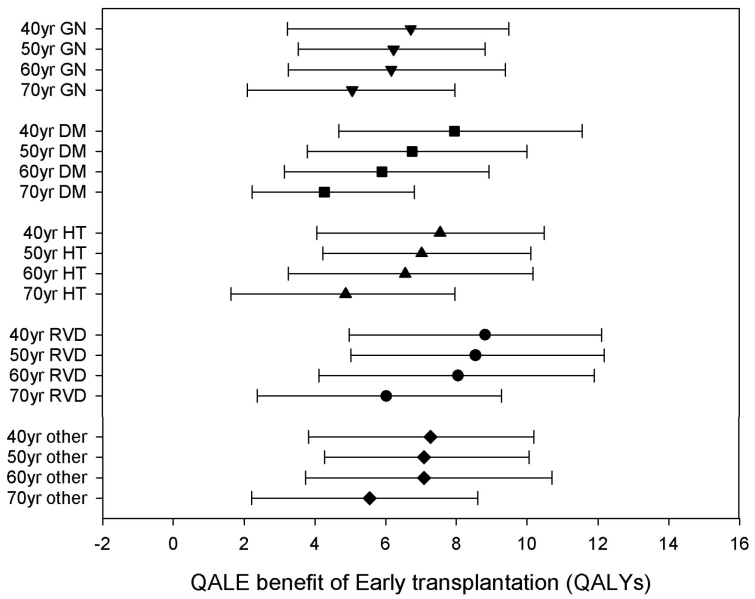
FIGURE 3. Survival benefit and 95% confidence intervals in terms of life expectancy (LE) for the *Early transplantation* compared with the *Dialysis* strategy by age and primary renal disease



DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, LYs = life years, other = other/unknown primary renal disease, RVD = renal vascular disease

Figure 4 depicts the QALE benefit of *Early transplantation* compared with *Dialysis* for different combinations of age and primary renal disease. The benefit varied from 6.7 to 8.8 QALYs for 40-yr-old patients and from 4.3 to 6.0 QALYs for 70-yr-old patients. For patients aged 40 through 60 years the absolute QALE survival benefit of *Early transplantation* was smaller than the LE benefit. For 70-year-old patients the absolute benefit was similar or slightly higher expressed in QALYs compared with LYs.

FIGURE 4. Survival benefit and 95% confidence intervals in terms of quality-adjusted life expectancy (QALE) for the *Early transplantation* compared with the *Dialysis* strategy by age and primary renal disease



DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, other = other/unknown primary renal disease, QALYs = quality-adjusted life years, RVD = renal vascular disease, yr = year

In 2005, there were 1,565 incident RRT patients on day 91, of whom 93.2% were treated with dialysis and 5.8% with an early living-donor RTx. Approximately 1% were treated with an early cadaveric RTx and these patients were not included in the calculation. According to the same report, patients were on average 61.2 yrs old and 39% were female. In such a cohort, LEs associated with the *Dialysis* and *Early transplantation* strategies were 10.1 and 17.4 LYs, respectively, and estimated QALEs were 6.9 and 13.9 QALYs. When considering that 5.8% of incident RRT patients receive an early living-donor RTx and 93.2% started on dialysis, the average survival for an incident RRT patient was estimated to be 10.5 LYs and 7.3 QALYs. Among ERA-EDTA countries,

Iceland reported the highest incident early living-donor RTx rate of 22.2%, with the remainder starting dialysis. If this rate could be attained in the Netherlands, the LE and QALE for average incident RRT patients would rise to 11.7 LYs and 8.4 QALYs. Thus, the increase in LE (QALE) would on average be 1.2 LYs (1.1 QALYs). Based on the 2005 incidence of Dutch RRT patients, the higher living donor RTx rate would increase survival by over 1,800 LYs or over 1,700 QALYs in the 1,565 incident RRT patients.

DISCUSSION

From our analyses we conclude that *Early transplantation* resulted in a considerable LE and QALE survival benefit, compared with *Dialysis* in all scenarios. Specifically, the LE (QALE) survival benefits of the *Early transplantation* versus *Dialysis* ranged from 7.5 – 9.9 LYs (6.7 – 8.8 QALYs) for 40-yr-old patients and from 4.3 – 6.0 LYs (4.3 – 6.0 QALYs) for 70-yr-old patients. This benefit decreased with increasing age. Improving the early transplantation rate of 5.8% in the Netherlands to the highest rate reported from the ERA-EDTA of 22.2% would increase average LE (QALE) for RRT patients by 1.2 LYs (1.1 QALYs) and increase survival in the incident RRT population in the Netherlands by 1,800 LYs or over 1,700 QALYs.

We compared our results with the survival for incident RRT patients reported in the literature for incident waitlisted dialysis patients. Inrig and colleagues[259] reported a 2-year survival of 93.3% for PD and 93.2% for HD patients (average age 47 years) in the United States. The 2- year survival estimates from our *Dialysis* strategy for 40- and 50-yr-old patients, were on average 95.8% and 92.5% respectively, suggesting good external validity of our model. A study in a Swedish population by Medin and colleagues,[29] however, showed a 5-year survival of 60% for waitlisted patients (average age 49-years old at waitlisting). The 5-year survival estimate from our *Dialysis* strategy for 50-yr-old patients was on average 80.5%. This discrepancy might be explained by differences in case mix. The patients included in the study by Medin had started dialysis in earlier years (1987-1996), a lower percentage was treated with PD, and there was a lower proportion of females, which could all have contributed to a lower survival. In addition, Medin and colleagues analyzed patients from the moment of waitlisting and not from the start of dialysis as we did. Lastly, if our dialysis survival estimates were more similar to those of Medin's, then the estimated benefit from transplantation would be even larger, making our results conservative.

The most important advantage of our study lies in the comparison of strategies from the initiation of RRT, thereby avoiding lead-time bias, which would have occurred in studies comparing the survival of post-dialysis cadaveric RTx and pre-emptive living donor RTx or in studies comparing the survival of waitlisted dialysis patients and cadaveric RTx patients.

Our model provides several important insights. We found that the estimated LE of patients receiving an early transplant approached the LE of the general population, particularly as age increased. Although this might in part be explained by a slight overestimation of *Early transplantation* LE due to lack of long-term follow-up of these patients in our data, registry data suggest that older patients receiving a RTx have a LE that approached that of the general population.[260] In addition, we found that the survival benefit of *Early transplantation* decreased with increasing age, as might be expected. Our results suggest that efforts to increase *Early transplantation* should particularly be aimed at younger patients, but the benefit in older patients remains substantial and justifies an active approach to achieve higher rates of early transplantation in all age groups.

Interestingly, when comparing the absolute survival benefit of *Early transplantation* compared with *Dialysis* in QALYs instead of LYs, quality of life adjustment reduced the incremental benefit for younger patients but not for older patients. The explanation for these findings lies in two counter balancing factors: quality of life decrement and survival because QALYs is the product of these 2 factors. Firstly, QoL adjustment reduces QALYs for *Dialysis* more than for *Early transplantation*. Secondly, however, patients receiving *Early transplantation* lived far longer than patients in the *Dialysis* strategy, so any QoL-adjustment for *Early transplantation* affects a greater duration of life than any for *Dialysis* where the decrement for a year may be higher but the duration of life is not as long. Therefore, younger patients lived so many more years with an RTx in the *Early transplantation* strategy that the small QoL-adjustment for transplantation accumulated over time, reduced the incremental benefit compared with dialysis. Older patients spent a lower number of years with an RTx and therefore the incremental benefit was similar or higher in terms of QALYs.

Increasing the national rate of early living-donor transplantation from 5.8 to 22.2% substantially increased the average LE for incident dialysis patients by 1.2 LYs (1.1 QALYs). In the absence of data on variation in rate of early transplantation by age, gender,

and primary renal disease in different countries, our calculation was based on average patient characteristics and on average rates of early transplantation and assumed that increasing the pre-emptive RTx rate would not change the characteristics of the pre-emptively transplanted population. With this assumption, the result suggests substantial gains in LE and QALE from increasing early transplantation rates. How to achieve a higher early transplantation rate remains a challenge. Previous research suggested that timely referral of patients with chronic renal disease to a nephrologist may be one factor.[261] Early referral to a nephrologist has been shown to be associated with both a lower dialysis mortality[262] and better access to the wait list and cadaveric transplantation,[24] therefore enhanced awareness of the importance of early diagnosis of renal disease and subsequent referral may markedly improve transplantation rates.

Some limitations of our study need mentioning. Firstly, the model did not account for outcomes for the living donor and the influence of those effects on the quality of life of the recipient. Although both short-term and long-term consequences for the donor are important, prospective long-term data on the consequences are currently lacking.[263] Secondly, we assumed that a living donor was sought and available only at the commencement of RRT. In reality, patients may receive a first or subsequent living-donor transplant in the course of their treatment. However, many factors may influence the availability and eligibility of a living donor and the impact of dialysis on subsequent living donor organ and patient survival are less well known; therefore we chose to restrict ourselves to the presented situation. However, when interpreting the results of the model, it must be kept in mind that the *Early transplantation* strategy reflects a combination of two advantageous treatments: living-donor over cadaveric RTx and pre-emptive over post-dialysis RTx. Another limitation is that we did not distinguish between early (< 3 months of start of dialysis) transplants and actual pre-emptive transplants. Several studies have shown, however, that patients receiving an early transplant, within 6 months[264] or within 1 year[265] of the start of dialysis have a survival comparable to pre-emptively transplanted patients. As for generalizability: the model was based on Dutch registry data from the period 1987-2002. Since the Dutch ESRD population may differ from other countries' populations with respect to demographics and clinical characteristics, we have presented results for subgroups. However, we cannot exclude differential effects of risk factors in different populations.

In conclusion, we found and quantified substantial survival benefits in terms of LE and QALE for patients commencing RRT with an early living-donor RTx compared with

those starting on dialysis and being listed for a deceased donor organ. This benefit decreased with advancing age and therefore, efforts to increase the rate of early transplantation should particularly focus on younger patients. Increasing rates of early transplantation to the highest rate reported among ERA-EDTA countries would be estimated to increase LE for an average patient with 1.2 years, amounting to an increase of over 1,800 LYs for an annual cohort of 1,565 patients commencing RRT in the Netherlands. Therefore, increasing early transplantation rates may substantially improve LE of RRT patients and national policies and research to promote organ donation should be pursued.

5

Methodological issues in the analysis of observational databases

5.1

Propensity scores in the presence of effect modification: a case study using the comparison of mortality on hemodialysis versus peritoneal dialysis

ABSTRACT

Objective: To control for confounding bias from non-random treatment assignment in observational data, both traditional multivariate models and, more recently, propensity score approaches have been applied. Our aim was to compare a propensity score-stratified model with a traditional multivariable-adjusted model, specifically in estimating survival of hemodialysis (HD) versus peritoneal dialysis (PD) patients.

Methods: Using the Dutch End Stage Renal Disease Registry, we constructed a propensity score, predicting PD assignment from age, gender, primary renal disease, center of dialysis, and year of first renal replacement therapy. We developed two Cox proportional hazards regression models to estimate survival on PD relative to HD, a propensity score-stratified model stratifying on the propensity score and a multivariable-adjusted model, and tested several interaction terms in both models.

Results: The propensity score performed well: it showed a reasonable fit, had a good c-statistic, calibrated well and balanced the covariates. The main-effects multivariable-adjusted model and the propensity score-stratified univariable Cox model resulted in similar relative mortality risk estimates of PD compared with HD (0.99 and 0.97, respectively) with fewer significant covariates in the propensity model. After introducing the missing interaction variables for effect modification in both models, the mortality risk estimates for both main effects and interactions remained comparable, but the propensity score model had nearly as many covariates because of the additional interaction variables.

Conclusion: Although the propensity score performed well, it did not alter the treatment effect in the outcome model and lost its advantage of parsimony in the presence of effect modification.

INTRODUCTION

Using observational data to compare outcomes associated with different treatments may result in biased estimates because of non-random treatment assignment. To correct for variables that may confound an association, the traditional approach is to apply multivariable-adjusted modeling, but in recent years, the use of propensity scores has become increasingly popular.[266] The concept of a multivariate confounder score was first introduced by Miettinen in 1976,[267] but the formal concept of propensity scores to estimate causal effects in observational studies was first described by Rosenbaum and Rubin.[41] A propensity score is a conditional probability of assignment to a particular treatment given a vector of baseline covariates. Two patients with the same propensity score but assigned to different treatments are considered to be equivalent to a random assignment of treatment. Thus, adjustment for the propensity score in the outcome model can balance the observed and included covariates and remove bias that may arise due to these confounders. This adjustment can be accomplished by either 1) selecting matched pairs of patients each on a different treatment arm, but with similar propensity scores, 2) stratifying the sample on the propensity score, calculating the treatment effect within strata and then pooling the strata-specific treatment effect estimates, or 3) including the propensity score itself as a covariate in the outcome model.

Several advantages of propensity score-stratified versus traditional multivariable-adjusted modeling have been suggested. The propensity model does not need to be parsimonious and easy to understand because it is not the focus of the study.[268] Furthermore, the propensity score enables a direct estimation of comparability of the treatment groups by assessing the covariate balance between groups. Inability to balance confounders alerts investigators that the treatment groups are not sufficiently overlapping with respect to these confounders and that selection bias may not be resolvable.[268] Traditional multivariable regression modeling will not detect this directly.

Patients with end-stage renal disease (ESRD) require renal replacement therapy (RRT). Of all therapeutic options, renal transplantation is generally associated with the highest survival and quality of life. However, due to the shortage of organs, the majority of ESRD patients are treated with renal dialysis. Two main forms of renal dialysis can be distinguished: hemodialysis (HD) and peritoneal dialysis (PD). Many factors influence dialysis treatment assignment: not only the clinical characteristics of a patient, but also patient and physician preference, cultural factors and reimbursement policy decisions

may play a role. Therefore, comparison of patient survival on HD and PD is complicated. Because the one randomized controlled trial that has been undertaken to assess survival differences had to be stopped prematurely because of low inclusion rates,[269] observational studies have to be relied upon to compare survival on HD versus PD. Our aim was to compare a propensity score-stratified model with a traditional multivariable-adjusted model, specifically in estimating survival of HD versus PD patients to assess the possible advantages of using a propensity score-adjustment approach.

METHODS

Patients

We included all incident patients who started RRT between January 1st 1987 (start of prospective registration) and December 31st 2002 from the Dutch End Stage Renal Disease Registry (RENINE). We excluded patients younger than 18 years, patients who underwent RRT for less than 30 days, patients who had more than one episode of recovery of renal function, or who died directly following a period of renal recovery, patients who received a pre-emptive transplantation, patients who died during the first 90 days of RRT and patients from centers treating fewer than 20 dialysis patients or fewer than 5 PD patients. The outcome of interest was all-cause mortality, as registered by RENINE. The registry collects information on date and cause of death and verifies its information yearly with all centers.[4,43] From registry data we also determined age and gender of patients, baseline dialysis modality, year of first dialysis, and the center at which dialysis was started. In the database, primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). After examining previously published disease categories and hazard rates in the Dutch registry, we aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM) and a category for all other renal diagnoses (PRD-OTH).

Analysis

We adopted an intention-to-treat perspective and, as is customary in previously published analyses, considered the dialysis modality on day 91 to be the definite modality. We left-censored survival time for the first 90 days and right-censored at first transplantation or December 31st 2002, whichever occurred first. To estimate the independent comparison between PD and HD mortality by controlling for observed potential confounders, we explored two analytical options: a propensity score-adjustment approach and the traditional multivariable-adjustment approach.

The propensity-score approach involved a two-step approach. First, we predicted PD versus HD treatment assignment by constructing a logistic regression model that estimated treatment assignment using all available variables, as well as age^2, age^3, and all possible 2-way interactions between the database-variables. As explained earlier, this model did not need to be parsimonious nor easy to understand, because it was not the focus of the study. The model calculated the expected probability or propensity score of each patient being assigned to PD, accounting for that individual's baseline characteristics. The propensity score was then evaluated for the following criteria: 1) a reasonable Nagelkerke's r^2- statistic as a measure of fit and a c-statistic between 0.65 and 0.85 as a measure of discriminative power, 2) good calibration as measured by the propensity score-predicted and observed proportion of PD patients within quintiles of the propensity score, and 3) balanced covariates within quintiles of the propensity score.[270] This third criterion is most important for assessing the appropriateness of the propensity score-model.[271] In the second-step, estimating the effect of treatment assignment on outcome adjusted for the propensity score, we stratified a Cox model containing dialysis modality as the only independent variable on intervals of 0.01 of the propensity score. Alternative techniques to adjust for the propensity score include matching or regression. However, regression is affected by measurement errors in the propensity score.[272] Furthermore, it assumes a linear relationship between the propensity score and the natural logarithm of the hazard. Matching or stratification techniques do not assume such a relationship, but matching entails exclusion of patients because of the unavailability of a match. Stratification on intervals of 0.01 closely resembles matching, but because the number of patients in either exposure group within a stratum may vary, only few patients will need to be excluded. In our analyses, ten strata not containing either HD or PD patients were excluded.

In the alternative multivariable-adjustment approach, the calculation of the relative mortality of PD patients compared to HD patients was conducted by entering observed characteristics as covariates into the survival regression model and thereby adjusting for potential confounders. The first step in this approach was to estimate univariable Cox proportional hazards models for all available variables. Age and year of start of dialysis were entered into the model as continuous variables and all other variables as categorical variables. All statistically significant variables ($P<0.05$) from the univariable analyses were introduced into a multivariable main-effects Cox proportional hazards model. From this multivariable model, we explored the significance of a quadratic term (age) and several two-way and three-way interaction terms. We tested for center effects by entering center as a categorical variable into the multivariable model. Finally, we compared the hazard ratios (HR) for mortality with PD versus HD from the propensity score-stratified and the multivariable-adjusted models.

RESULTS

The RENINE Registry prospectively collected data of 20,687 patients who started RRT between January 1st 1987 and December 31st 2002. We discarded 4,044 patients that did not meet inclusion criteria. As a result, our final sample included 16,643 patients from 47 centers. Mean age was 59 years (standard deviation, SD: 15.3) and 58.8% were male. Additional descriptive characteristics are shown in Table 1.

Propensity score analysis

The propensity score model containing age, age^2, age^3, all other variables and all possible two-way interactions had a Nagelkerke's r^2 of 0.240 and a c-statistic of 0.752. Leaving all non-significant variables out of the model did not alter these quality indicators substantially.

The propensity score in quintiles showed good calibration. The mean propensity scores (the probability of receiving PD) were 9.1%, 21.4% 32.9%, 46.3% and 64.6% for each quintile, respectively and were very similar to the actual proportions of patients on peritoneal dialysis in all quintiles (see Figure 1). Furthermore, the propensity score balanced the covariates between the HD and PD groups except for a slight (1.4 year) difference in age within the fifth quintile and in the starting year within the second and

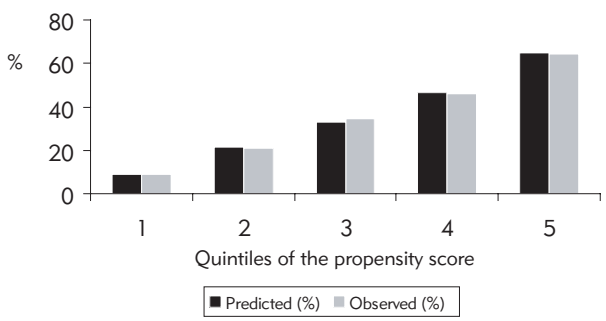
TABLE 1. Baseline characteristics of study cohort

	All patients	HD	PD	P-value
Number (%)	16,643	10,841 (65.1)	5,802 (34.9)	
Age (SD) (years)	59.0 (15.3)	61.8 (14.6)	53.6 (15.0)	<0.001
Female gender (%)	41.2	42.5	38.7	<0.001
Primary renal disease (%)				<0.001
GN	13.7	11.1	18.5	
HT	11.4	11.7	10.8	
RVD	8.7	9.8	6.6	
DM	15.2	14.9	16.0	
Other	51.0	52.5	48.1	
Year of first RRT (%)				<0.001
1987-1990	17.0	18.0	14.9	
1991-1994	23.5	23.2	24.0	
1995-1998	28.6	28.3	29.0	
1999-2002	31.0	30.5	32.0	
Years of follow-up (SD)	2.38 (2.14)	2.42 (2.24)	2.32 (1.95)	0.007

DM = diabetes mellitus, GN = glomerulonephritis, HD = hemodialysis, HT = hypertension, PD = peritoneal dialysis, RRT = renal replacement therapy, RVD = renovascular disease, SD = standard deviation

the fifth quintile (Table 2). Stratifying the univariable Cox model on 0.01 intervals of the propensity score yielded no difference in mortality risk between PD and HD patients (HR=0.97; 95% CI 0.92-1.03) (Table 3a).

FIGURE 1. Mean predicted and observed probability of peritoneal dialysis assignment per quintile of the propensity score



Predicted (%): probability of assignment to peritoneal dialysis as predicted by the propensity score; Observed (%): actual prevalence of peritoneal dialysis assignment.

TABLE 2. Baseline characteristics of study cohort, by quintile of propensity score

Quintile	1			2			3			4			5		
	HD	PD	P	HD	PD	P	HD	PD	P	HD	PD	P	HD	PD	P
n	3046	295		2643	691		2157	1127		1813	1548		1182	2141	
(%)	(91.2)	(8.8)		(79.3)	(20.7)		(65.7)	(34.3)		(53.9)	(46.1)		(35.6)	(64.4)	
Age (year)	72.5	72.2	0.66	65.0	65.7	0.16	59.0	58.6	0.38	52.7	52.5	0.19	46.6	45.2	0.003
Male gender (%)	49.0	50.2	0.71	58.2	58.5	0.90	62.8	62.6	0.92	61.0	61.0	0.98	63.0	63.1	0.95
Primary renal disease (%)			0.27			0.74			0.89			0.37			0.08
GN	7.4	4.4		7.3	6.1		11.1	11.4		12.3	14.5		27.3	31.2	
HT	11.2	12.9		12.4	11.7		12.1	11.8		13.0	12.9		8.8	8.2	
RVD	13.0	14.2		11.8	12.7		9.6	8.5		6.5	6.3		3.2	2.7	
DM	14.0	15.9		14.7	14.5		15.4	16.0		14.3	13.0		17.3	18.6	
Other	54.5	52.5		53.8	55.0		51.9	52.4		53.9	53.3		43.3	39.3	
Year of first RRT (%)			0.34			0.001			0.40			0.76			0.011
1987-1990	19.4	16.6		19.4	13.0		18.6	16.7		16.7	14.4		12.4	14.8	
1991-1994	24.1	27.1		24.3	27.5		24.2	26.3		22.1	25.1		18.0	20.6	
1995-1998	28.5	25.8		28.1	30.1		28.0	27.3		27.6	28.5		30.3	30.5	
1999-2002	28.0	30.5		28.2	29.4		29.2	29.7		33.6	32.0		39.3	34.1	

DM = diabetes mellitus, GN = glomerulonephritis, HD = hemodialysis, HT = hypertension, n = number of patients, P = P-value, PD = peritoneal dialysis, RRT = renal replacement therapy, RVD = renovascular disease, SD = standard deviation

TABLE 3a. Multivariable-adjusted and propensity score-stratified models without interaction variables

	Multivariable-adjusted model		Propensity score-stratified model	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Age (per year)	1.05	(1.05-1.05)	-	-
Female vs. male gender	0.89	(0.85-0.93)	-	-
Primary renal disease vs. GN*			-	-
HT	1.25	(1.13-1.38)	-	-
RVD	1.74	(1.57-1.92)	-	-
DM	2.24	(2.05-2.46)	-	-
Other	1.33	(1.22-1.44)	-	-
Year of first RRT (per year)	0.99	(0.98-1.00)	-	-
Dialysis center	0.13 – 1.61#		-	-
Peritoneal vs. hemodialysis	0.99	(0.94-1.05)	0.97	(0.92-1.03)

* Compared with GN as reference group.
# Range of HRs, we did not provide 95% CIs for center because of the large number of estimates.
DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, RVD = renovascular disease, RRT = renal replacement therapy, HR = hazard ratio

TABLE 3b. Multivariable-adjusted and propensity score-stratified models with interaction variables

	Multivariable-adjusted model		Propensity score-stratified model	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Age (per year)	1.05	(1.04-1.05)	1.05	(1.04-1.05)
Female vs. male gender	0.87	(0.83-0.91)	0.87	(0.83-0.91)
Primary renal disease vs. GN*			-	-
HT	1.22	(1.10-1.35)	-	-
RVD	1.68	(1.51-1.85)	-	-
DM	5.65	(3.95-8.09)	5.36	(3.73-7.70)
Other	1.31	(1.21-1.42)	-	-
Year of first RRT (per year)	0.99	(0.99-1.00)	-	-
Dialysis center	0.13 – 1.61#		-	-
Peritoneal vs. hemodialysis	0.43	(0.32-0.57)	0.44	(0.32-0.60)
Age x Dialysis modality	1.01	(1.01-1.02)	1.01	(1.01-1.02)
DM x Dialysis modality	1.22	(1.08-1.38)	1.23	(1.08-1.40)
Age x DM	0.98	(0.98-0.99)	0.98	(0.97-0.99)
Gender x DM	1.20	(1.07-1.34)	1.20	(1.07-1.35)

* Compared with GN as reference group.
# Range of HRs.
DM = diabetes mellitus, GN = glomerulonephritis, HT = hypertension, RVD = renovascular disease, RRT = renal replacement therapy, HR = hazard ratio

Multivariable regression analysis

In the unadjusted Cox model, patients receiving PD had a 30% lower mortality compared to HD patients (HR=0.70; 95% CI: 0.67-0.74; P<0.001). The coefficients of all other univariable models were also statistically significant (P-values ranging from <0.001 to 0.02), both in the overall population and in the HD and PD groups separately. The coefficient for the year of starting RRT was not significant in the total population, because with increasing year of start of RRT, the relative risk of dying increased for HD patients and decreased for PD patients.

In contrast to the univariable model, the multivariable Cox model, adjusted for main effects of age, gender, primary renal disease, year of first RRT and treatment center but without interaction terms revealed that mortality of PD patients and HD patients did not differ significantly (Table 3a). The HR of PD compared with HD patients was 0.99 (95% CI: 0.94-1.05), which did not differ from the relative risk estimated by the propensity score-stratified model (HR 0.97; 95% CI 0.92-1.03). However, the propensity score model involved only one covariate as opposed to nine in the multivariable Cox model.

Exploration of effect modification

The constructed Cox models did not consider the possibility of effect modifiers on outcome. When tested in the multivariable model, four interaction variables were statistically significant: two with modality (age by modality (HD or PD) and diabetes as the primary cause of renal disease (PRD-DM) by modality), and two other interaction variables (age by PRD-DM and gender by PRD-DM). After entering these interaction variables into both the propensity score-stratified and the multivariable-adjusted model (Table 3b), the hazard ratios of dialysis modality and all interaction variables with dialysis modality were statistically significant in both models. As before, the results from the propensity score-stratified and multivariable-adjusted models were essentially identical. The propensity score-stratified model, however, included almost the same number of variables as the multivariable-adjusted model. The only two additional variables in this multivariable-adjusted model were year of first RRT and dialysis center. Hazard ratios for the combinations of the interaction variables as estimated by the multivariable-adjusted model are presented in Table 4. They show a relative survival benefit of PD compared to HD that diminishes with increasing age and in the presence of diabetes.

Since the proportionality assumption was not satisfied, time-stratified analyses are presented. The clinical issues associated with these findings are discussed more in depth elsewhere.[61]

TABLE 4. Associations between dialysis modality and mortality

		Hazard ratios of peritoneal dialysis vs. hemodialysis (95% Confidence Intervals) *		
Age	**DM**	**>3-6 months**	**>6-15 months**	**>15 months**
40	No	0.26 (0.17-0.41)	0.51 (0.39-0.68)	0.86 (0.74-1.00)
40	Yes	0.40 (0.23-0.68)	0.59 (0.44-0.81)	1.06 (0.88-1.26)
50	No	0.35 (0.25-0.48)	0.62 (0.51-0.76)	0.95 (0.85-1.05)
50	Yes	0.53 (0.34-0.83)	0.72 (0.56-0.93)	1.17 (1.00-1.35)
60	No	0.46 (0.37-0.58)	0.75 (0.65-0.87)	1.05 (0.97-1.13)
60	Yes	0.71 (0.48-1.04)	0.87 (0.71-1.09)	1.29 (1.12-1.48)
70	No	0.62 (0.50-0.76)	0.92 (0.80-1.05)	1.16 (1.07-1.25)
70	Yes	0.95 (0.64-1.39)	1.07 (0.85-1.33)	1.42 (1.23-1.65)

* From models including age, gender, primary renal disease, year of start of RRT, center and the interaction terms age by modality, diabetes by modality, age by diabetes and gender by diabetes.
DM = diabetes as primary renal disease

DISCUSSION

In this study of patients who initiated chronic dialysis treatment between 1987 and 2002 in the Netherlands, we developed a propensity score that fulfilled accepted quality criteria: it showed a reasonable fit, had a good c-statistic, calibrated well and balanced the covariates. The Cox model that solely adjusted for propensity score yielded essentially identical effect estimates of PD versus HD mortality compared with the multivariable-adjusted model while having the advantage of being much more parsimonious. When excluding interaction terms, dialysis modality was not an independent predictor of mortality in either model, but both models were misspecified, because effect modification was present. After introducing both interaction terms and all corresponding main effect variables to account for effect modification, the propensity score-stratified model contained almost the same number of covariates as the multivariable-adjusted model. When the models included interaction variables, dialysis modality and its interaction variables became statistically significant. The identified effect modifiers, age and diabetes as primary renal disease, correspond to those found in previous studies.[18,49-51]

Our study informs the discussion of the utility of propensity score in outcomes research. In theory, the use of propensity score-stratified modeling may allow for a more straightforward estimation of the relative mortality risk in comparison with multivariable-adjusted modeling. However, our study shows that neglecting effect modification in propensity score-stratified models may lead to erroneous conclusions. Incorporating effect modification however removes the direct interpretability of the main treatment effect one wishes to estimate, thereby limiting the benefit of using a propensity score. Still, Sturmer and colleagues[273] suggest that the propensity score-adjustment approach may yet have an advantage over traditional methods when effect modification is present, because it allows for a summary effect size across all strata of the effect modifiers. This can be relevant in pharmacoepidemiology, to estimate how a total population might benefit from a particular drug. However, in the setting of end-stage renal disease, the assignment of a patient to a specific dialysis modality should be tailored to a patient's specific pretreatment characteristics and should not be determined by the summary effect size across all strata of the effect modifiers.

Other studies that compared propensity score-stratified versus multivariable-adjusted modeling have been reviewed by Shah and colleagues[268] and Sturmer and colleagues.[266] Similar to our findings, both studies concluded that propensity score-stratified modeling rarely led to a different result compared to multivariable-adjusted modeling. Choosing which method may depend on the quantity of data. Cepeda and colleagues[274] report from their simulation study that with eight or more outcomes per confounder, the multivariable-adjusted logistic regression model showed better precision. However, with fewer than eight events per confounder, propensity score-stratified modeling performed better. Furthermore, the choice also depends on the research question, as suggested by Kurth and colleagues.[275] They showed that when there is a non-uniform treatment effect, different adjustment methods can result in divergent results, which may all be correct but depend on the research question implied by the adjustment method.

For the propensity score-adjustment approach, there are no accepted rules for construction and evaluation of the propensity score model. It has been argued that the model to estimate the propensity score need not be parsimonious.[268] However, several authors reported that including variables related only to exposure into the propensity score did not influence bias or effect size, but did increase variance.[276,277] Hence, these studies recommend incorporating only true confounders and variables related to the outcome into the propensity score model to decrease variance without increasing bias. Evalu-

ation of a propensity score model often consists of assessing discrimination with the c-statistic and calibration with goodness-of-fit tests. However, Weitzen and colleagues[278] in their simulation study showed that neither the c-statistic nor the Hosmer-Lemeshow goodness-of-fit test was sensitive to omission of an important confounder from the propensity score model.

Failure to include important confounders can lead to biased estimates of the treatment effect.[276] Austin and colleagues[279] reported that propensity scores estimated on administrative data might not balance all clinical characteristics. This could be particularly relevant to our study, because the RENINE database is administrative and does not contain clinical data, in particular it lacks co-morbidity data. Information on primary renal diagnosis, however, is available and the most important co-morbid condition, diabetes, is likely well-represented among patients with PRD-DM. Further, Weitzen and colleagues[278] report that omitting a confounder in a propensity model has little effect on the treatment effect estimate. This could imply that the propensity score is fairly robust to unobserved confounders if, as also reported by Rosenbaum,[41] at least some of the key variables that explain treatment assignment are included in the score. Moreover, omitting a confounder also leads to biased estimates when using a multivariable-adjusted model.

To summarize: if propensity score models are constructed well and no important confounders are missing, a treatment effect with a reliable significance level can usually be estimated, with the advantage of a more parsimonious outcome model and the advantage of assessing covariate balance between treatment groups explicitly. When the outcome is rare, propensity score-adjustment yields effect size estimates with a higher precision. Reviews of studies applying propensity score-adjustment methods have shown however, that propensity score-stratified modeling was often not implemented or reported appropriately.[266,268,272] Researchers should carefully assess whether propensity score-adjustment methods are appropriate for their specific situation.

From our study, we conclude that although the propensity score performed well, it did not alter the treatment effect in the outcome model and lost its advantage of parsimony because effect modification was present. Thus, using a model of mortality of patients on renal replacement therapy as a special case study, our study contributes to the growing literature supporting the comparability of traditional multivariable regression and propensity score methods unless sample size is small and outcome is rare.

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6
General discussion

We presented studies into the long-term outcome of renal dialysis and renal transplantation (RTx) patients in the Netherlands, consisting of both patient-level survival studies and study-level literature reviews. We integrated these studies into a decision analytic model and assessed the impact of early transplantation on the life expectancy and quality-adjusted life expectancy of a patient starting renal replacement therapy (RRT).

In this final chapter, we will summarize and discuss the main findings of our studies. We structured this discussion according to three groups of RRT: renal dialysis, cadaveric transplantation and living-donor transplantation. Subsequently, we will highlight some limitations and methodological issues and we will conclude with suggestions for further research.

RENAL DIALYSIS

For renal dialysis patients we estimated mortality in three separate studies. Firstly, we studied all patients who initiated chronic dialysis treatment between 1987 and 2002 in the Netherlands, using data from the Dutch End Stage Renal Disease Registry (RENINE). We aimed to assess whether hemodialysis (HD) and peritoneal dialysis (PD) patients have a significantly different mortality (chapter 2.1). With a multivariable Cox regression model, adjusted for age, gender, primary renal disease and dialysis center, we showed that the hazard ratio (HR) was not constant, but increased in favor of hemodialysis, with longer dialysis duration, advancing age and in patients whose primary renal disease was diabetes mellitus (PRD-DM). From the cumulative survival curves based on the Cox model we assessed overall survival. For non-PRD-DM patients, RRT initiation with PD was associated with a comparable or better overall survival compared with HD, whereas among PRD-DM patients, RRT initiation with PD was associated with a comparable or worse survival.

Our findings confirmed the existing literature on the decrease in relative survival of PD patients as compared with HD patients over time.[19-22,44] Explanations for the initial survival advantage of PD patients in our study might be explained by HD patients having more co-morbidity at the initiation of dialysis therapy;[18] however several studies corrected for this difference and found a similar time-trend.[19-22] Another explanation might be that initially, a higher dose of dialysis is delivered to PD patients, though it was also reported that initial delivered dose was not as different for HD and PD patients

as had generally been believed.[19] Finally, it has been suggested that the short-term survival advantage of PD patients might be explained by better preservation of residual renal function in patients treated with PD as compared with patients treated with HD.[45] Residual renal function has shown to be an independent predictor for both HD[46] and PD[280] patients. The finding from our study that the HR of PD compared with HD patients increased with age and in the presence of PRD-DM had also been described previously,[18,49-51] although Keshaviah and colleagues[52] reported a similar 2-year survival for HD and PD patients, irrespective of age and PRD-DM. The fact that this study corrected for dialysis dose, whereas our study and the other studies did not, might explain these contrasting findings. It has indeed been suggested that diabetic patients require a higher delivered dialysis dose.[281] Other factors have been reported to be associated with dialysis modality selection, such as a nephrologist's preference, the reimbursement system in a specific country;[57,282] and to influence dialysis mortality, such as ethnicity[19,53] and nutritional markers.[53-55]

Secondly, we studied the value of propensity scores, an alternative method to correct regression analyses for confounding,[41] in comparison with traditional multivariable modeling in the same sample of dialysis patients (chapter 5.1). We developed a propensity score that fulfilled the accepted quality criteria: it showed a reasonable fit, had a good c-statistic, calibrated well and balanced the covariates. The Cox model that solely adjusted for propensity score yielded essentially identical effect estimates of PD versus HD mortality compared with the multivariable-adjusted model while having the advantage of being much more parsimonious. However, after introducing both interaction terms and all corresponding main effect variables to account for effect modification, the propensity score-stratified model contained almost the same number of covariates as the multivariable-adjusted model.

We showed that, although in theory the use of propensity score-stratified modeling may allow for a more straightforward estimation of the relative mortality risk in comparison with multivariable-adjusted modeling, when effect modification is present, this benefit is limited. Sturmer and colleagues[273] suggested that the propensity score-adjustment approach may have an advantage over traditional methods when effect modification is present, because it allows for a summary effect size across all strata of the effect modifiers. This may be of relevance in pharmaco-epidemiology, when estimating how a total population might benefit from a particular drug. However in the setting of end-stage renal disease (ESRD), the assignment of a patient

to a specific dialysis modality should be tailored to a patient's specific pre-treatment characteristics and should not be determined by the summary effect size across all strata of the effect modifiers. In their reviews of other studies that compared propensity score-stratified versus multivariable-adjusted modeling, Shah and Sturmer concluded that propensity score-stratified modeling rarely led to a different result compared with multivariable-adjusted modeling.[266,268] The choice of method may depend on the quantity of data. Cepeda and colleagues[274] report from their simulation study that with eight or more outcomes per confounder, the multivariable-adjusted logistic regression model showed better precision and with fewer than eight, the propensity score-stratified model performed better.

Lastly, for a sample of patients in RENINE that had initiated renal dialysis between 1998 and 2006, waitlisting data from the Dutch Organ Transplant Registry (NOTR) was made available, enabling us to adjust mortality in dialysis patients for waitlist status (chapter 2.2). We confirmed that mortality in dialysis patients was strongly associated with being transplantable on the wait list. This association was strongest in the first few years of dialysis (>70% lower mortality during the first year of RRT) and disappeared after 5 years of dialysis treatment. Similar to our analyses in chapter 2.1, the difference in HD vs. PD mortality was also modified by PRD-DM, but not by age.

A substantially lower mortality for waitlisted patients has been reported from several other studies. In a Canadian population, crude mortality of non-waitlisted patients was estimated to be 4-fold higher than that of waitlisted patients.[30] Wolfe and colleagues[25] reported from a U.S. Renal Data System (USRDS) data sample of 228,552 patients that patients on dialysis that were waitlisted for transplantation had a substantially higher likelihood of survival. Their mortality was approximately 50% lower compared with all patients on dialysis for all subgroups by age, gender, ethnicity and cause of ESRD. This mortality risk reduction falls within the range of values we found for several time-strata. What had not been reported previously was our finding that this survival advantage of waitlisted patients diminished over time and was no longer present after 5 years of RRT.

CADAVERIC RENAL TRANSPLANTATION

In chapter 2.2, we studied predictors of waitlisting for and access to cadaveric RTx. We found that waitlisting was significantly associated with age, primary renal disease, dialysis modality, year of start of dialysis and dialysis center. Among waitlisted patients, only primary renal disease and center of dialysis were significant predictors of access to RTx. The fact that there were less predictors of access to cadaveric RTx in the waitlisted population compared with the predictors of waitlisting in the total dialysis population indicates that the waitlisting procedure selects more comparable patients for access to RTx. This phenomenon has also been described by Oniscu and colleagues[62] from data from the Scottish Renal Registry.

However, access to RTx was not equal among those that are waitlisted. We found that patients with PRD-DM had a higher probability of transplantation within the first 3 years of waitlisting (univariate HR: 2.22, 95% CI 1.55 – 3.19) and access differed significantly by dialysis center. After 3 years, primary disease was not associated with the access to RTx. The finding that patients with PRD-DM had a higher likelihood of RTx once waitlisted has not been reported in earlier studies. Others studies reported a similar access for patients with PRD-GN and PRD-DM.[62,64] A possible explanation for our findings could be that the difference in prognosis between waitlisted and non-waitlisted patients is larger for PRD-DM patients than for the other types of primary disease. Dialysis patients with PRD-DM that do get waitlisted may have such a good prognosis that they are more likely to get transplanted.

Other variables associated with higher rates of waitlisting and RTx have been reported in addition to those we found. These include socio-demographic variables such as male gender,[60,62,64,70] Caucasian ethincity,[60,64,65] a better insurance policy;[60] and clinical variables such as a lower BMI,[58,60] and absence of co-morbid conditions.[23,60,66]

LIVING-DONOR RENAL TRANSPLANTATION

We performed several studies in the field of living-donor transplantation, both relating to the donor and to the recipient. For the donor, we estimated the optimal imaging strategy of the kidney and its vessels for the pre-operative work-up (chapter 4.1) and we assessed the return to work after donor nephrectomy (chapter 2.3). With a simulation

model, we quantified the benefit of early living-donor transplantation for a potential recipient, compared with dialysis and possible cadaveric transplantation (chapter 4.2).

Living donor: imaging

The objective of our study described in chapter 4.1 was to identify the optimal strategy for the pre-operative evaluation of living-related potential renal donors. Based on a decision- and cost-effectiveness analysis, we concluded that from the perspective of the donor magnetic resonance (MR) angiography would be the optimal strategy whereas from the combined perspective of donor and recipient, digital subtraction angiography (DSA) would be the optimal strategy. If, however, specificity of DSA for detecting renal disease would be 99% or lower, a combination of MR angiography and computed tomographic (CT) angiography would be most cost-effective from the combined perspective.

After we performed our study, imaging techniques and their evaluation continued to develop. We assumed a 100% sensitivity and specificity for DSA. However, it was reported recently that DSA had a sensitivity of 97% compared with intra-operative findings.[283] In the same study, the accuracy of MR angiography was reported to be 90%,[283] a higher estimate than the mean estimate from the studies we found. However, these values for DSA and MR angiography accuracy were within the ranges of the sensitivity analyses we performed and our results have shown to be robust to these sensitivity analyses. The accuracy estimates for CT angiography were based solely on studies using single-detector spiral CT equipment and one might argue that with multi-detector spiral CT-scanning, a higher diagnostic performance of CT angiography could be reached, making CT angiography more likely to be a cost-effective option. Furthermore, it has been reported that several branches of the renal vein which were poorly visualised by MR angiography, may be better visualised with CT angiography.[284] Even so, the harmful effects of radiation exposure and contrast allergy and nephropathy remain important drawbacks of CT angiography.

Living donors: return to work

A long convalescence period and absence from work may be important disincentives to a potential living donor. As the laparoscopic nephrectomy (LDN) or the hand-assisted nephrectomy (HA) is less invasive than an open donor nephrectomy (ODN), we

aimed to investigate whether the type of surgical technique is associated with duration of convalescence (chapter 2.3). We showed that there was a large variability in return to work but on average, donors resumed work significantly earlier after LDN (6 weeks) than after HA (10 weeks) or ODN (12 weeks).

Several studies showed a reduced discomfort and convalescence for the donor after both LDN and HA donor nephrectomy.[75,82] This may be explained by the similarity of the locations of the incision for LDN and HA and the small difference in size of the incision (2-3 cm). Therefore, the significant discrepancy between return to work after LDN and HA in our study was unexpected. It was most likely caused by the difference in advice on expected duration of sick-leave which was similar for HA and ODN donors (3 months) and shorter for LDN donors (6 weeks). A more recent study from our center showed a slightly longer convalescence period after LDN (55 days)[285] compared with our study. In this recent study, ODN donors returned to work after 58 days which was comparable to LDN donors' return to work. However, this study was performed after the introduction of a different surgical technique, a mini-incision open donor nephrectomy, which is associated with a better preservation of the abdominal wall integrity and has shown to be a safe approach which reduces hospital stay in comparison with the previously used open technique.[286]

Recipients of a living-donor transplant: benefit of early transplantation

In chapter 4.2, we explored the benefit of early living-donor transplantation compared with dialysis and possible cadaveric transplantation for a patient that is starting RRT. From our analyses, we conclude that early transplantation resulted in a considerable survival benefit compared with dialysis and that this benefit decreased with age. The survival benefit in terms of quality-adjusted life years (QALYs) showed a similar pattern. Increasing the early transplantation rate of 5.8% to the highest rate in Europe of 22.2% reported by the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) would result in an average increase in life expectancy (LE) of 1.2 life years (LYs) and an annual total population increase of over 1,800 LYs for an incident Dutch RRT cohort.

We compared our results with the survival for incident RRT patients reported in the literature for incident waitlisted dialysis patients. Inrig and colleagues[259] reported a 2-year survival of 93.3% for PD and 93.2% for HD patients (average age 47 years) in

the United States. The 2-year survival estimates from our *Dialysis* strategy for 40- and 50-yr-old patients, were on average 95.8% and 92.5% respectively, suggesting good external validity of our model. A study in a Swedish population by Medin and colleagues,[29] however, showed a 5-year survival of 60% for waitlisted patients (average age 49-years old at waitlisting). The 5-year survival estimate from our *Dialysis* strategy for 50-yr-old patients was on average 80.5%. This discrepancy might be explained by differences in case-mix. The patients included in the study by Medin had started dialysis in earlier years (1987-1996), a lower percentage was treated with PD, and there was a lower proportion of females, which could all have contributed to a lower survival. In addition, Medin and colleagues analyzed patients from the moment of waitlisting and not from the start of dialysis as we did. Lastly, if our dialysis survival estimates were more similar to those of Medin's, then the estimated benefit from transplantation would be even larger, making our results conservative.

The most important advantage of our study lies in the comparison of strategies from the initiation of RRT. Therefore no lead-time bias occurred, which would have been present in a study comparing the survival of post-dialysis cadaveric RTx and pre-emptive living-donor RTx or in a study comparing the survival of waitlisted dialysis patients and cadaveric RTx patients. In this study, we did not incorporate the perspective of the donor. The reason was that detailed information on long-term consequences, as we had available for the recipient, is lacking for the living donor.[263] Furthermore, combining the perspectives of donor and recipient is not straightforward, since it raises issues of equity and efficiency, which we will discuss in the section on limitations of our studies.

QUALITY OF LIFE OF PATIENTS ON RENAL REPLACEMENT THERAPY

The meta-analyses of quality of life (QoL) of patients on RRT (chapter 3.1 and chapter 3.2) showed that QoL differs across the different forms of RRT, most prominently between RTx and dialysis patients. Although time trade-off-scores of RTx patients were not significantly higher than those of dialysis patients, there was a significant difference between Euro Qol-5D values for RTx vs. dialysis patients. QoL as measured by the The Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) was also significantly higher among RTx patients than among dialysis patients, except for the Mental Health-dimension. SF-36 and utility scores among HD patients compared with PD patients were not statistically significantly different.

The finding of relatively more statistically significant differences between RTx and dialysis patients in our study of SF-36 scores may be explained by the higher number of studies found, rendering more statistical power to find a difference. Other explanations could be a larger variability in patient population or in elicitation techniques among the utility-studies or a lower sensitivity to treatment changes for utility measures. However, we did not find any evidence in support of these hypotheses. Meta-regression analyses of SF-36 studies revealed that some of the differences in scores between RTx recipients and dialysis patients could be partly explained by differences in age and in the presence of diabetes between these treatment groups. These findings were also supported by several studies which showed that correcting SF-36 scores for variables such as age, gender, education and clinical characteristics decreased the number and magnitude of differences in QoL among RRT patients.[124,147] Studies that compared utilities of RTx and dialysis patients described a higher QoL for RTx patients, even when correcting for similar factors.[151,153] This discrepancy suggests a different impact of factors that determine quality of life on either health-profile or preference-based measures. Methodological issues in quality of life measurement will be discussed below.

LIMITATIONS AND METHODOLOGICAL ISSUES

A general limitation of our studies on registry data is the lack of detailed, clinical information. The RENINE does not include clinical data. Ideally, we would have wanted to correct for all variables that have been reported to influence dialysis modality selection, waitlisting for and access to RTx and mortality associated with the different forms of RRT, which were discussed previously. Of these predictors, co-morbidity might be of greatest significance. Diabetes mellitus is an important co-morbid condition that determines mortality. From the registry we were able to identify those patients with diabetes mellitus as underlying disease and the presence of diabetes as primary disease and as co-morbid condition are likely to correlate strongly. Furthermore, Van Manen and colleagues[287] showed in their survival analyses of HD, PD, and RTx patients from five registries within ERA-EDTA, that after adjustment for age, gender, primary renal disease, treatment modality, and country, the influence of co-morbidity was less important than expected.

An important issue in meta-analysis is that it always relies on completeness of available published literature and thus is known to be influenced by publication bias. However, our meta-analyses were of mostly non-comparative studies, therefore, the effect of publication bias can be assumed to be very small. The number of studies reporting QoL – especially utility-values – of RRT patients was too limited to perform meta-regression analyses to adjust for all possible case-mix differences that might influence QoL. Many demographic (age, gender, ethnicity, socio-economic status) and disease-associated factors (PRD, treatment history, anemia and co-morbidity) are known to be associated with QoL.[148] Unfortunately, these covariates were not consistently published in the studies. But even if more studies reporting all these covariates had been available, it would still have been important to pre-specify covariates to avoid data dredging.[97] Since we did not have utilities available for different subgroups of patients defined by those covariates, we had to use the mean utility for the overall group for our decision-analytic model in chapter 4.2.

Although it is generally accepted that quality of life is an important parameter in economic analyses, the operationalization of the concept is still under debate. As has already been described in the eighties by Mulley, there are many pitfalls in QoL assessment, such as the decline of QoL with increasing age and the response shift during disease progression in chronic diseases.[185] Another issue is the choice of measurement method; whether to use a health-profile or a preference-based measure. The Panel on Cost-effectiveness in Health and Medicine recommended the use of methods that allow patients' values of health profiles to be converted into utilities using a tariff based on utilities of the general public for the health profiles.[184] Examples of such methods include the EQ-5D-index and the health utilities index.

A specific problem concerning QoL in our study was the weighting of QALYs of two subjects, in this case donor and recipient. According to utility-theory, applied in the context of cost-effectiveness analysis of health care, all QALYs are equal, irrespective of who benefits from the gained QALYs.[184] In our imaging study, we thus valued a QALY of a donor equal to a QALY of the recipient. It may, however, be argued, that a QALY of the donor should be weighted more heavily than a QALY of the recipient, considering that 'losses loom larger than gains',[243] as the donor gives up QALYs for the benefit of the recipient. Aside from weighting these QALYs, other aspects that affect QoL such as the effect of losing the living donor due to surgical complications or altruistic motives of the donor should be taken into account. However, these aspects are difficult, if not

impossible, to quantify. Notwithstanding these limitations in the use of QoL measures, the importance of incorporation of QoL into the evaluation of outcomes is generally recognized. New techniques are still being developed in the field of QoL assessment, such as methods to correct for biases in utility measurement[288] and to incorporate equity issues into the QALY-model.[289]

We presented two decision-analytic models. The model for assessing the optimal imaging strategy for a living donor was a Markov cohort model, based mostly on literature data. To account for the uncertainty in the results of this model, we performed 1- and 2-way sensitivity analyses to assess the effect of varying the parameters over plausible ranges on the outcomes of the model. Recently, it has been recognized that a probabilistic sensitivity analysis (PSA) should be performed to address uncertainty.[290] Because in PSA, distributions around all parameters are incorporated in the model rather than point estimates, the results reflect the effect of the combined uncertainty in all these parameters.[291] In addition, it allows for accurate estimation of the outcome of a nonlinear model.[290] Therefore, in our later – patient-level-data – model assessing the effect of early living-donor transplantation, we used PSA.

Decision analytic modeling is subject to certain general limitations and assumptions. Often, the extensiveness of the models requires the use of information from multiple data sources, as illustrated by both our modeling studies. Even though many sources are available, usually some data are lacking, necessitating expert opinion in making assumptions in the model. However, the significance of the assumptions can be tested in sensitivity analyses, as described above. The results of these analyses provide the decision makers, both doctors and patients, with information about the uncertainty around the outcomes associated with the options under consideration and therefore enable them to make informed choices.

Our studies on outcome in terms of survival and quality of life have mainly highlighted the benefits of RTx. Naturally, negative consequences of RTx should be taken into account as well, most notably the need for life-long immunosuppressive therapy. Immunosuppressive therapy is associated with cardiovascular risk factors, an increased risk of infections, and importantly, an increased risk of malignancies. Recently, it was reported that RTx patients do not only have an increased risk to develop non-melanoma skin cancers, Kaposi's sarcoma and non-Hodgkin's lymphoma, but also cancers of the oral cavity, and the respiratory, digestive, and genitourinary tracts.[292] In our models, these

consequences are not explicitly taken into account, but are modeled implicitly through their effect on QoL and survival. The negative effects of these cancers, which occur in a relatively small proportion of RTx patients, are off-set by the enormous gain in QoL and survival, as exemplified by our calculations in chapter 4.2.

DIRECTIONS FOR FUTURE RESEARCH

A remarkable finding from our analyses on the RENINE database was the importance of center as a predictor of mortality of RRT patients, and of waitlisting for and access to RTx. A possible explanation of this center effect would be that patients with similar prognostic factors tend to cluster within centers. Worse prognostic factors could lead to increased mortality, a lower probability of waitlisting and a lower access to RTx. Furthermore, it has been suggested that center characteristics, size, organizational aspects and attitudes of health care staff towards transplantation may be of influence.[62] Although some of these factors mediating the center effect cannot be modified, factors such as organizational aspects and attitudes could be acted upon. Knowledge of these factors is essential in the development of practice guidelines in order to optimize care for RRT patients.

We estimated a large gain in LE of increasing the early living-donor transplantation rate. However, how to achieve a higher early transplantation rate remains a challenge. Previous research suggested early transplantation was underutilized due to a delay of referral to a nephrologist.[261] More awareness of the importance of early diagnosis of renal disease and benefits of early referral to a nephrologist is imminent, also because it has been shown to be associated with a lower dialysis mortality,[262] and with better access to the wait list and to cadaveric transplantation.[24] Furthermore, it has been shown that recipients have difficulties, raising the possibility of living-donor transplantation with their family and friends.[293] Future research should focus on how health-care professionals can help in the communication between patients and their potential living donors. If a donor is available, the diagnostic work-up should be as accurate and non-invasive as possible to reduce the possibility of harms and the burden to the donor. The currently available imaging modalities still have their drawbacks: DSA is accurate but invasive, venous imaging with DSA is cumbersome, it requires iodine-containing contrast material and exposes the subject to radiation. MR angiography is non-invasive but cannot be performed in potential living donors with claustrophobia and is unsuitable

to depict fibromuscular dysplasia (FMD)[194] and certain lumbar renal vein branches.[284] CTA is accurate, but may also be unable to depict FMD[294] and – similarly to DSA – exposes the subject to iodine-containing contrast material and radiation. Therefore, new developments in imaging are warranted. Similarly, the continuing development of new surgical techniques to improve safety and reduce burden of donor nephrectomy is of great importance.

Several extensions of our model would be worthwhile to explore. First of all, it would be informative to add cost-data to the patient-level data model in order to assess the cost-effectiveness of early transplantation. Dutch cost-estimates are available for both dialysis[295] and transplantation,[296] however since dialysis cost-data were collected and calculated in 1994, an updated calculation would be required. Secondly, the model could be extended with pre-RRT information on the progression of chronic renal disease. Such an extension would allow for assessment of other interventions, such as preventive measures or timing of early transplantation.

As mentioned in our limitations, we would have wanted to include more demographical and clinical data in our analyses. It would be preferable to collect such data on a national scale, because this would allow for generalization of outcomes to the entire Dutch ESRD population. Fortunately, RENINE is planning to include more information in its registry. It is important to assess how this data-collection can be established with a minimal burden to the nephrologists. If more data becomes available, modeling of outcome of patients on RRT can be refined, which will hopefully contribute to the care for and outcome of this patient population.

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Summary / Samenvatting

SUMMARY

The incidence of end-stage renal disease is increasing and therefore, the number of patients requiring renal replacement therapy (RRT), renal dialysis or renal transplantation (RTx), has been rising. The various forms of RRT are associated with differences in survival and quality of life. Knowledge of long-term outcomes of these patients is imperative to the optimal implementation of treatment modalities and care for this patient population.

Chapter 1 provides an overview of what is known about these long-term outcomes and additionally, introduces the methodological concepts that were implemented in our studies. In this thesis, we describe patient-level studies on clinical outcomes of patients on RRT and literature studies on their quality of life. We integrate these studies into decision analytic models, which are reported in two papers. We conclude this thesis with a methodological paper on the analysis of observational databases.

Clinical outcomes in renal replacement therapy: patiens and donors

In **chapter 2.1**, we compare the survival of patients initiating RRT with either hemodialysis (HD) or peritoneal dialysis (PD) in the Netherlands. We show that there is an initial survival advantage for PD patients compared with HD patients. However, with increasing time on renal dialysis, with advancing age, and in the presence of diabetes as primary disease, this relative survival advantage vanishes, and even reverses.

We report in **chapter 2.2** that dialysis patients selected to be waitlisted for a cadaveric RTx are younger, more likely to have glomerulonephritis as primary renal disease, are more often treated with PD, and are more likely to have started dialysis in earlier years in comparison with non-waitlisted patients. In addition, the dialysis center in which patients are being treated is an independent predictor of being waitlisted. Furthermore, we confirm with our analyses that patients on the wait list have a better survival than those who are not on the wait list. What had not been reported previously is our finding that this survival advantage of waitlisted patients diminishes over time and is no longer present after 5 years of RRT. Among waitlisted patients, access to cadaveric RTx is significantly predicted by primary renal disease within the first 3 years of dialysis treatment and by dialysis center.

In **chapter 2.3**, we describe return to work for living renal donors after their surgery, comparing three different surgical techniques. We show that donors were able to return to work on average 6 weeks after laparoscopic donor nephrectomy. This is significantly shorter than the time needed for recovery after open donor nephrectomy and hand-assisted nephrectomy, after which donors could return to work after 12 and 10 weeks respectively. This study also shows that the physician's approach and his or her advice to the donor regarding the moment of resumption of work largely influences the convalescence period.

Quality of life of patients on renal replacement therapy

The meta-analysis reported in **chapter 3.1** corroborates the consensus that health-related quality of life differs across the different forms of RRT. In this chapter we summarize and compare the literature on quality of life as measured by the Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) for patients treated with dialysis and RTx. Except for the Mental Health-dimension, health-related quality of life as measured by the SF-36 is higher among transplanted patients than among dialysis patients. However, meta-regression analyses revealed that some of the differences in scores between dialysis patients and RTx recipients can be partly explained by differences in age and presence of diabetes between these treatment groups. SF-36 scores among HD patients compared with PD patients are not statistically significantly different.

In **chapter 3.2**, we summarize and compare utility-values of patients on RRT in a meta-analysis. A utility is a single index value expressed on a ratio scale with length of life as the metric for measuring the subject's preference for the quality of life in a given health state. Comparisons of utilities of the alternative forms of RRT resulted in mostly non-significant differences, although quality of life tends to be highest for RTx and lowest for HD patients. For the EuroQol EQ-5D utilities, RTx patients do have a significantly higher quality of life than dialysis patients. There is no statistically significant difference in utilities between HD and PD patients, although when measured with the time trade-off, PD patients tend to have a higher quality of life than HD patients.

Decision analytic studies in renal replacement therapy: patiens and donors

We performed a decision- and cost-effectiveness analysis to assess the optimal imaging strategy for potential living renal donors (**chapter 4.1**). We show that from the perspective of the donor, magnetic resonance (MR) angiography is the most cost-effective strategy, whereas from the combined perspective of donor and recipient, digital subtraction angiography (DSA) is the most cost-effective strategy. If, however, specificity of DSA for the detection of renal disease in the donor would be 99% or less, a combination of MR angiography with computed tomographic (CT) angiography would be most cost-effective from the combined perspective of donor and recipient.

In **chapter 4.2**, we compare survival of patients commencing RRT with an early living-donor RTx with survival of those starting on dialysis and being listed for a cadaveric donor organ. We report substantial survival benefits in terms of life expectancy and quality-adjusted life expectancy for early living-donor transplantation. This benefit decreases with advancing age; therefore, efforts to increase the rate of early transplantation should particularly focus on younger patients. Increasing the rate of early transplantation among patients initiating RRT from 5.8% to 22.2% is estimated to yield a gain in life expectancy for an average patient of 1.2 life years (LYs), amounting to a gain of over 1,800 LYs for an annual cohort of 1,565 patients commencing RRT in the Netherlands. Therefore, increasing early transplantation rates may considerably improve life expectancy of RRT patients.

Methodological issues in the analysis of observational databases

In **chapter 5.1**, we describe a propensity score that estimated the likelihood of treatment assignment (HD or PD) for patients on RRT. Propensity scores are used to balance confounders among treatment groups, in order to accomplish pseudo-randomization. The propensity score we constructed balanced the confounders among the treatment groups; however, it did not alter the treatment effect in the outcome model estimating mortality. Furthermore, the propensity score lost its advantage of parsimony in comparison with multivariable modeling because effect modification was present. Thus, using a model of mortality of patients on RRT as a special case study, we show that traditional multivariable regression and propensity score methods may offer similar results.

An overview of our findings, the general study limitations and methodological issues and directions for future research are discussed in **chapter 6**.

SAMENVATTING

De incidentie van eindstadium nierziekte stijgt en daarom neemt het aantal patiënten toe dat nierfunctievervangende therapie behoeft in de vorm van nierdialyse of niertransplantatie (NTx). De vormen van nierfunctievervangende therapie zijn geassocieerd met verschillen in overleving en kwaliteit van leven. Kennis van deze lange-termijn uitkomsten van patiënten met eindstadium nierziekte is van belang voor een optimale implementatie van de behandelingsmodaliteiten en voor de zorg voor deze patiëntenpopulatie.

Hoofdstuk 1 biedt een overzicht van de stand van zaken wat betreft deze lange-termijn uitkomsten en daarnaast introduceert het de methodologische concepten die zijn toegepast in onze studies. Vervolgens beschrijven we in dit proefschrift klinische studies naar patiëntuitkomsten en literatuurstudies naar kwaliteit van leven van patiënten met nierfunctievervangende therapie. We hebben deze studies geïntegreerd in besliskundige modellen die we rapporteren in twee artikelen en sluiten het proefschrift af met een methodologisch artikel over de analyse van observationele databases.

Klinische uitkomsten in nierfunctievervangende therapie: patiënten en donoren

In **hoofdstuk 2.1** beschrijven we het verschil in overleving tussen patiënten die nierfunctievervangende therapie startten met hemodialyse (HD) of peritoneaal dialyse (PD) in Nederland. We laten een overlevingsvoordeel voor PD patiënten, vergeleken met HD patiënten zien. Na verloop van tijd op nierdialyse, met stijgende leeftijd en bij patiënten met diabetes mellitus als primaire nierziekte, verdwijnt dit relatieve overlevingsvoordeel en draait het zelfs om, in het voordeel van HD patiënten.

We rapporteren in **hoofdstuk 2.2** dat patiënten die op de wachtlijst worden geplaatst voor een niertransplantaat (NTx) van een overleden donor jonger zijn, vaker glomerulonefritis als primaire nierziekte hebben, vaker worden behandeld met PD en dialyse zijn gestart in eerdere kalenderjaren, in vergelijking tot patiënten die niet op de wachtlijst komen. Daarnaast is dialyse centrum een onafhankelijke predictor voor wachtlijstplaatsing. Ook bevestigden we met onze analyses dat dialysepatiënten op de wachtlijst een betere overleving hebben dan patiënten die niet op de wachtlijst staan. Wat nog niet eerder werd beschreven, is onze bevinding dat dit overlevingsvoordeel van wachtlijstpatiënten vermindert over de tijd en niet meer aanwezig is na 5 jaar van nierfunctie-

vervangende therapie. Onder patiënten op de wachtlijst zijn primaire nierziekte (in de eerste 3 jaar van dialysebehandeling) en dialyse centrum significante onafhankelijke voorspellers voor het krijgen van een niertransplantaat via de wachtlijst.

In **hoofdstuk 2.3** beschrijven we de terugkeer in het arbeidsproces na operatie voor levende nierdonoren en vergelijken daarbij drie verschillende chirurgische technieken. We laten zien dat levende donoren die laparoscopisch waren behandeld na 6 weken terugkeerden naar hun werkzaamheden. Dit is significant korter dan na een open operatie of na een handgeassisteerde operatie, waarbij terugkeer plaatsvond na respectievelijk 12 en 10 weken. Deze studie laat ook zien dat de het advies van de arts aan de donor over de te verwachten terugkeer naar het arbeidsproces van grote invloed is op de daadwerkelijke herstelperiode.

Kwaliteit van leven van patiënten met nierfunctievervangende therapie

De meta-analyse in **hoofdstuk 3.1** bevestigt de consensus dat gezondheidsgerelateerde kwaliteit van leven verschilt voor de verschillende vormen van nierfunctievervangende therapie. In dit hoofdstuk hebben we de literatuur over kwaliteit van leven, gemeten met de Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) samengevat en vergeleken voor dialyse en NTx patiënten. Kwaliteit van leven gemeten met de SF-36 is hoger onder NTx dan onder dialyse patiënten, met uitzondering van de Mentale Gezondheid subschaal. Echter, metaregressie analyses toonden aan dat een deel van de verschillen in SF-36 scores tussen dialyse en NTx patiënten verklaard kan worden door verschillen in leeftijd en het voorkomen van diabetes mellitus tussen deze patiëntengroepen. SF-36 scores van HD en PD patiënten zijn niet significant verschillend.

In **hoofdstuk 3.2** hebben we utiliteit-waarden samengevat en vergeleken voor patiënten die worden behandeld met nierfunctievervangende therapie door middel van een meta-analyse. Een utiliteit geeft de patiëntwaardering van een bepaalde gezondheidstoestand weer, uitgedrukt als een ratio ten opzichte van de te verwachten levensduur. Vergelijking van utiliteiten voor de verschillende vormen van nierfunctievervangende therapie resulteerde in veelal non-significante verschillen, hoewel kwaliteit van leven het hoogst leek te zijn voor NTx patiënten en het laagst voor HD patiënten. Voor de EuroQol EQ-5D utiliteiten hadden NTx patiënten wel een significant hogere waarde dan dialyse patiënten. Er waren geen significante verschillen in utiliteiten tussen HD en

PD patiënten; echter gemeten met de time trade-off, leken PD patiënten een hogere kwaliteit van leven te hebben dan HD patiënten.

Besliskundige studies naar interventies in nierfunctievervangende therapie: patiënten en donoren

We verrichtten een besliskundige en kosteneffectiviteitanalyse ter bepaling van de optimale strategie voor de afbeelding van de nieranatomie van een potentiële levende nierdonor (**hoofdstuk 4.1**). De analyses laten zien dat vanuit het perspectief van de donor, magnetische resonantie (MR) angiografie de meest kosteneffectieve strategie is, terwijl vanuit het gecombineerde perspectief van donor en ontvanger, digitale subtractie angiografie (DSA) de meest kosteneffectieve strategie is. Als echter de specificiteit van DSA voor de vaststelling van nierziekte 99% of lager zou zijn, dan zou een combinatie van MR angiografie en computer tomografische (CT) angiografie het meest kosteneffectief zijn vanuit het gecombineerde perspectief van donor en ontvanger.

In **hoofdstuk 4.2** vergelijken we de overleving van patiënten die nierfunctievervangende therapie aanvingen met een vroege NTx van een levende donor, in vergelijking tot patiënten die startten met dialyse en op de wachtlijst werden geplaatst. We rapporteren een substantieel overlevingsvoordeel in termen van (voor kwaliteit van leven geadjusteerde) levensverwachting, voor vroege NTx. Dit voordeel neemt af op oudere leeftijd, daarom dienen inspanningen ter verhoging van het aantal vroege niertransplantaties in het bijzonder gericht te zijn op jongere patiënten. Het verhogen van het percentage vroege niertransplantaties als initiële vorm van nierfunctievervangende therapie van 5.8% naar 22.2%, zou de levensverwachting voor een gemiddelde patiënt met 1.2 jaar verhogen, wat voor een gemiddeld Nederlands incident cohort van 1,565 patiënten een verhoging van ruim 1,800 levensjaren zou betekenen. Het verhogen van het aantal vroege transplantaties kan daarom de levensverwachting van patiënten met nierfunctievervangende therapie substantieel verbeteren.

Methodologische overwegingen in de analyse van observationele databases

In **hoofdstuk 5.1** beschrijven we een propensity score die behandelingstoewijzing (HD of PD) voorspelde voor patiënten die startten met nierfunctievervangende therapie. Een propensity score wordt toegepast om de confounders tussen behandelingsgroepen in evenwicht te brengen en daarmee pseudo-randomisatie te bewerkstelligen. De propen-

sity score die we construeerden, bracht een goede balans van de confounders teweeg tussen de behandelingsgroepen. Echter, toepassing ervan in het uitkomstenmodel dat mortaliteit schatte, had geen verandering van het behandelingseffect tot gevolg. Bovendien ging het voordeel van eenvoud ten opzichte van multivariabele modellering verloren vanwege de aanwezigheid van effect modificatie. Samenvattend laat ons onderzoek, via een model betreffende de mortaliteit van patiënten met nierfunctievervangende therapie als een speciale case-studie, zien dat traditionele multivariabele regressie en propensity-score methoden vergelijkbare resultaten kunnen geven.

Onze bevindingen, algemene beperkingen en methodologische kwesties en suggesties voor toekomstig onderzoek worden bediscussieerd in **hoofdstuk 6**.

Appendices

Quality of life assessed with the Medical Outcomes Study Short Form 36-Item Health Survey of patients on renal replacement therapy: a systematic review and meta-analysis

Technical appendix

Mean age, proportion of males, proportion with diabetes and mean SF-36 scores for all included groups from the studies reported in the meta-analysis per treatment modality

a. Hemodialysis groups

Author	Publication year	n	Age (years)	Proportion male	Proportion diabetes	PF	RP	BP	GH	VT	SF	RE	MH
Arogundade, et al.	2004	55	40.8	0.49		58.6	29.6	66.2	42.4	47.5	54.8	57.6	57.0
Baiardi, et al.	2002	171	61.9	0.63	0.06	58.0	58.0	70.0	50.7	41.4	80.7	56.3	60.0
Buemi, et al.	2003	50	63.0	0.64		51.6	47.0	50.1	33.3	42.4	55.3	51.1	57.8
Carmichael, et al.	2000	49	57.8	0.65	0.14	44.4	21.4	49.2	35.7	38.0	44.9	39.4	65.0
Chang, et al.	2004	68	58.8	0.49	0.41	43.9	40.3	46.6	42.9	46.8	35.1	38.7	46.5
Chang, et al.	2004	51	57.6	0.65	0.65	42.2	40.3	44.6	38.6	46.5	34.7	35.5	44.1
Chiang, et al.	2004	497	57.8	0.45		48.3	50.0	73.6	44.0	48.8	60.7	47.2	60.5
DeOreo, et al.	1997	1,000	58.2	0.50		44.3	39.7	60.4	50.0	46.5	66.0	58.2	69.7
Diaz-Buxo, et al.	2000	16,755	59.4	0.52	0.45	41.4	33.1	57.2	43.7	44.7	64.1	53.0	68.7
Fujisawa,et al.	2000	49	45.8	0.76	0.04	81.7	73.5	74.1	49.6	61.2	74.9	80.3	67.8
Fujisawa, et al.	2000	65	45.7	0.69	0.05	81.5	63.8	67.2	52.0	57.6	74.2	70.3	69.0
Fukuhara, et al.	2003	2,406	59.9	0.58	0.19	46.9	34.4	57.9	36.9	41.9	62.1	46.1	59.9
Fukuhara, et al.	2003	2,087	58.4	0.63	0.25	65.3	48.7	64.6	43.4	53.0	70.1	53.6	63.5
Fukuhara, et al.	2003	2,885	59.6	0.53	0.44	40.8	31.7	59.0	40.2	42.9	62.1	51.8	67.3
Hamilton, et al.	2003	69	63.4	0.54		48.8	33.0	58.6	47.9	49.9	63.2	57.0	75.0
Hays, et al.	1994	165	53.0	0.48		51.8	32.5	57.6	43.9	45.9	63.6	57.8	69.5
Iliescu, et al.,	2003	89	60.1	0.62	0.29	49.6	36.2	60.2	46.7	43.1	63.5	63.7	73.4
Khan, et al.	1995	43	52.6			46.4	51.1	82.0	42.2	40.9	54.1	74.7	65.7
Kurtin, et al.	1992	23	52.9	0.55		47.5	35.1	50.3	38.1	34.7	54.7	34.7	62.3
Lee, et al.	2004	28	53.5	0.54	0.25	52.1	33.9	65.7	40.2	59.6	55.8	39.3	62.7
Lee, et al.	2004	28	51.4	0.57	0.21	58.2	53.6	66.3	43.2	52.3	50.9	51.2	57.6

Manu, et al.	2001	66				81.8	65.6	69.2	49.8	59.4	72.2	70.6	74.2
Merkus, et al.	1997	120	59.3	0.57	0.16	50.7	28.6	63.7	43.0	48.9	63.1	52.5	63.3
Molsted, et al.	2004	112	57.8	0.64		53.0	33.0	66.0	47.0	49.0	77.0	55.0	75.0
Painter, et al.	2000	87	57.9			30.4	19.5	44.1	34.2	35.2	59.3	56.1	69.1
Painter, et al.	2000	79	54.2			67.2	67.2	79.8	79.8	58.8	76.9	73.4	75.1
Perneger, et al.	2003	83	60.0	0.63		53.7	38.6	58.3	44.4	43.2	66.9	51.5	66.0
Rebollo, et al.	1998	100	72.0	0.51		47.8	63.8	66.6	36.3	50.1	80.0	74.0	76.4
Sesso, et al.	2003	90	48.0	0.56		53.0	43.0	68.0	61.0	50.0	67.0	56.0	61.0
Sloan, et al.	1998	101	52.2	0.60	0.38	43.0	62.0	55.0	39.0	41.0	63.0	47.0	65.0
Taji, et al.	2004	30	59.1	0.40	0.30	68.9	65.4	62.4	44.2	49.4	72.9	63.1	64.2
Taji, et al.	2004	31	58.8	0.48	0.32	70.2	60.3	60.6	46.2	52.6	64.5	64.3	66.2
Taskapan, et al.	2005	26	48.3	0.63		47.1	1.0	40.5	28.0	28.1	34.0	11.5	43.9
Taskapan, et al.	2005	14	48.3	0.63		62.5	25.0	76.6	46.7	65.9	61.6	40.4	65.1
Tawney, et al.	2000	39	59.6	0.37	0.49	59.4	47.5	67.9	43.5	46.2	67.3	65.0	68.6
Tawney, et al.	2000	43	59.6	0.44	0.50	52.1	49.4	64.8	43.3	52.8	77.6	66.7	75.9
Turk, et al.	2004	104	47.0		0.20	29.0	52.0	59.0	38.0	51.0	65.0	34.0	56.0
Turk, et al.	2004	44	43.0		0.07	49.0	70.0	71.0	47.0	68.0	75.0	51.0	71.0
Unruh, et al.	2004	1813	57.6	0.44	0.44	48.1	44.0	62.8	46.3	50.0	70.6	63.8	71.6
Vazquez, et al.	2005	194	48.6	0.43		67.4	48.0	65.7	39.2	53.7	74.0	77.4	68.3
Walters, et al.	2002	422	59.0	0.54		39.4	17.4	55.5	40.6	36.9	53.6	49.5	64.6
Wight, et al.	1998	100	55.9	0.56	0.11	33.6	23.6	48.6	31.6	34.5	41.9	31.0	60.0
Wight, et al.	1998	41	58.7		0.20	28.3	16.7	55.3	31.6	32.0	48.8	29.7	66.6
Wu, et al.	2004	452	59.0	0.52		45.4	28.1	57.5	44.5	44.4	64.5	57.0	70.4

BP = Bodily Pain, GH = General Health perceptions, MH = Mental Health, n = number of patients, PF = Physical Functioning, RE = Role limitations due to Emotional functioning, RP = Role limitations due to Physical functioning, SF = Social Functioning, VT = Vitality

b. Peritoneal dialysis groups

Author	Publication year	n	Age (years)	Proportion male	Proportion diabetes	PF	RP	BP	GH	VT	SF	RE	MH
Baiardi, et al.	2002	30	64.0	0.63	0.07	57.7	51.7	69.6	56.3	43.2	74.3	51.7	58.4
Bro, et al.	1999	13	54.2	0.62	0.08	71.0	46.5	76.5	56.5	53.5	78.0	60.0	76.5
Bro, et al.	1999	12	50.2	0.67	0.00	58.0	46.5	71.0	46.5	42.5	74.0	67.5	77.0
Carmichael, et al.	2000	97	57.0	0.60	0.17	40.3	19.7	54.1	37.7	37.6	53.2	45.4	67.9
Chen, et al.	2000	38	44.7	0.21	0.05	64.0	43.0	69.0	49.0	53.0	63.0	57.0	63.0
Chen, et al.	2000	29	47.9	0.52	0.17	62.0	25.0	70.0	46.0	46.0	60.0	29.0	57.0
De Wit, et al.	2001	37	55.0	0.49		66.0	52.0	75.0	42.0	57.0	79.0	86.0	78.0
Diaz-Buxo, et al.	2000	1260	53.5	0.50	0.38	44.8	33.3	60.1	42.3	42.3	65.2	58.4	69.7
Goller, et al.	1997	57	56.0	0.47	0.19	50.0	37.5	67.5	46.5	56.0	75.0	61.5	75.0
Juergensen, et al.	2002	147	47.0	0.51		60.0	41.0	66.0	42.0	51.0	68.0	57.0	61.0
Juergensen, et al.	2002	96	57.0	0.66		45.0	36.0	58.0	45.0	45.0	65.0	55.0	71.0
Khan, et al.	1995	27	49.3			39.0	29.7	59.3	40.0	37.7	49.8	66.7	73.0
Manns, et al.	2003	41	56.1	0.49		40.0	29.3	63.1	39.1	39.6	62.2	64.2	66.7
Merkus, et al.	1997	106	52.3	0.65	0.19	60.9	31.7	74.2	46.4	51.6	68.9	63.8	72.2
Morton, et al.	1996	60	55.1	0.57	0.27	45.0	20.0	61.0	43.0	39.0	61.0	45.0	70.0
Paniagua, et al.	2005	460	47.5	0.60	0.43	52.2	38.8	68.8	47.2	53.2	67.9	63.5	67.1
Paniagua, et al.	2005	463	46.7	0.56	0.42	54.0	39.4	69.3	49.2	54.9	68.5	65.4	68.4
Pucheu, et al.	2004	47	56.6	0.62	0.00	58.5	40.4	64.6	46.1	40.1	66.5	47.5	57.9
Wight, et al.	1998	109	55.3		0.22	40.6	20.4	59.0	35.1	35.8	50.0	55.5	65.9
Wu, et al.	2004	133	54.0	0.49		47.7	27.5	62.6	40.8	39.7	64.9	63.7	72.5

BP = Bodily Pain, GH = General Health perceptions, MH = Mental Health, n = number of patients, PF = Physical Functioning, RE = Role limitations due to Emotional functioning, RP = Role limitations due to Physical functioning, SF = Social Functioning, VT = Vitality

c. Renal transplantation groups

Author	Publication year	n	Age (years)	Proportion male	Proportion diabetes	PF	RP	BP	GH	VT	SF	RE	MH
Baiardi, et al.	2002	34	44.0	0.65	0.03	82.4	84.8	84.0	64.4	52.7	83.9	74.7	57.9
Cleemput, et al.	2004	217	51.7	0.60		84.0	71.5	80.1	65.3	68.7	83.2	78.5	72.8
Cleemput, et al.	2004	133	51.7	0.60		55.3	45.9	63.3	53.7	54.6	71.6	66.2	69.8
Franke, et al.	2003	52	43.4	0.58	0.09	75.8	70.2	82.8	64.6	66.9	88.5	76.9	75.9
Franke, et al.	2003	28	43.4	0.58	0.09	73.5	57.1	66.3	51.4	58.9	67.9	70.2	63.0
Franke, et al.	2003	146	46.1	0.54	0.10	75.0	76.0	78.8	58.5	61.3	87.2	85.6	75.5
Franke, et al.	2003	76	46.1	0.54	0.10	65.3	53.3	57.3	48.2	47.7	67.4	61.0	59.3
Fujisawa, et al.	2000	117	43.9	0.43	0.04	86.2	77.6	80.2	56.4	63.3	82.1	78.0	70.0
Groothoff, et al.	2003	107	29.2	0.53		85.8	76.9	86.1	67.1	67.0	84.7	81.9	75.9
Khan, et al.	1995	102	45.2			67.5	63.2	78.4	63.9	62.6	80.2	80.1	78.6
Manu, et al.	2001	92				84.6	77.4	78.6	56.3	64.1	80.2	79.1	68.8
Matas, et al.	1998	157	47.0			69.0	58.0	70.0	62.0	57.0	77.0	78.0	76.0
Matas, et al.	1998	121	42.0			67.0	68.0	72.0	69.0	61.0	82.0	84.0	79.0
Matas, et al.	1998	72	37.0			74.0	71.0	79.0	67.0	59.0	81.0	81.0	76.0
Matas, et al.	1998	46	37.0			70.0	57.0	68.0	66.0	59.0	82.0	78.0	77.0
Matas, et al.	1998	83	39.0			62.0	64.0	73.0	54.0	56.0	79.0	90.0	76.0
Matas, et al.	1998	55	39.0			59.0	57.0	71.0	47.0	49.0	77.0	81.0	74.0
Matas, et al.	1998	39	37.0			57.0	59.0	76.0	55.0	53.0	78.0	83.0	76.0
Matas, et al.	1998	45	36.0			62.0	65.0	69.0	48.0	53.0	76.0	79.0	76.0
Oberbauer, et al.	2003	183	45.7	0.62	0.08	77.2	62.8	74.5	62.7	63.5	78.7	76.4	75.8
Oberbauer, et al.	2003	178	47.0	0.68	0.04	75.3	60.9	70.9	60.5	59.8	79.1	71.0	71.8
Ozminkowski, et al.	1997	211	43.3	0.54		69.9	60.5	76.4	58.0	58.0	82.4	78.7	77.0

Painter, et al.	2003	23	48.1	0.74		77.2	68.2	70.5	62.8	65.1	74.4	83.2	81.6
Rebollo, et al.	1998	24	68.0	0.75		75.4	81.3	78.5	68.8	66.7	93.2	93.1	83.7
Shield, et al.	1997	303	44.0	0.62		56.8	29.0	60.3	37.1	38.4	53.0	48.2	62.6
Sureshkumar, et al.	2002	27	44.8	0.59		69.0	54.0	72.0	55.0	56.0	75.0	77.0	78.0
Tanriverdi, et al.	2004	49	31.4	0.76		70.6	53.0	72.9	52.5	60.0	68.4	51.7	59.8
Wight, et al.	1998	228	47.5		0.10	62.5	53.5	70.2	54.3	53.2	75.2	68.8	73.2

BP = Bodily Pain, GH = General Health perceptions, MH = Mental Health, n = number of patients, PF = Physical Functioning, RE = Role limitations due to Emotional functioning, RP = Role limitations due to Physical functioning, SF = Social Functioning, VT = Vitality

Living renal donors: optimizing the imaging strategy - decision- and cost-effectiveness analysis

Technical appendix

CONTENTS

I. MODEL

We built a decision tree (Treeage 3.5.7, TreeAge Software, Inc., Williamstown, Massachusetts), comparing six work-up strategies and two reference strategies (Table 1). For each specific test, failure rate, mortality rate and complication rate were defined.

For the calculation of the expected value of each branch of the decision tree, a Markov model was implemented, with four attributes: donor costs, donor quality-adjusted life years (QALYs), recipient costs, and recipient QALYs. The length of a Markov-cycle was assumed to be 1 year. This implies that a change of state can only occur once per year. All time-dependent variables were modeled, however, using a variable (dt) for cycle-length so that it could be varied in the sensitivity analyses (from 0.5 to 2).

Half-cycle correction was applied for yearly costs and quality-of-life estimates, because we assumed changes occured, on average, halfway through a cycle. To take into account time preference – i.e.: health or financial gains in the near future are generally valued higher than gains in the future – we used a discount rate for discounting both yearly costs and QALYs, using Treeage's formula UtilDiscount. The rate used in our base-case analysis was 0.03 (range explored in sensitivity analysis: 0 – 0.1).

The donors started the Markov model with the test. The donors surviving the test were split up into four categories. First, the cohort was divided into diseased and non-diseased donors, based on the prevalence of renal disease, and second, both groups

TABLE 1. Abbreviations of strategies

DSA*	Current imaging strategy, DSA, with urography, was performed
MR angiography†	Performed with enhancement with gadolinium-based contrast material
Spiral CT angiography†	Performed with contrast enhancement
DSA with MR angiography‡	Current imaging strategy, performed first, and MR angiography were performed during one visit
MR angiography, DSA†,‡	If results of MR angiography were inconclusive, the current imaging strategy was performed during a second visit
MR angiography with CT angiography§	MR angiography, performed first, and CT angiography were performed during one visit
No test, always transplantation||	No test, and transplantation was always performed
No test, no transplantation||	No test, and transplantation was not performed

* Standard of reference for detection of renal disease; we assumed DSA does not fail technically.
† If the donor has any contraindication to MR angiography (e.g. claustrophobia, metal implants), or if MR angiography or CT angiography failed technically, the donor underwent the current imaging strategy.
‡ If both MR angiography and DSA are performed but MR angiography failed technically, results of only DSA were considered.
§ If MR angiography was contraindicated, only CT angiography was performed and when the latter failed technically, DSA was performed. When both MR angiography and CT angiography were performed, but one failed technically, we assumed that the transplantation team relied on the results of the successful imaging strategy. If both tests failed, DSA was performed.
|| Reference strategy.

were split up by test result - either positive or negative for renal disease - according to the sensitivity and specificity of the test. Test complications were modeled in the donor QALYs, using disutilities. Disutility was expressed in the number of days hospitalized (or the proportion of a day spent in a hospital), assuming the time spent in the hospital was associated with a quality of life of 0. Test costs were added to the donor costs. When no disease was detected, both the donor and recipient underwent an operation, with its associated morbidity (modeled in both donor and recipient QALYs as disutilities, assuming the hospitalization days to be associated with a quality of life of 0) and mortality. Costs of the operations were incorporated separately for donor and recipient.

The presence of renovascular anomalies affected operation duration and thus operation costs only. Different health states were defined according to donor renal disease, donor survival, and recipient survival. For one state, donor as well as recipient 'health state' was defined. Recipients who could not be transplanted were assumed to stay on dialysis. For patients that did get transplanted, a transplant failure rate was incorpo-

rated. For every state a mortality rate was defined for both donor and recipient. For a percentage of donors who had renal disease, which was left detected or undetected, mortality was assumed to become equal to that of dialysis patients after a certain time period. Recipients with a diseased transplant were assumed to have a mortality rate equal to that of dialysis patients after a certain time period. Costs for each state were modeled for donor and recipient separately. The Markov model was set to terminate after 70 cycles.

A spreadsheet was used to calculate the incremental cost-effectiveness ratios from the three different perspectives: the donor, the recipient and the combined perspective (summing the costs of donor and recipient and the QALYs of donor and recipient), using the Threshold of Society's 'Willingness-To-Pay' (R). From the literature[1] R was estimated to be 100,000 Dutch guilders = €45,000 = K€45 per QALY, ranging from 25,000 to 400,000 Dutch guilders (K€11 to K€182), which we used for our base-case and sensitivity analysis respectively.

II. DEMOGRAPHIC VARIABLES

a. Age

For both the donor and the recipient, age was calculated in the model, using the following formula:

ageMKV = age - corrAge + (_stage - corrTime)*dt

Where:
ageMKV = age in the Markov model
age = age at diagnostic work-up = 40 for both the donor and the recipient
corrAge = correction for age = 0.65
corrTime = correction for time = 0.5

b. Gender

Gender of both donor and recipient was defined using a binary variable (1=male, 0=female).

III. PREVALENCE OF ANOMALIES AND DISEASE AMONG RENAL DONORS

a. Prevalence of anomalies

To estimate the prevalence of vascular anomalies, we selected the three most recent studies which had at least included 200 patients in their study. The anomalies investigated in those particular studies and their prevalence estimates are listed in Table 2.

TABLE 2. Computation of the prevalence of anomalies

Author	Kjellevand	Shokeir	Pozniak	TOTAL
Year	1991	1994	1998	
Reference	[4]	[3]	[2]	
Number of patients	258	1000	205	1463
Age	47	43	?	
Diagnostics	angiography	IV-DSA + IVU (+ IA-DSA)	spiral CT	
ARTERIAL ANOMALIES				0.407
Multiple renal arteries	0.340	0.280	0.400	0.307
Early arterial branching	0.100			0.100
VENOUS ANOMALIES				0.132
Multiple renal veins			0.132	0.132
TOTAL ANOMALIES				
assuming total dependence of arteriovenous anomalies				0.407
assuming conditional independence of arteriovenous anomalies				0.486
BASELINE (in between)		0.447		
Sensitivity analysis		(0.407- 0.486)		

Multiple arteries and early arterial branching are assumed not to coexist, so prevalence estimates of these anomalies were summed to an estimate for prevalence of arterial anomalies. Arterial and venous anomalies were then combined to estimate the prevalence of anomalies, in two different ways, first assuming total dependence, secondly assuming conditional independence of the two groups of anomalies. The average of these two estimates of prevalence of anomalies was used as a baseline estimate. A sensitivity analysis was performed over the entire range between the two estimates.

b. Prevalence of both arterial and venous anomalies among all anomalies

Since DSA can only detect arterial anomalies, we had to adjust its sensitivity and specificity for detecting anomalies. We estimated sensitivity and specificity for detecting arterial anomalies from the literature (see Chapter III, paragraph a) and assumed the sensitivity and specificity for detecting venous anomalies to be 0.

To compute an overall sensitivity and specificity (for computation see Chapter III, paragraph a) we needed to know the percentage of venous anomalies among all anomalies. For this computation, we used the only study, that reported both arterial and venous anomalies,[2] see Table 3.

TABLE 3. Computation of prevalence of both arterial and venous anomalies among all anomalies

Author	Pozniak
Year	1998
Reference	[2]
Number of patients	205
Age	?
Diagnostics	spiral CT
ARTERIAL	
Multiple renal arteries & Early arterial branching	0.400
VENOUS	
Multiple renal veins	0.132

c. Prevalence of renal disease

To compute the prevalence of renal disease (Table 4), we used the same studies as we used to compute the prevalence of renal anomalies. We excluded renal diseases with little prognostic consequences, i.e.: unilateral cysts, calculi, and parenchymatous lesions. When a specific disease was reported in more than one study, a weighted average of the prevalence estimates according to the number of patients in the study was computed. Since we assumed that one patient can have no more than one renal disease, the prevalence estimates of all diseases were summed to estimate the total prevalence of renal disease.

TABLE 4. Computation of prevalence of renal disease

Author	Kjellevand	Shokeir	Pozniak	Total
Year	1991	1994	1998	
Reference	4	3	2	
Number of patients	258	1000	205	1463
Age	47	43	?	
Diagnostics	Angio	IV-DSA + IVU (+ IA-DSA)	spiral CT	
RENOVASCULAR				
atherosclerosis	0.058	0.000		
fibromuscular dysplasia	0.054	0.004		
arterial stenosis	0.112	0.004	0.015	0.025
AV-malformations unilateral	0.004			0.004
multiple bilateral small arteries		0.004		0.004
unilateral hypoplastic artery		0.003		0.003
unilateral absent artery		0.004		0.004
KIDNEY				0.014
horseshoe kidney		0.003		0.003
bilateral cysts	0.004	0.004		0.004
angiomyolipoma		0.007		0.007
COLLECTING SYSTEM AND DISTAL URINARY TRACT				0.009
obstruction		0.004		0.004
ureteral stricture		0.005		0.005
TOTAL DISEASES				0.063
BASELINE		0.063		
Sensitivity analysis		(0.042 - 0.179)		

For the sensitivity analysis, we used as the lower boundary the lowest prevalence estimate for each disease. As the upper boundary we used the highest estimate of each disease and included all diseases regardless of their prognostic consequences, i.e. we incorporated the prevalence of renal calculi (0.007)[3] and ureteral calculi (0.006)[3] and parenchymatous lesions (0.016).[4]

IV. TEST CHARACTERISTICS

a. Sensitivity and specificity

Sensitivity and specificity were computed, using DSA as the reference standard for disease and operation as the reference standard for renal anomalies.

In the literature we found different test characteristics for different diseases. Therefore, we needed to average the test characteristics of a particular test for the different diseases into one sensitivity estimate and one specificity estimate for 'disease' in general.

To obtain such summary estimates for two different diseases or anomalies, we assumed that:

$D+ = D_1+$ or D_2+ $\qquad$ $D- = D_1-$ and D_2-
$T+ = T_1+$ or T_2+ $\qquad$ $T- = T_1-$ and T_2-

Where:
D+= disease present
D- = disease absent
D_1 = disease 1
D_2 = disease 2
T+ = test result is positive
T- = test result is negative
T_1 = test for disease 1
T_2 = test for disease 2

Sensitivity of the test for disease 1 (Se_1) can thus be represented by the following formula:

$$Se_1 = P(T_1+ | D_1+)$$

Where:
P = probability
$|D_1+$ = given that disease 1 is present

Similarly specificity of the test for disease 1 (Sp_1) can be represented by the formula:

$$Sp_1 = P(T_1-|D_1-)$$

Furthermore, we assumed that prevalence estimates of the two diseases were conditionally independent, i.e., the prevalence of disease 1 is equal for those with disease 2 as those without disease 2 and vice versa.

The probability that the test for disease 1 was positive and disease 1 was present and at the same time, the test for disease 2 was positive, while disease 2 was also present ($P(T_1+,D_1+,T_2+,D_2+)$) was calculated, assuming conditional independence:

$$P(T_1+,D_1+,T_2+,D_2+) = P(D_1+)^* P(D_2+)^* Se_1^* Se_2$$

Similar calculations were performed for all sixteen possible situations.

Using these formulas, combined sensitivity (Se^{tot}) was calculated as follows:

$$Se^{tot} = P(T+|D+) = P(T+,D+)/P(D+)$$

$Se^{tot} = [P(T_1+,D_1+,T_2+,D_2+) + P(T_1+,D_1+,T_2-,D_2+) + P(T_1-,D_1+,T_2+,D_2+) + P(T_1+,D_1+,T_2+,D_2-) + P(T_1+,D_1+,T_2-,D_2-) + P(T_1-,D_1+,T_2+,D_2-) + P(T_1+,D_1-,T_2+,D_2+) + P(T_1+,D_1-,T_2-,D_2+) + P(T_1-,D_1-,T_2+,D_2+)]/(P(D_1+)+P(D_2+)- P(D_1+,D_2+))$

$Se^{tot} = P(D_1+)^*P(D_2+)^*[Se_1+Se_2- Se_1^*Se_2+(1/ P(D_2+)-1)^*(1- Sp_2+Se_1^*Sp_2) +(1/ P(D_1+)-1)^*(1-Sp_1+Sp_1^*Se_2)]/(P(D_1+)+P(D_2+)-P(D_1+)^*P(D_2+))$

Similarly, combined specificity (Sp^{tot}) was calculated as follows:

$$Sp^{tot} = P(T-|D-) = P(T-,D-)/P(D-)$$

$$Sp^{tot} = P(T_1-,D_1-,T_2-,D_2-)/ P(D_1-,D_2-)$$

$$Sp^{tot} = P(D_1-)^*P(D_2-)^*Sp_1^*Sp_2/ P(D_1-)^*P(D_2-)$$

Similar calculations for combined sensitivity and specificity for anomalies of a test were calculated. The test characteristics for DSA, MR angiography and CT angiography, resulting from these computations are shown in Table 5.

TABLE 5a. Sensitivity and specificity for DSA

Author	Year	n	Definition of a positive test result	Se	Sp
REFERENCE STANDARD = DSA					
Total disease					
By definition				**1.00**	**1.00**
REFERENCE STANDARD = OPERATION					
Anomalies - multiple renal arteries					
El-Azab	1996	64	multiple renal arteries	0.91	0.96
Shokeir	1994	100	multiple renal arteries	0.75	0.95
				0.81	0.95
Anomalies - multiple renal veins					
By definition				0.00	0.00
Total anomalies				**0.82**	

TABLE 5b. Sensitivity and specificity for MRI

Author	Year	n	Definition of a positive test result	Se	Sp
REFERENCE STANDARD = DSA					
Total disease (not from donor-data)					
Hany	1998	205	arterial stenosis ('significant')	**0.93**	**0.90**
REFERENCE STANDARD = OPERATION					
Anomalies - multiple renal arteries					
Low	1998	22	accessory renal arteries	1.00	1.00
Nelson	1999	50	accessory renal arteries	0.71	0.96
				0.80	0.97

Anomalies - early arterial branching					
Low	1998	22	early arterial branching	0.80	1.00
Total anomalies				**0.82**	

TABLE 5c. Sensitivity and specificity for CT

Author	**Year**	**n**	**Definition of a positive test result**	**Se**	**Sp**
REFERENCE STANDARD = DSA					
Total disease					
Kim	1998	50	arterial stenosis > 50%	0.90	0.97
Platt	1996	48	arterial stenosis	1.00	1.00
				0.95	**0.98**
REFERENCE STANDARD = OPERATION					
Anomalies - multiple renal arteries					
Del Pizzo	1999	175	arterial anatomy	0.91	0.98
Kaynan	1999	45	multiple renal arteries	0.33	1.00
Pace	1998	40	renal arterial anatomy	0.92	1.00
Pozniak	1998	136	main renal arteries	1.00	1.00
				0.87	0.99
Anomalies - early arterial branching					
Kaynan	1999	45	early arterial branching	0.50	0.98
Anomalies - total arterial				0.81	0.97
Anomalies - renal veins					
Del Pizzo	1999	175	venous anatomy	0.65	1.00
Pace	1998	40	renal venous anatomy	0.80	1.00
Pozniak	1998	136	main renal veins	0.99	0.96
				0.80	0.98
Total anomalies				**0.83**	

b. Test complications

From the literature we estimated the percentage of complications from DSA and CT angiography. For MR angiography, no quantitative literature was available, and since the rate of complications is generally believed to be negligible, we assumed it to be 0 and varied it in our sensitivity analyses from 0 to 0.031 (the estimate of occurrence complications due to CT angiography, see Table 6). For the combination strategies, we summed the complication rates of the imaging tests.

The disutility associated with complications due to the test was assumed to be 2 days. So to calculate the disutility associated with the strategy, the proportion of complications was multiplied with 2 days. The value of this multiplication was subtracted from the total of quality adjusted life years (QALYs) associated with the specific strategy.

TABLE 6. Estimates of test complications

Test	Estimate (%)	Range (%)	Source
DSA	1.7	0.5 - 3	[12,13]
MR angiography	0	0 - 0.031	
CT angiography	0.031	0.002 - 0.062	[14]

c. Test mortality

Mortality due to DSA and CT angiography were estimated from literature data. Again, for MR angiography no quantitative literature was available but we assumed mortality for MR angiography to be 0 and varied between 0 and 0.0009 (mortality associated with CT angiography, see table 7). Test mortality also incurred costs, which will be described in more detail in paragraph VII.

TABLE 7. Estimates of test mortality

Test	Estimate (%)	Range (%)	Source
DSA	0.033	0.029 - 0.162	[12,13]
MR angiography	0	0 - 0.0009	
CT angiography	0.0009	0.0003 - 0.0026	[14]

For the combined test strategies we calculated the mortality rates as follows:
Mortality of first test performed + (1- mortality of first test) * mortality of second test.

d. Test failure

We assumed DSA not to fail technically. Failure rates of MR angiography and CT angiography were estimated from the literature. MR angiography is contraindicated for persons with metal implants or with claustrophobia, an estimate of the percentage of patients in which MR angiography could not be performed due to these reasons was provided by Dr. P. Nederkoorn (Table 8).

TABLE 8. Estimates of failure and contraindication rates

Rate	Estimate (%)	Range (%)	Source
DSA failure	0	Not available	
MR angiography failure	2.5	1 - 4	[15,16]
CT angiography failure	1.9	0.5 - 3.5	[17]
MR angiography contraindicated	6.7	3 - 10	Personal communication, P. Nederkoorn, MD

We assumed that if the donor had any contraindication to MR angiography or if MR angiography or CT angiography failed technically, the donor would receive the current strategy (DSA including urography). For the three strategies DSA with MR angiography, MR angiography, and DSA if MR angiography results were inconclusive, we assumed that if both DSA and MR angiography were performed but MR angiography failed technically, only the results of DSA were considered and if the donor had any contraindication to MR angiography, only DSA would be performed. For the combination strategy MR angiography with CT angiography, we assumed that if one failed technically, the transplant team would rely on the other imaging test. If both tests failed, DSA would be performed and when MR angiography was contraindicated, CT angiography would be performed (followed by DSA if it failed).

V. OPERATION CHARACTERISTICS

a. Complications of the operation

We estimated the probability of complications during the operation of the donor from the literature. The estimate for the recipient was an expert's opinion (Table 9). Disutility due to complications of the donor nephrectomy was assumed to be 5 days, disutility of complications of the recipient operation was assumed to be 10 days.

TABLE 9. Estimates of operation complications

	Complications (%)	Range (%)	Source
Donor operation	14	5 - 20	[18]
Recipient operation	33	10 - 50	Expert opinion

b. Operation mortality

Since a reliable estimate of the operative mortality of laparoscopic donor nephrectomy was not yet available, we assumed it to be equal to the mortality of the open operation, which was estimated from the literature. The operative mortality estimate for the recipient was based on expert opinion (Table 10). Operation mortality also incurred costs (for details on computation, see paragraph VII).

TABLE 10. Estimates of operation mortality

	Mortality (%)	Range (%)	Source
Donor operation	0.03	0 - 0.05	[18-20]
Recipient operation	1	0.5 - 3	Expert opinion

VI. LONG-TERM ESTIMATES

The mortality of both donor and recipient were incorporated in the model using Dutch life tables of the general population,[5] multiplied with a relative risk, according to the population under consideration.

a. Donor

For the donor, the relative risk of mortality compared with the general population was assumed to be 1 (Table 11). However, the donor population is highly selected, having undergone the first stages of screening without disease having been detected. It was also suggested by Fehrman-Ekholm and colleagues that kidney donors live longer than an average person from the general population.[6] From the 20-year survival rate reported in their article, a relative risk of mortality was computed and used as the lower limit in the sensitivity analyses. We assumed the upper limit to be 1.5 (Table 11).

TABLE 11. Long-term estimates for the donor

	Estimate	Range	Source
Relative risk of mortality compared to general population	1	0.39 - 1.5	[6]
Dialysis-free survival if renal disease was present (years)	15	10 - 20	Assumption
Proportion developing renal disease of donors in whom disease was not detected (%)	25	0 - 100	Assumption
Proportion developing renal disease of donors in whom disease was detected (%)	5.3	0 - 10	Expert opinion

The donors that had renal disease, a proportion was assumed to have a higher mortality. This percentage was assumed to be different among donors whose disease was detected and donors whose disease was not detected. For the donor in whom disease was detected, we estimated from our clinical data that 5.3% would develop renal disease and varied this percentage over a plausible range. For the donor whose disease was left undetected, and thus untreated, we assumed a percentage of 25%, but since this was an estimated guess, we varied this percentage from 0 to 100%. Donors who developed renal disease were assumed to have a relative risk of 1 during the first 15 years after the work-up and to have a relative risk, similar to dialysis patients in the years thereafter. This estimate of 15 years was also varied over a plausible range.

b. Recipient

To estimate the relative risk of mortality of transplant recipients, literature studies on survival of transplantation recipients were selected that met the following criteria: transplants from living donors, a study population of 100 or more subjects, and for every survival estimate (e.g. 1-year or 2-year survival), at least two studies available to compute

an average estimate. Estimates from studies were weighted according to number of subjects in the study (Table 12a). The averaged survival estimates were converted into a mortality rate. A relative risk estimate was computed by diving the mortality rate over the mortality rate of a 32-year old subject (the average age of the subjects in the studies used) from the general population[5] (Table 12b). For the sensitivity analyses, we used the studies reporting the highest survival for the lower limits and the studies reporting the lowest survival for the upper limits (see Tables 12c and 12d).

TABLE 12a. Averaging of transplant recipient survival

Author	Year	Source	n	age	1-yr	3-yr	5-yr
Ben Abdallah	1997	[21]	144	28	0.97	0.95	0.92
Donnelly	1995	[22]	2155	31	0.99	0.98	0.96
Kuo	1998	[23]	124	45	0.95		
Medin	2000	[24]	197	40			0.94
TOTAL				32	0.99	0.97	0.96

TABLE 12b. Computation of relative risk of mortality for transplant recipient

year (t)	P (surv<t)	P (event<t)	P (-1<T<t)	P (t-1<T<t |T>t-1)	mortality rate	mortality rate general population[5]	relative risk of mortality
1	0.99	0.01	0.01	0.01	0.014	0.001476	9.7
3	0.98	0.02	0.01	0.00997	0.0050	0.001638	3.6
5	0.96	0.04	0.02	0.01742	0.0088	0.001838	5.0

TABLE 12c. Computation of lower limit for sensitivity analysis

year (t)	P (surv<t)	P (event<t)	P (-1<T<t)	P (t-1<T<t |T>t-1)	mortality rate	mortality rate general population[5]	relative risk of mortality
1	0.99	0.01	0.01	0.01	0.011	0.001476	7.5
3	0.98	0.02	0.00	0.00	0.00	0.001638	0
5	0.96	0.04	0.02	0.01742	0.0088	0.001838	4.8

TABLE 12d. Computation of upper limit for sensitvity analysis

year (t)	P (surv<t)	P (event<t)	P (-1<T<t)	P (t-1<T<t |T>t-1)	mortality rate	mortality rate general population[5]	relative risk of mortality
1	0.95	0.05	0.05	0.05	0.052	0.001476	35.5
3	0.95	0.05	0.00	0.00	0.00	0.001638	0
5	0.92	0.08	0.03	0.032	0.016	0.001838	8.7

For the computation of the graft survival, similar calculations were performed (Tables 13a-d). Kidney survival was averaged from studies found in the literature, using the same criteria (recipients of transplants of living renal donors and study population of 100 or more subjects, at least two studies for each survival estimate). From these averaged graft-survival estimates, failure rates were computed to model the transition from a transplant recipient state to a dialysis state.

TABLE 13a. Averaging of graft survival

Author	Year	Source	n	1-yr	3-yr	5-yr
Ben Abdallah	1997	[21]	144	0.98	0.93	0.86
Donnelly	1995	[22]	2155	0.91	0.84	0.76
Hariharan	2000	[25]	3436	0.94		
Kuo	1998	[23]	124	0.94		
Park	1996	[26]	1275			0.82
TOTAL				0.93	0.84	0.79

TABLE 13b. Computation of graft failure rate

Year (t)	P (surv<t)	P(event<t)	P(-1<T<t)	P(t-1<T<t |T>t-1)	Failure rate
1	0.93	0.07	0.07	0.07	0.072443
3	0.84	0.16	0.09	0.095868	0.05039
5	0.79	0.21	0.05	0.065037	0.033624

TABLE 13c. Computation of lower limit for sensitivity analysis

Year (t)	P (surv<t)	P(event<t)	P(-1<T<t)	P(t-1<T<t |T>t-1)	Failure rate
1	0.98	0.02	0.02	0.02	0.020203
3	0.93	0.07	0.05	0.05102	0.026184
5	0.86	0.14	0.07	0.075269	0.039126

TABLE 13d. Computation of upper limit for sensitivity analysis

Year (t)	P (surv<t)	P(event<t)	P(-1<T<t)	P(t-1<T<t |T>t-1)	Failure rate
1	0.91	0.09	0.09	0.09	0.092115
3	0.84	0.17	0.08	0.08443	0.044104
5	0.76	0.24	0.08	0.091018	0.047715

The relative risk of mortality of dialysis patients was computed by comparing mortality rates for both hemodialysis (HD) patients and continuous ambulatory peritoneal dialysis (CAPD) patients from a study by Fenton and colleagues[7] with the mortality rate of the general population in the Netherlands as reported by the Dutch Central Bureau of Statistics.[5] From the paper by Fenton and colleagues, the mortality rates of the age-groups 45-64 were used, since in the model the recipient was assumed to be 40 years at the start of the model. This general population mortality rate was computed by averaging the estimates for subjects aged 45 to 64, for males and females separately and averaging these according to the gender distribution. The estimates are presented in Table 14. The relative risks of mortality of CAPD and HD patients were averaged in the model according to prevalence of CAPD and HD patients in the Netherlands.[8] In table 15, we summarized all long-term estimates for the recipient.

TABLE 14. Computation of relative risk of mortality for HD and CAPD patients

	CAPD			HD		
	Mortality rate general population	**Mortality rate patient**	**Relative risk of mortality**	**Mortality rate general population**	**Mortality rate patient**	**Relative risk of mortality**
Base-case	0.008802	0.122	13.9	0.008802	0.185	21.0
Lower limit sensitivity analysis	0.008802	0.100	11.4	0.008802	0.158	18.0
Upper limit sensitivity analysis	0.008802	0.143	16.2	0.008802	0.211	24.0

TABLE 15. Long-term estimates for the recipient

	Estimate	Range	Source
Relative risk of mortality of RTx recipient compared to general population			
1 year after transplantation	9.7	7.5 - 35.5	21-24
3 years after transplantation	3.6	NA	21-24
5 years after transplantation	5.0	4.8 - 8.7	21-24
Relative risk of mortality of CAPD patient compared to general population	14	11 - 16	7
Relative risk of mortality of HD patient compared to general population	21	18 - 24	7
Proportion of CAPD patients among total dialysis population (%)	28	10 - 50	8
Graft failure rate			
1 year after transplantation	0.072	0.020 - 0.092	21-23,25,26
3 years after transplantation	0.050	0.026 - 0.044	21-23,25,26
5 years after transplantation	0.034	0.039 - 0.048	21-23,25,26

VII. COST ESTIMATES

Cost estimates were calculated according to the Dutch guidelines for computing costs in health care.[9]

We computed direct health care costs and direct non-health care costs for the different radiological strategies, the operations of donor and recipient and the yearly costs associated with having donated a kidney, having a renal transplant and being treated with CAPD or HD.

Direct health care costs consist of directly assignable and non-directly assignable costs. This first category consists of costs of personnel, material, and equipment. The second consists of costs of supporting departments, housing, and overhead. Direct non-health care costs consist of travel costs and time-costs.

a. Costs of radiological strategies and operations

1. Direct health care costs

For the radiological tests and the operations, direct health care costs were available from the Erasmus MC, University Medical Center Rotterdam. Personnel costs were computed, by estimating time spent on an intervention for each personnel-category, using mean wages. There was no information available on overhead costs for personnel; we assumed it to be 15% of total personnel costs.

Costs of materials used per intervention were summed to obtain an estimate of material costs.

For equipment costs, the annuitization method was used for the initial investment. With this method, the annuitized annual costs (M) are given by the following formula:

$$M = P * i * (1+i) (N - 1) / ((1 + i) (N - 1) - 1)$$

Where:
P = purchase price
i = interest (discount) rate
N = expected useful life

This method takes into account the devaluation of the asset and the fact that the money invested cannot be spent otherwise. The annual service costs were discounted over the expected useful life of the equipment, to obtain the present value of annual service (PV), using the formula:

$$PV = C / i * [1 - (1 / (1 + i)N)]$$

Where:
C = constant amount of service costs
i = interest (discount) rate
N = expected useful life

The annual investment and service costs were summed and the costs of an intervention were computed according to the time needed for this intervention relative to the time per year that the equipment is available.

Information on costs of supporting departments was obtained from records of the Financial and Economical Department of the Erasmus MC, University Medical Center Rotterdam. Costs on housing could only be computed for the radiological tests, through measurement of surface and housing costs per m^2. Overhead costs for the radiological tests were assumed to be 15% of directly assignable costs. For the operations, a percentage of 35% of directly assignable costs was used to estimate housing and overhead costs.

Costs of the donor operation were higher for a nephrectomy of a kidney with renovascular anomalies, because of the increased duration of the operation (1 hour extra). If the anomalies were detected, the costs were only incurred if the anomalies were bilateral; if they were unilateral, the other kidney was removed. If the anomalies were left undetected, the extra costs were incurred if the anomalies were bilateral or if the donor happened to be operated on the kidney with renovascular anomalies.

2. Direct non-health care costs

To calculate travel costs of the donor, hospital records were used to estimate an average travel distance and for the recipient an average travel distance was obtained from the guidelines.[9] In the base-case analysis, it was assumed that all donors and recipients traveled by car, thus the distances were multiplied by the travel costs per kilometer, obtained from the guidelines. Costs of parking were added to these costs. The travel costs per visit were multiplied by the number of visits needed for an intervention.

For time costs, the time in hours that a donor or recipient needed to undergo an intervention was estimated. Travel time, waiting time, and time of the intervention and possible hospitalization or observation were taken into account. From the Dutch Central Bureau of Statistics, we obtained average age and gender dependent wages and multiplied these with the time spent for each intervention.

3. Costs of mortality and complications

The costs of mortality and of complications from both the imaging tests and the operations were computed assuming several days of hospitalization.

b. Yearly costs associated with the health states

For the yearly costs of the different health states, direct health care costs were obtained from the literature. For the transplant recipient these did not include the costs of complications. Direct non-health care costs (travel costs and time costs) were estimated using the same method as for the computation of direct non-health care costs of imaging tests and operations.

All costs in this appendix are presented in Euros from the year 2000.

Tables 16 to 20 show the costs of a DSA, MR angiography, CT angiography, the operation of the donor, the operation of the recipient, the extra costs of operation per hour, the costs of complications, the costs of mortality and the yearly costs associated with the health states.

VIII. QUALITY-OF-LIFE ESTIMATES

Since no quantitative literature was available to estimate the quality of life of renal transplant donors we needed to make an assumption. Because donors are healthy individuals, their quality of life was considered to be equal to 1. However, for donors who need dialysis after 15 years, the estimate was assumed to be 1 for the first 15 years and equal to the estimate for dialysis patients after this period.

The quality of life estimates for transplant recipients and dialysis patients were obtained from the literature.[10,11] The estimates reported by Churchill and colleagues[10] were used as a baseline estimate and lower limit of the sensitivity analysis and the estimate from Sesso and colleagues[11] was used as the upper limit for the sensitivity analysis, since their study population was much smaller. The values are presented in Table 21.

TABLE 16. Computation of costs of DSA, MR angiography and CT angiography

	DSA costs (euro)	MR angiography costs (euro)	CT angiography costs (euro)
Direct health care costs			
I. Procedure			
A. Directly assignable costs			
A1. Personnel costs	83.74	50.14	31.46
A2. Material costs	73.76	89.13	42.68
A3. Equipment costs	76.25	279.31	124.60
B. Non-directly assignable costs			
B1. Costs supporting departments	0.37	0.37	0.37
B2. Housing and liquidation costs	12.53	9.57	7.24
B3. Overhead costs	35.06	62.79	29.81
II. Hospital admittal costs	170.17		
Direct non-health care costs			
1. Travel costs	11.80	11.80	11.80
2. Time costs	14.42	5.86	4.96
TOTAL	478	509	253

TABLE 17. Computation of operation costs

	Donor costs (euro)			Recipient costs (euro)		
	Base-line	SA-lower	SA-upper	Base-line	SA-lower	SA-upper
Direct health care costs						
I. Procedure						
A. Directly assignable costs						
A1. Personnel costs	1,230	987	1,474	810	566	1,054
A2. Material costs	1,863	1,794	1,931	172	103	240
A3. Equipment costs	1.43	1.08	1.80	1.21	0.73	1.69
B. Non-directly assignable costs						
B1. Costs supporting departments	301	226	377	188	113	264
B2. Housing, liquidation and overhead costs	1,083	974	1,193	344	234	453
II. Hospital admittal costs	1,664	1,664	1,664	4,764	4,764	4,764
III. Consultation costs	223	223	223	74	74	74
Direct non-health care costs						
1. Travel costs	46.29	46.29	46.29	3.63	3.63	3.63
2. Time costs	263	263	263	609	609	609
TOTAL	6,629	6,131	7,127	6,962	6,465	7,460

SA-lower = lower limit of sensitivity analysis, SA-upper = upper limit of sensitivity analysis

TABLE 18. Computation of costs of one hour of surgery

	1 hour of surgery (euro)
A. Directly assignable costs	
A1. Personnel costs	280
A2. Material costs	1.36
A3. Equipment costs	0.45
B. Non-directly assignable costs	
B1. Costs supporting departments	2.27
B2. Housing, liquidation and overhead costs	98
TOTAL	383

TABLE 19. Computation of complications- and mortality- induced costs

	Baseline (euro)	SA-lower (euro)	SA-upper (euro)
Complications diagnostic test	681	340	1,021
Complications donor operation	1,701	1,021	2,382
Complications recipient operation	3,402	1,701	5,104
Complications of dialysis	*	*	*
Complications of having a renal transplant	3,402	1,701	5,104
Mortality	2,337	1,168	3,505

*Costs are incorporated in yearly costs of dialysis.
SA-lower = lower limit of sensitivity analysis, SA-upper = upper limit of sensitivity analysis

TABLE 20. Computation of yearly costs of the different states (euro)

	D: 1nRD	R: RtxW First year	R: RtxW Later years	CAPD	HD
Direct health care costs	74	4,043	3,076	27,407	40,763
Direct non-health care costs					
Travel costs	12	33	9	23	287
Time costs	5	98	27	69	2,818
TOTAL	92	4,173	3,112	27,498	43,867

D:1nRD = donor with one non-diseased kidney, R: RtxW = recipient with a non-diseased transplant,
CAPD = continuous ambulatory peritoneal dialysis, HD = hemodialysis

TABLE 21. Quality-of-life estimates

	Estimate	Range	Source
Renal transplant donor	1	0.9 - 1	
Renal transplant recipient	0.84	0.84 – 0.94	[10,11]
CAPD patient	0.56	0.56 – 0.79	[10,11]
HD patient	0.43	0.43 – 0.63	[10,11]

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Quantifying the benefit of early living-donor transplantation with a simulation model of the Dutch renal replacement therapy population

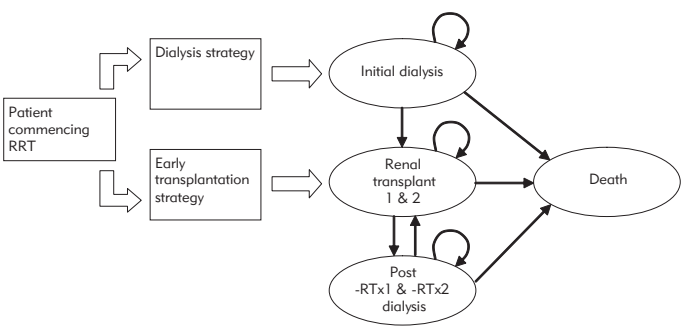
Technical appendix

CONTENTS

I. MODEL

We developed a state-transition model to estimate the life-expectancy (LE) of patients commencing renal replacement therapy (RRT), comprising 4 states: 1) hemodialysis (HD), 2) peritoneal dialysis (PD), 3) RTx and 4) death. Two treatment strategies were evaluated for these patients. In the first strategy, *Dialysis*, patients start dialysis therapy, with the chance of being wait-listed and of receiving a renal transplant from a cadaveric donor. Dialysis therapy is subdivided into HD and PD; subsequent switches were not modeled explicitly but were reflected in the source data. If patients receive a renal transplant, graft failure may occur and patients return to HD or PD. Patients can receive a maximum of two renal transplants. The second strategy, *Early transplantation*, patients receive a pre-emptive or early renal transplant (within the first 90 days of dialysis) from a living donor. If the transplant fails, patients will be treated with HD or PD. Patients may receive a cadaveric RTx at a later stage. A schematic overview of the model is presented in Figure 1.

FIGURE 1. Schematic overview of the simulation model.



RRT = renal replacement therapy, RTx = renal transplantation

We used a Markov process model, with a cycle length of three months. State-transition rates, dependent on patient covariates were estimated from Cox models and transformed into 3-monthly transition probabilities. We estimated the Cox models for death and for transitions to other treatments for three treatment periods: initial dialysis, transplantation and post-transplant dialysis. Patient history in terms of type of previous dialysis modality and previous transplants was tracked using additional health states. Outcome measures were LE and quality-adjusted life-expectancy (QALE) from the perspective of the patients receiving RRT.

II. DATA SOURCES AND ASSUMPTIONS

Initial dialysis models

For the initial dialysis models, we used a sample of 15,435 patients from the RENINE registry who started RRT between January 1st 1987 and December 31st 2002, excluding patients younger than 18 years, patients who underwent RRT for less than 30 days, patients who had more than one episode of recovery of renal function, or who died directly following a period of renal recovery, patients who received a pre-emptive transplantation, patients who died during the first 90 days of RRT and patients from centers treating fewer than 20 dialysis patients or fewer than 5 PD patients. We also excluded patients older than 78 years, because no patient was transplanted beyond that age.

Both initial dialysis Cox models (mortality and rate of first RTx) were left-truncated for the first 90 days. Because several variables had a significant interaction with time, we estimated initial dialysis mortality using a time-stratified Cox-proportional hazards regression model that included the covariates dialysis modality (at day 91), age, gender, primary renal disease, year of start of RRT, dialysis center and the interaction variables, age with PD and with PRD-DM and DM with PD and with gender. In the database, primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). We aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM), and a category for all other renal diagnoses (PRD-OTH). Patients were censored at transplantation or the end of follow-up. The transplantation rate for initial dialysis patients was estimated with a time-stratified Cox-proportional hazards model that was adjusted for dialysis modality,

age, age^2, gender, primary renal disease, year of start of RRT, dialysis center and interaction variables. In addition to censoring at death or at the end of follow-up, patients were censored at the age of 78 years or at a maximum dialysis time of 13 years because no patient was transplanted beyond that age or dialysis duration.

Although we did not have information on transplantability for all dialysis patients, such information was available for another subset of RENINE data. Based on this sample, we estimated the hazard ratios (HRs) of transplantable patients compared with the entire initial dialysis population for both mortality and transplantation rates and used these HRs as relative risks to adjust the mortality and transplantation rates obtained from the initial dialysis models.

Transplant models (first and second transplant)

Both RTx patient mortality and graft failure for first and second transplants were modeled from the dialysis mortality model patients that were transplanted before December 31st 2002, (4,390 patients, of which 309 patients also received a second transplant) and on 719 patients that received an early transplant (either preemptive or within the first 90 days of dialysis) and their second transplants (for 53 patients). This resulted in a total of 5,471 transplants. Three Cox-models were constructed for patient mortality, graft failure and return to HD and graft failure and return to PD. Covariates included pre-transplant dialysis modality (HD, PD or early transplant), age, gender, primary renal disease, year and center of transplantation, type of donor (living or cadaveric) and total RRT duration preceding transplantation (only for the patient mortality model) and number of transplant (first or second, only for the graft failure models). The transplant mortality analysis was censored for graft failure and graft failure analyses were censored for patient death and for graft failure with transition to the other dialysis modality.

Post-transplant dialysis models

Post-transplant dialysis mortality was modeled on the data of patients included in the transplant models that returned to dialysis after failure of a first (n=893) or a second renal transplant (n=102). The Cox model included the covariates dialysis modality after transplantation, age at restart of dialysis, gender, primary renal disease, total duration of RRT and the interaction variable of age and PRD-DM. Patients were censored at transplantation or at the end of follow-up. The rate of receiving a second transplant was

modeled on the sample that returned to dialysis after failure of a first renal transplant (n=893). Covariates included in the Cox model were dialysis modality after transplantation, age and age^2 at restart of dialysis, gender, primary renal disease, year of restart of dialysis, total RRT duration preceding restart of dialysis and the interaction variable of dialysis modality and gender. Patients were censored at death or at the end of follow-up.

Extrapolating survival data beyond observed follow-up time

We extrapolated our survival data beyond the observed follow-up time to allow for a lifetime time-horizon. The extrapolation was accomplished by fitting weighted quadratic regression functions on the baseline cumulative hazard over time of all Cox models. To obtain the instantaneous baseline hazard as a function of time, we computed the first derivative of the quadratic functions, resulting in a linear function over time. A linear function has shown to be adequate for extrapolation of instantaneous hazard data.[1]

Quality of life

For estimates of utilities of HD, PD, and RTx patients, we used EuroQoL EQ-5D estimates from a recently published from systematic review of the literature,[2] in accordance with recommendations from the Panel on Cost-Effectiveness in Health and Medicine to prefer values from an indirect method.[3] The means and standard deviations (SDs) were 0.5560 (0.0283) for HD, 0.5817 (0.0385) for PD and 0.8077 (0.0407) for RTx patients. To account for short-term disutilities from procedures, we deducted the duration of procedure-related hospitalization, i.e., assumed a quality of life of 0 for those days. The duration of hospitalization was based on expert opinion (J.F.M.W.) for HD shunt and PD catheter implantation and on data from the Dutch Organ Transplant Registry for cadaveric and living RTx.[4]

Uncertainty and variability

We performed second-order Monte Carlo simulations to account for parameter-uncertainty. Parameter uncertainty of transition probabilities was accounted for by estimating the Cox-proportional hazards models on 1,000 bootstrap samples of the RENINE patient sample, and estimating a weighted quadratic regression model on the baseline cumulative survival of each of the 1,000 Cox models. Bootstrapping was performed

separately for the three different treatment periods (R, version 2.5.1, The R Foundation for Statistical Computing, Vienna, Austria). For the uncertainty in quality of life estimates, we fitted beta distributions on the means and SDs of the EQ-5D values that we obtained from our meta-analysis.

Analyses

The model was developed and analyzed in TreeAge Pro Suite 2007 (TreeAge software, Inc., Williamstown, MA). We calculated LE, expressed in life-years (LYs) and QALE, expressed in quality-adjusted life-years (QALYs) for the two strategies for a patient commencing RRT. For the *Dialysis* strategy, the patient entered the model in the initial dialysis state, for the *Early Transplantation* strategy, the patient entered in the transplantation state, with the variable 'type of donor' set to 'living-related' and the variable 'pre-transplant dialysis modality' set to 'early transplant'. As mentioned earlier, these early transplants included both pre-emptive transplants as well as transplants within the first 90 days of dialysis. We assessed the outcome measures for different scenarios defined by age (40, 50, 60 or 70 years), gender and primary renal disease of the patient. The LEs associated with both strategies were compared to that of the Dutch general population,[5] 2007 which we computed using general population mortality rates in 1996, the mean year of start of dialysis in our cohort.

Based on the incidence of RRT-patients and the percentages of early transplantation and dialysis as initial RRT modalities on day 91 in the Netherlands in 2005,[6] we calculated the absolute number of incident early transplantation patients and incident dialysis patients. We estimated mean LEs associated with the *Early transplantation* and *Dialysis* strategies for the mean age and gender distribution of the incident 2005 cohort and multiplied these estimated LEs with the incidence rates and numbers for early transplantation and dialysis to obtain an estimated average LE for an individual patient as well as for the entire incident cohort. We repeated this calculation, assuming the highest early transplantation rate reported in incident patients among ERA-EDTA affiliated countries[6] and calculated the benefit of increasing the early transplantation rate to this higher rate for both a potential patient as well as for the Dutch incident RRT population.

III. INITIAL AND TRANSITION PROBABILITIES

The initial probabilities were defined by two variables, *prevPD* and *prevPERTx;* these were set differently for each strategy (see Table 1).

TABLE 1. Initial probabilities

name	description	value Dialysis	value Early RTx
prevPD	probability of initial assigment to PD	vDial_initial_PD	0
prevPERTx	probability of receiving a pre-emptive RTx	0	1

TABLE 2. Transition probabilities

name	description	value
pDieDial_initial	probability of dying on initial dialysis	IF(hTot_dial_initial>0;(hDieDial_initial/hTot_dial_initial)*(1-Exp(-hTot_dial_initial));(1-Exp(-hDieDial_initial)))
pDieDial_postTx	probability of dying on dialysis post renal transplant	IF(hTot_dial_postRTx>0;(hDieDial_postTx/hTot_dial_postRTx)*(1-Exp(-hTot_dial_postRTx));(1-Exp(-hDieDial_postTx)))
pDieRTx	probability of dying with renal transplant	IF(hTot_RTx>0;(hDieRTx/hTot_RTx)*(1-Exp(-hTot_RTx));(1-Exp(-hDieRTx)))
pHDFailRTx	probability of graft failure and return to HD	IF(hTot_RTx>0;(hHDFailRTx/hTot_RTx)*(1-Exp(-hTot_RTx));(1-Exp(-hHDFailRTx)))
pPDFailRTx	probability of graft failure and return to PD	IF(hTot_RTx>0;(hPDFailRTx/hTot_RTx)*(1-Exp(-hTot_RTx));(1-Exp(-hPDFailRTx)))
pRTx1	probability of receiving 1st renal transplant	IF(hTot_dial_initial>0;(hRTx1/hTot_dial_initial)*(1-Exp(-hTot_dial_initial));(1-Exp(-hRTx1)))
pRTx2	probability of receiving 2nd renal transplant	IF(hTot_dial_postRTx>0;(hRTx2/hTot_dial_postRTx)*(1-Exp(-hTot_dial_postRTx));(1-Exp(-hRTx2)))

For the transition probabilities (Table 2), the Cox regression equations were used. Hazard rates from the Cox models were converted into probabilities assuming an exponential distribution. Since competing risks were present during each of the three defined periods (initial dialysis, transplantation and post-transplant dialysis), we defined the individual transition probabilities (e.g. the probability of dying with an RTx) as the total transition probability for the period (e.g. for the transplant period: the total probability of dying, failing with return to HD and failing with return to PD) times the fraction of the

TABLE 3. Total hazards for the three periods

name	description	value
hTot_dial_initial	total hazard for initial dialysis patient	hDieDial_initial + hRTx1
hTot_dial_postRTx	total hazard for dialysis post transplant patient	hDieDial_postTx + hRTx2
hTot_RTx	total hazard for renal transplant patient	hDieRTx + hHDFailRTx + hPDFailRTx

individual hazard divided by the total of all hazards for the specific period. Furthermore, we defined in an if-statement that this equation should only be used if the total hazard for the period is more than 0, because if all hazards for a specific period are 0, then the denominator of the fraction of hazards is 0 and the fraction approaches infinity. If all hazards were 0, the transition probability was only defined by the hazard. Definitions of the total hazards for each of the treatment periods are shown in Table 3.

In Table 4, the definitions of the individual hazards are listed. These definitions were based on the Cox models. Each definition consists of two parts: the instantaneous baseline hazard (*h0i*) and the exponent of the linear predictor of the Cox model. For both hazards in the initial dialysis period (*hDieDial_initial* and *hRTx1*), we used several definitions, as these Cox models were time-stratified because of violation of the proportional hazards assumption. Therefore, we defined discrete time strata within the initial dialysis period (Table 5), in which different Cox models for each of the two competing risks operated (Table 4, numbered I through III for *hDieDial*, and I and II for *hRTx1*). Time was counted using TreeAge's *_stage* counter for the initial period and the *_tunnelfunction* for the other periods (Table 6). It was converted into years using the definition of cycle length, in our analyses 3 months (*dt*, Table 7). Every cycle, the time counter was compared to the time strata defined for the initial dialysis period, and the appropriate Cox model was used accordingly.

The instantaneous baseline hazards were defined by the weighted quadratic regressions which we modeled on the cumulative baseline hazard as a function of time (Table 8). For the betas from the first derivative of these quadratic regressions, describing the instantaneous baseline hazard, we defined tables, with a row for each of the 1,000 bootstrap samples (*p*, Table 7). Time was evaluated using the same counter as described previously (Table 6). The hazards were again defined using an if-statement, which allowed them to be 0 if the (modeled) hazard dropped below 0.

TABLE 4. Definition of hazards

name	description	value
hDieDial_initial	hazard of dying on initial dialysis	RR_hDieDial_initial*If(dial_initial_period_mort = 0; hDieDial_initial_I; If(dial_initial_period_mort = 0.25;hDieDial_initial_II; hDieDial_initial_III))
hDieDial_initial_I	hazard of dying on initial dialysis timeperiod I	(h0i_d_mort)*(Exp(BdmortI[p;1]*vDial_initial_age + BdmortI[p;2]*vFemale + BdmortI[p;3]*vPrdHT + BdmortI[p;4]*vPrdRVD + BdmortI[p;5]*vPrdDM + BdmortI[p;6]*vPrdoth + BdmortI[p;7]*vDial_initial_PD + BdmortI[p;8]*vDial_initial_year + BdmortI[p;9]*vDial_initial_ctr+ BdmortI[p;10]*vInt_Dial_initial_age_PD + BdmortI[p;11]*vInt_Dial_initial_DM_PD + BdmortI[p;12]*vInt_Dial_initial_age_DM + BdmortI[p;13]*vInt_Dial_initial_F_DM))
hDieDial_initial_II	hazard of dying on initial dialysis timeperiod II	(h0i_d_mort)*(Exp(BdmortII[p;1]*vDial_initial_age + BdmortII[p;2]*vFemale + BdmortII[p;3]*vPrdHT + BdmortII[p;4]*vPrdRVD + BdmortII[p;5]*vPrdDM + BdmortII[p;6]*vPrdoth + BdmortII[p;7]*vDial_initial_PD + BdmortII[p;8]*vDial_initial_year + BdmortII[p;9]*vDial_initial_ctr+ BdmortII[p;10]*vInt_Dial_initial_age_PD + BdmortII[p;11]*vInt_Dial_initial_DM_PD + BdmortII[p;12]*vInt_Dial_initial_age_DM + BdmortII[p;13]*vInt_Dial_initial_F_DM))
hDieDial_initial_III	hazard of dying on initial dialysis timeperiod III	(h0i_d_mort)*(Exp(BdmortIII[p;1]*vDial_initial_age + BdmortIII[p;2]*vFemale + BdmortIII[p;3]*vPrdHT + BdmortIII[p;4]*vPrdRVD + BdmortIII[p;5]*vPrdDM + BdmortIII[p;6]*vPrdoth + BdmortIII[p;7]*vDial_initial_PD + BdmortIII[p;8]*vDial_initial_year + BdmortIII[p;9]*vDial_initial_ctr+ BdmortIII[p;10]*vInt_Dial_initial_age_PD + BdmortIII[p;11]*vInt_Dial_initial_DM_PD + BdmortIII[p;12]*vInt_Dial_initial_age_DM + BdmortIII[p;13]*vInt_Dial_initial_F_DM))
hDieDial_postTx	hazard of dying on dialysis post transplant	(h0i_dr_mort)*(Exp(Bdr_mort[p;1]*vDial_postRTx12_age + Bdr_mort[p;2]*vFemale + Bdr_mort[p;3]*vPrdHT + Bdr_mort[p;4]*vPrdRVD + Bdr_mort[p;5]*vPrdDM + Bdr_mort[p;6]*vPrdoth + Bdr_mort[p;7]*vDial_postRTx_PD + Bdr_mort[p;8]*vRRTdur_postRTx12 + Bdr_mort[p;9]*vInt_Dial_postRTx_age_DM))
hDieRTx	hazard of dying with renal transplant	(h0i_r_mort)*(Exp(Br_mort[p;1]*vDial_initial_PD + Br_mort[p;2]*vRTx_PE + Br_mort[p;3]*vRTx_LR + Br_mort[p;4]*vRRTdur_RTx + Br_mort[p;5]*vRTx_age + Br_mort[p;6]*vFemale + Br_mort[p;7]*vPrdHT + Br_mort[p;8]*vPrdRVD + Br_mort[p;9]*vPrdDM + Br_mort[p;10]*vPrdoth + Br_mort[p;11]*vRTx_year + Br_mort[p;12]*vRTx_ctr))
hHDFailRTx	hazard of graft failure and return to HD	(h0i_r_HDfail)*(Exp(Br_HDfail[p;1]*vDial_initial_PD + Br_HDfail[p;2]*vRTx_PE + Br_HDfail[p;3]*vRTx_2nd + Br_HDfail[p;4]*vRTx_LR + Br_HDfail[p;5]*vRTx_age + Br_HDfail[p;6]*vFemale + Br_HDfail[p;7]*vPrdHT + Br_HDfail[p;8]*vPrdRVD + Br_HDfail[p;9]*vPrdDM + Br_HDfail[p;10]*vPrdoth + Br_HDfail[p;11]*vRTx_year + Br_HDfail[p;12]*vRTx_ctr))

hPDFailRTx	hazard of graft failure and return to PD	(h0i_r_PDfail)*(Exp(Br_PDfail[p;1]*vDial_initial_PD + Br_PDfail[p;2]*vRTx_PE + Br_PDfail[p;3]*vRTx_2nd + Br_PDfail[p;4]*vRTx_LR + Br_PDfail[p;5]*vRTx_age + Br_PDfail[p;6]*vFemale + Br_PDfail[p;7]*vPrdHT + Br_PDfail[p;8]*vPrdRVD + Br_PDfail[p;9]*vPrdDM + Br_PDfail[p;10]*vPrdoth + Br_PDfail[p;11]*vRTx_year + Br_PDfail[p;12]*vRTx_ctr))
hRTx1	hazard of receiving 1st renal transplant	RR_hRTx1*If(dial_initial_period_pTx = 0; hRTx1_I; hRTx1_II)
hRTx1_I	hazard of receiving 1st renal transplant timeperiod I	(h0i_d_RTx1)*(Exp(Bd_RTx1_I[p;1]*vDial_initial_PD + Bd_RTx1_I[p;2]*vDial_initial_age + Bd_RTx1_I[p;3]*vDial_initial_agesq + Bd_RTx1_I[p;4]*vFemale + Bd_RTx1_I[p;5]*vPrdHT + Bd_RTx1_I[p;6]*vPrdRVD + Bd_RTx1_I[p;7]*vPrdDM + Bd_RTx1_I[p;8]*vPrdoth + Bd_RTx1_I[p;9]*vDial_initial_year + Bd_RTx1_I[p;10]*vDial_initial_ctr+ Bd_RTx1_I[p;11]*vInt_Dial_initial_age_PD + Bd_RTx1_I[p;12]*vInt_Dial_initial_age_DM + Bd_RTx1_I[p;13]*vInt_Dial_initial_F_DM))
hRTx1_II	hazard of receiving 1st renal transplant timeperiod II	(h0i_d_RTx1)*(Exp(Bd_RTx1_II[p;1]*vDial_initial_PD + Bd_RTx1_II[p;2]*vDial_initial_age + Bd_RTx1_II[p;3]*vDial_initial_agesq + Bd_RTx1_II[p;4]*vFemale + Bd_RTx1_II[p;5]*vPrdHT + Bd_RTx1_II[p;6]*vPrdRVD + Bd_RTx1_II[p;7]*vPrdDM + Bd_RTx1_II[p;8]*vPrdoth + Bd_RTx1_II[p;9]*vDial_initial_year + Bd_RTx1_II[p;10]*vInt_Dial_initial_age_PD + Bd_RTx1_II[p;11]*vInt_Dial_initial_age_DM + Bd_RTx1_II[p;12]*vInt_Dial_initial_F_DM))
hRTx2	hazard of receiving 2nd renal transplant	(h0i_dr_RTx2)*(Exp(Bdr_RTx2[p;1]*vDial_postRTx_PD + Bdr_RTx2[p;2]*vDial_postRTx1_age + Bdr_RTx2[p;3]*vDial_postRTx_agesq + Bdr_RTx2[p;4]*vFemale + Bdr_RTx2[p;5]*vPrdHT + Bdr_RTx2[p;6]*vPrdRVD + Bdr_RTx2[p;7]*vPrdDM + Bdr_RTx2[p;8]*vPrdoth + Bdr_RTx2[p;9]*vDial_postRTx_year + Bdr_RTx2[p;10]*vRRTdur_postRTx1 + Bdr_RTx2[p;11]*vInt_Dial_postRTx_PD_F))

TABLE 5. Definitions of time-strata within initial dialysis period

name	description	value
dial_initial_period_mort	dialysis period as defined by baseline hazard initial dialysis patients	If(t_dial_initial*dt<=0.25;0;If(0.25<t_dial_initial*dt<=1;0.25;1))
dial_initial_period_pTx	dialysis period as defined by baseline pTx hazard initial dialysis patients	If(t_dial_initial*dt<=6;0;6)

TABLE 6. Definitions of time-counters

name	description	value
t_dial_initial	time on initial dialysis in cycles minus first 90 days	_stage-extracyc+1
t_dial_postRTx	time on dialysis post renal transplant in cycles	_tunnel
t_RTx	time on transplantation in cycles	_tunnel

TABLE 7. Variables for general model-adjustment

name	description	value
corrHalfCyc	half cycle correction	0.5
dt	cycle length in years	3/12
extracyc	extra time to account for left censoring	
p	sample	sampleBootstrap

TABLE 8. Definition of instantaneous baseline hazards

name	description	value
h0i_d_mort	baseline instantaneous hazard of initial dialysis mortality	IF((1.55*h0dmort[p;1] + 2.8*h0dmort[p;2]*(t_dial_initial-corrBaseHaz)*dt)*dt>0; (1.55*h0dmort[p;1] + 2.8*h0dmort[p;2]*(t_dial_initial-corrBaseHaz)*dt)*dt;0)
h0i_d_RTx1	baseline instantaneous hazard of receiving 1st renal transplant	IF((1.7*h0d_RTx1[p;1] + 0*h0d_RTx1[p;2]*(t_dial_initial-corrBaseHaz)*dt)*dt>0; (1.7*h0d_RTx1[p;1] + 0*h0d_RTx1[p;2]*(t_dial_initial-corrBaseHaz)*dt)*dt;0)
h0i_dr_mort	baseline instantaneous hazard of mortality on dialysis after renal transplant	IF((h0dr_mort[p;1] + 0.6*h0dr_mort[p;2]*(t_dial_postRTx-corrBaseHaz)*dt)*dt>0; (h0dr_mort[p;1] + 0.6*h0dr_mort[p;2]*(t_dial_postRTx-corrBaseHaz)*dt)*dt;0)
h0i_dr_RTx2	baseline instantaneous hazard of receiving 2nd renal transplant	IF((1.1*h0dr_RTx2[p;1] + h0dr_RTx2[p;2]*(t_dial_postRTx-corrBaseHaz)*dt)*dt>0; (1.1*h0dr_RTx2[p;1] +h0dr_RTx2[p;2]*(t_dial_postRTx-corrBaseHaz)*dt)*dt;0)
h0i_r_mort	baseline instantaneous hazard of dying with renal transplant	IF((2.35*h0r_mort[p;1] + 0.2*h0r_mort[p;2]*(t_RTx-corrBaseHaz)*dt)*dt>0; (2.35*h0r_mort[p;1] + 0.2*h0r_mort[p;2]*(t_RTx-corrBaseHaz)*dt)*dt;0)
h0i_r_HDfail	baseline instantaneous hazard of graft failure and return to HD	IF((2.05*h0r_HDfail[p;1] + h0r_HDfail[p;2]*(t_RTx-corrBaseHaz)*dt)*dt>0; (2.05*h0r_HDfail[p;1] +h0r_HDfail[p;2]*(t_RTx-corrBaseHaz)*dt)*dt;0)
h0i_r_PDfail	baseline instantaneous hazard of graft failure and return to PD	IF((0.75*h0r_PDfail[p;1] + h0r_PDfail[p;2]*(t_RTx-corrBaseHaz)*dt)*dt>0; (0.75*h0r_PDfail[p;1] + h0r_PDfail[p;2]*(t_RTx-corrBaseHaz)*dt)*dt;0)

The linear predictor for each hazard function was defined by: 1. the betas for all covariates, and 2. the values for the covariates. Since we estimated Cox models on 1,000 bootstrap samples, we used tables to model the betas, again defining the bootstrap samples in rows and the different betas pertaining to the different covariates in columns. The variable definitions for the covariate values are listed in Table 9. Table 9a contains variables that are used throughout all three treatment periods, including an age-counter, tracking the patients' age throughout the model (*vAgeMKV*), the initial

age of a patient starting the model, the year of start of RRT and the variables that do not change with advancing time: gender and primary renal disease. These variables are shown at the population means; age, gender and primary renal disease were varied in our analyses, as described above. Tables 9b, 9c and 9d show the specific variables for each of the treatment periods. In general, the variables that change over time (age, age-squared, year, and RRT-duration) were defined using time counters. In addition, the population-means were subtracted from each variable because the Cox models were modeled at the means of the covariates for all continuous variables. For the center-variables, the linear predictor of all centers times their beta was calculated for each bootstrap sample and entered into the table, therefore the value of the center-variables is 1 (which gets multiplied with the linear predictor from the table). For the *Dialysis* strategy, extra cycles were added at the start of the model in the initial dialysis models because of the left-censored 90 days. This was accomplished by defining the variable *extracyle* (Table 7).

TABLE 9a. Definitions and values for covariate-variables used throughout all three periods

name	description	value
vAgeMKV	age in Markov	vInitial_age+_stage*dt
vInitial_age	age at baseline	57.24092696
vInitial_year	year at baseline	1995.393886
vFemale	female; 0=no, 1=yes	0.411734164
vPrdDM	primary renal disease diabetes	0.157385774
vPrdHT	primary renal disease hypertension	0.11201973
vPrdoth	primary renal disease other	0.508307373
vPrdRVD	primary renal disease renal vascular disease	0.080023364

For the initial dialysis period, the Cox models were based on the entire dialysis population, consisting of both waitlisted and non-waitlisted patients, as described previously. We adjusted these hazards using as RRs, the HRs from Cox models comparing mortality and RTx access of waitlisted patients with the entire dialysis population. The definition of these RRs can be found in Table 10. For the RTx access analyses, the RR differed with age and the presence of diabetes mellitus as primary renal disease, and therefore 9 definitions for these RR were defined. The definition of the RRs will be discussed in more detail in the Distributions section.

TABLE 9b. Definitions and values for covariate-variables initial dialysis period

name	description	value
vDial_initial_age	age at baseline for dialysis patients	vInitial_age+extracyc*dt - vDial_initial_age_mean
vDial_initial_age_mean	mean age at baseline for dialysis patients from analyses	57.24092696
vDial_initial_agesq	age-squared at baseline for dialysis patients	(vInitial_age+extracyc*dt) ^ 2 - vDial_initial_agesq_mean
vDial_initial_agesq_mean	mean age-squared at baseline for dialysis patients from analyses	3485.784059
vDial_initial_ctr	initial dialysis center	1
vDial_initial_PD	initial dialysis modality; HD=0, PD=1	0.367146937
vDial_initial_year	year of start of RRT for dialysis patients	vInitial_year+extracyc*dt - vDial_initial_year_mean
vDial_initial_year_mean	mean year of start or RRT for dialysis patients from analyses	1995.393886
vInt_Dial_initial_age_PD	interaction variable initial age and dialysis modality	vInitial_age+extracyc*dt*vDial_initial_PD - vInt_Dial_initial_age_PD_mean
vInt_Dial_initial_age_PD_mean	mean for interaction variable initial age and dialysis modality	19.41730813
vInt_Dial_initial_DM_PD	interaction variable initial prevalence of diabetes and dialysis modality	vPrdDM*vDial_initial_PD
vInt_Dial_initial_age_DM	interaction variable initial age and prevalence of diabetes	vInitial_age+extracyc*dt*vPrdDM - vInt_Dial_initial_age_DM_mean
vInt_Dial_initial_age_DM_mean	mean for interaction variable initial age and prevalence of diabetes	9.232135204
vInt_Dial_initial_F_DM	interaction variable gender and prevalence of diabetes	vFemale*vPrdDM

TABLE 9c. Definitions and values for covariate-variables post-transplant dialysis period

name	description	value
vDial_postRTx1_age	age at restart dialysis post 1st renal transplant	vInitial_age+extracyc*dt+(_stage-extracyc-_tunnel+1)*dt - vDial_postRTx12_age_mean
vDial_postRTx1_age_mean	mean age at restart dialysis post 1st renal transplant	47.5725108
vDial_postRTx12_age	age at restart dialysis post 1st & 2nd renal transplant	vInitial_age+extracyc*dt+(_stage-extracyc-_tunnel+1)*dt - vDial_postRTx12_age_mean
vDial_postRTx12_age_mean	mean age at restart dialysis post 1st & 2nd renal transplant	47.47924738
vDial_postRTx_agesq	age-squared at restart dialysis post renal transplant	(vInitial_age+extracyc*dt+(_stage-extracyc-_tunnel+1)*dt) ^ 2 - vDial_postRTx_agesq_mean
vDial_postRTx_agesq_mean	mean age-squared at restart dialysis post renal transplant	2432.731156
vDial_postRTx_PD	dialysis modality post renal transplant; 0=HD, 1=PD	At HD post-RTx1 or post-RTx2 = 0; at PD post-RTx1 or post-RTx2 = 1
vDial_postRTx_year	year of restart of dialysis post renal transplant	vInitial_year+extracyc*dt+(_stage-extracyc-_tunnel+1)*dt - vDial_postRTx_year_mean
vDial_postRTx_year_mean	mean year of restart of dialysis post renal transplant	1996.137033
vInt_Dial_postRTx_age_DM	interaction variable post renal transplant age and prevalence of diabetes	vDial_postRTx_age*vPrdDM - vInt_Dial_postRTx_age_DM_mean
vInt_Dial_postRTx_age_DM_mean	mean for interaction variable post renal transplant age and prevalence of diabetes	3.64192484
vInt_Dial_postRTx_PD_F	interaction variable post renal tansplant dialysis modality and gender	vDial_postRTx_PD*vFemale
vRRTdur_postRTx1	total RRT duration for post 1st renal transplant patients	(_stage-extracyc-_tunnel+1)*dt - vRRTdur_postRTx1_mean
vRRTdur_postRTx1_mean	mean total RRT duration for post 1st renal transplant patient	4.258471098
vRRTdur_postRTx12	total RRT duration for post 1st and 2nd renal transplant patients	(_stage-extracyc-_tunnel+1)*dt - vRRTdur_postRTx12_mean
vRRTdur_postRTx12_mean	mean total RRT duration for post 1st and 2nd renal transplant patient	4.4964664

TABLE 9d. Definitions and values for covariate-variables transplantation period

name	description	value
vRTx_2nd	number of renal transplant; 0=1st, 1=2nd	At root = 0; At 2nd RTx state = 1
vRTx_age	age at transplantation	vInitial_age+extracyc*dt+(_stage-extracyc-_tunnel+1)*dt - vRTx_age_mean
vRTx_age_mean	mean age at transplantation	46.8022
vRTx_ctr	center of renal transplantation	1
vRTx_LR	type of tranpslant; 0=PM, 1=LR	For 1st RTx in Early RTx strategy = 1, otherwise = 0
vRTx_PE	type of pre-RTx treatment, 1=pre-emptive transplant	For 1st RTx in Early RTx strategy = 1, otherwise = 0
vRTx_year	year of transplantation	vInitial_year+extracyc*dt+(_stage-extracyc-_tunnel+1)*dt - vRTx_year_mean
vRTx_year_mean	mean year of transplantation	1995.898
vRRTdur_RTx	total RRT duration for renal transplant patients	(_stage-extracyc-_tunnel+1)*dt - vRRTdur_RTx_mean
vRRTdur_RTx_mean	mean total RRT duration for renal transplant patient	2.160501

TABLE 10. Relative risks to adjust hazards of initial dialysis period for waitlisting

name	description	value
RR_hDieDial_initial	relative risk of dying for waitlisted compared to non-waitlisted initial dialysis pts	Exp(Dist_lnHR_hDieDialinitial)
RR_hRTx1	relative risk of first Tx for waitlisted compared to non-waitlisted initial dialysis pts	IF(vInitial_age<45; RR_hRTx1_0; IF(vInitial_age>=45 & vInitial_age<60; RR_hRTx1_45; RR_hRTx1_60))
RR_hRTx1_0	relative risk of first Tx for waitlisted compared to non-waitlisted initial dialysis pts for pts aged <45yrs	IF(vPrdDM=0; Exp(Dist_lnHR_hRTx1_0noDM); IF(vPrdDM=1; Exp(Dist_lnHR_hRTx1_0DM); Exp(Dist_lnHR_hRTx1_0mean)))
RR_hRTx1_45	relative risk of first Tx for waitlisted compared to non-waitlisted initial dialysis pts for pts aged 45-60yrs	IF(vPrdDM=0; Exp(Dist_lnHR_hRTx1_45noDM); IF(vPrdDM=1; Exp(Dist_lnHR_hRTx1_45DM); Exp(Dist_lnHR_hRTx1_45mean)))
RR_hRTx1_60	relative risk of first Tx for waitlisted compared to non-waitlisted initial dialysis pts for pts aged >=60yrs	IF(vPrdDM=0; Exp(Dist_lnHR_hRTx1_60noDM); IF(vPrdDM=1; Exp(Dist_lnHR_hRTx1_60DM); Exp(Dist_lnHR_hRTx1_60mean)))

IV. REWARDS

The definitions we used in our model for the rewards are shown in Table 11. The rewards were calculated using TreeAge's discount function. For our analyses, the discount rate (*discRATEutil*) was set to 0; however, it can be adjusted in future versions of the model that include costs. TreeAge allows the user to define an initial reward (evaluated only during the first stage, _stage = 0, when the cohort is divided over the initial states), an incremental reward evaluated at each subsequent state and a final reward, which is calculated after the model has been terminated and is added to the total reward. We used the initial and the final rewards to model half cycle correction (*corrHalfCyc*, Table 7)

TABLE 11. Definitions of rewards

name	definition
Initial reward	corrHalfCyc * (Discount(utility*dt-IF(_tunnel=1;disutility;0);discRATEutil; _stage*dt))
Incremental reward	Discount(utility*dt-IF(_tunnel=1;disutility;0);discRATEutil;_stage*dt)
Final reward	corrHalfCyc * (Discount(utility*dt;discRATEutil;_stage*dt))

For the LE analyses, all utilities were set to 1. For the QALE analyses, the rewards were calculated using EQ-5D utilities. For these utilities a mean and standard deviation (SD) value (Table 12) were used to parameterize the beta-distributions described below. For the utility associated with RTx, several variables were defined, because we assumed that during the first 3 months after transplantation, quality of life of RTx patients with preceding dialysis treatment was equal to that of dialysis patients. Therefore, the initial 3-month quality of life associated with a second transplant (*uRTx2*) was always adjusted. In the *Dialysis* strategy, the first RTx could only be obtained after dialysis, so *uRTx1* was equal to *uRTx2*. In the *Early transplantation* strategy, the first RTx was not preceded by dialysis and therefore the associated utility did not need to be adjusted (*uRTx1 = uPERTx*). Disutilities (Table 13) were subtracted from the reward, when the patient first entered the state.

TABLE 12. Utilities

name	description	value
uHD	utility hemodialysis patient	Dist_uHD
uHDmean	utiltity HD mean	uEQ5D_HDmean
uHDse	utility HD SEM	uEQ5D_HDse
uPD	utility peritoneal dialysis patient	Dist_uPD
uPDmean	utility PD mean	uEQ5D_PDmean
uPDse	utility PD SEM	uEQ5D_PDse
uPERTx	utility of pre-emptive (1st) transplant	Dist_uRTx
uRTx1	utility renal transplant patient 1st transplant	uRTx2
uRTx2	utility renal transplant patient 2nd transplant	IF(_tunnel<=0.25/dt; (1-vDial_initial_PD)*Dist_uHD + vDial_initial_PD*Dist_uPD; Dist_uRTx)
uRTxmean	utility RTx mean	uEQ5D_RTxmean
uRTxse	utility RTx SEM	uEQ5D_RTxse
uEQ5D_HDmean	EQ5D index mean value for HD	0.556
uEQ5D_HDse	EQ5D index SEM for HD	0.02833
uEQ5D_PDmean	EQ5D index mean value of utility PD	0.5817
uEQ5D_PDse	EQ5D index SEM utility PD	0.0385
uEQ5D_RTxmean	EQ5D index mean value of utility RTx	0.8077
uEQ5D_RTxse	EQ5D index SEM utility RTx	0.04071

TABLE 13. Disutilities

name	description	value
uDisHD	disutility of HD shunt construction	(2+IF(vAgeMKV<60;0.1;0.2)*2)/365.25
uDisPD	disutility of PD catheter insertion	uDisHD
uDisPERTx	disutility of pre-emptive Tx (LR) implantation	19.8/365.25
uDisRTx1	disutility of 1st RTx implantation	uDisRTx2
uDisRTx2	disutility of 2nd RTx implantation	27.2/365.25

TABLE 14. Distributions

name	description	type	Parameter 1	Parameter 2
sampleBootstrapDialinitial	samples from bootstrapping initial dialysis patients	Uniform	1	1000
sampleBootstrapRTx	samples from bootstrapping renal transplant patients	Uniform	1	1000
sampleBootstrapDialpostTx	samples from bootstrapping postTx dialysis patients	Uniform	1	1000
Dist_lnHR_hDieDialinitial	distribution of lnHR hDieDial_initial	Normal	lnHR_hDieDial_initial [_stage*dt;1]	lnHR_hDieDial_initial [_stage*dt;2]
Dist_lnHR_hRTx1_0mean	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_upto45mean [_stage*dt;1]	lnHR_hRTx1_upto45mean [_stage*dt;2]
Dist_lnHR_hRTx1_0noDM	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_upto45noDM [_stage*dt;1]	lnHR_hRTx1_upto45noDM [_stage*dt;2]
Dist_lnHR_hRTx1_0DM	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_upto45DM [_stage*dt;1]	lnHR_hRTx1_upto45DM [_stage*dt;2]
Dist_lnHR_hRTx1_45mean	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_45to60mean [_stage*dt;1]	lnHR_hRTx1_45to60mean [_stage*dt;2]
Dist_lnHR_hRTx1_45noDM	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_45to60noDM [_stage*dt;1]	lnHR_hRTx1_45to60noDM [_stage*dt;2]
Dist_lnHR_hRTx1_45DM	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_45to60DM [_stage*dt;1]	lnHR_hRTx1_45to60DM [_stage*dt;2]
Dist_lnHR_hRTx1_60mean	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_60mean [_stage*dt;1]	lnHR_hRTx1_60mean [_stage*dt;2]
Dist_lnHR_hRTx1_60noDM	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_60noDM [_stage*dt;1]	lnHR_hRTx1_60noDM [_stage*dt;2]
Dist_lnHR_hRTx1_60DM	distribution of lnHR hRTx1 for pts up to 45 yrs of age, mean prd	Normal	lnHR_hRTx1_60DM [_stage*dt;1]	lnHR_hRTx1_60DM [_stage*dt;2]

Dist_uHD	distribution of utility HD	Beta	uHDmean ^ 2*(1-uHDmean)/ uHDse ^ 2	uHDmean*(1-uHDmean)/ uHDse ^ 2-(uHDmean ^ 2* (1-uHDmean)/uHDse ^ 2)
Dist_uPD	distribution of utility PD	Beta	uPDmean ^ 2*(1-uPDmean)/ uPDse ^ 2	uPDmean*(1-uPDmean)/ uPDse ^ 2-(uPDmean ^ 2* (1-uPDmean)/uPDse ^ 2)
Dist_uRTx	distribution of utility RTx	Beta	uRTxmean ^ 2*(1-uRTxmean)/ uRTxse ^ 2	uRTxmean*(1-uRTxmean)/ uRTxse ^ 2-(uRTxmean ^ 2* (1-uRTxmean)/uRTxse ^ 2)

V. DISTRIBUTIONS

The model was run using 2nd order Monte Carlo Simulations in order to perform probabilistic sensitivity analyses. In TreeAge, these model runs are defined as *Samples*. For each analysis we ran 1,000 Samples, seeding the simulations to ensure comparability.

The distributions of the model are shown in Table 14; the type of variable defined by parameter 1 and parameter 2 differed for the different types of distributions. The first three distributions were used to draw the betas from the Cox models and from the instantaneous baseline hazard functions. Therefore, these were uniform distributions, with a lower value of 1 (parameter 1, denoting the first bootstrap sample) and an upper value of 1,000 (parameter 2, denoting the last bootstrap sample), randomly drawing a matching set of Cox betas and instantaneous hazard function betas per *Sample*. These betas were pulled separately for the three different treatment periods.

The subsequent ten distributions are normal distributions describing the variability around the natural logarithms of the HRs (lnHRs) used to adjust the initial dialysis models. Since these HRs were time-dependent, the distributions refer to tables with a row for each time stratum, containing in the columns the mean (parameter 1) and standard deviation (parameter 2) of the lnHR respectively. The underlying assumption of modeling these time-dependent HRs in tables is that patients who are e.g. in the lower end of the distribution within the first time stratum, remain in the lower end of the distribution within subsequent time strata.

The last three distributions describe the variability around the utility estimates. We used the mean and standard deviation of the EQ-5D values to compute the alfa (parameter 1) and beta (parameter 2) values for these beta-distributions.

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ABBREVIATIONS

ACE-I	angiotensin-converting-enzyme-inhibitor
AMC	University Hospital Amsterdam
ARB	angiotensin-receptor-II-blocker
CAPD	continuous ambulatory peritoneal dialysis
CI	confidence interval
CT	computed tomographic
DSA	digital subtraction angiography
EMC	Erasmus Medical Center
EO	expert opinion
EQ-5D	EuroQol-5D
ERA-EDTA	European Renal Association-European Dialysis and Transplantation Association
ESRD	end-stage renal disease
FMD	fibromuscular dysplasia
f-up	follow-up
HA	hand-assisted donor nephrectomy
HD	hemodialysis
HR	hazard ratio
HUI	health utilities index
LDN	laparoscopic donor nephrectomy
LE	life expectancy
LY	life year
mo	months
MR	magnetic resonance
n	sample size
NA	not available
NOTR	Dutch Organ Transplant Registry
ODN	open donor nephrectomy
OR	odds ratio
P	P-value
PD	peritoneal dialysis
pmp	per million population
PRA	panel reactive antibody
PRD-DM	primary renal disease - diabetes mellitus

PRD-GN	primary renal disease - glomerulonephritis
PRD-HT	primary renal disease - hypertension
PRD-OTH	primary renal disease - other renal diagnoses
PRD-RVD	primary renal disease - renovascular disease
PS	present study
PSA	probabilistic sensitivity analysis
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life year
QoL	quality of life
R	threshold of society's willingness to pay for gaining 1 QALY
REM	random-effects model
RENINE	Dutch End Stage Renal Disease Registry
RRT	renal replacement therapy
RS	rating scale
RTx	renal transplantation
SD	standard deviation
Se	sensitivity
SF-36	Medical Outcomes Study Short Form 36-Item Health Survey
SG	standard gamble
Sp	specificity
St Radboud	University Hospital Nijmegen
TTO	time trade-off
US	ultrasonography
USRDS	United States Renal Data System
VAS	visual analogue scale
yr	years

CONTRIBUTING AUTHORS

L.R. Arends, PhD
Department of Epidemiology and Biostatistics, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

Prof. W.A. Bemelman, MD, PhD
Department of Surgery, Academic Medical Center Amsterdam, Amsterdam, the Netherlands.

J.L. Bosch, PhD
Program for the Assessment of Radiological Technology (ART Program), Department of Epidemiology and Biostatistics and Department of Radiology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

F.Th. de Charro, PhD
Dutch End Stage Renal Disease Registry RENINE, Rotterdam, the Netherlands.

P.M.M. Dooper, MD, PhD
Department of Internal Medicine, Division of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

M.H. Heijenbrok-Kal, PhD
Nederlandse Brandwonden Stichting, Beverwijk, the Netherlands.

Prof. A.J. Hoitsma, MD, PhD
Department of Internal Medicine, Division of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

W.C.J. Hop, PhD
Department of Epidemiology and Biostatistics, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

Prof. M.G.M. Hunink, MD, PhD
Program for the Assessment of Radiological Technology (ART Program), Department of Epidemiology and Biostatistics and Department of Radiology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands; Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts, USA.

Prof. J.N.M. IJzermans, MD, PhD
Department of Surgery, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

M.C.J.M. Kock, MD, PhD
Department of Radiology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

M.Y. Lind, MD, PhD
Department of Surgery, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

K. Visser, PhD
ZonMw, The Netherlands Organization for Health Research and Development, the Hague, the Netherlands.

Prof. W. Weimar, MD, PhD
Department of Internal Medicine, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

Prof. J.F.M. Wetzels, MD, PhD
Department of Internal Medicine, Division of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

W.C. Winkelmayer, MD, ScD
Division of Pharmacoepidemiology and Pharmacoeconomics and Renal Division, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Prof. J.B. Wong, MD
Division of Clinical Decision Making, Informatics and Telemedicine, Department of Medicine, Tufts Medical Center, Tufts University School of Medicine, Boston, USA.

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ABOUT THE AUTHOR

Ylian Serina Liem was born in 's-Gravenhage (the Hague), the Netherlands, as the eldest of identical twins on March 14th 1978. She received her primary education at the Montessori School in Delft and her secondary education at the Christelijk Lyceum Delft, from which she graduated in 1996. In the same year, she started her medical studies at the Erasmus University Rotterdam. In 1998, she entered the Master of Science program in Clinical Epidemiology at the Netherlands' institute for health sciences (Nihes). As part of this training, she conducted her first research project with Prof.dr. M.G.M. Hunink of the Department of Epidemiology & Biostatistics (Erasmus MC University Medical Center in Rotterdam), resulting in one of the manuscripts published in this thesis. In addition, she attended a summer school in Clinical Epidemiology at the Harvard School of Public Health (Boston, USA). During her studies she worked as a National Officer on Research Exchange for the International Federation of Medical Students' Associations (IFMSA) in the Netherlands. She obtained both master degrees in Medicine and Clinical Epidemiology in 2000 and received her medical degree in 2003. She subsequently spent two months in Ecuador, learning Spanish and working as a volunteer at the Hospital de Sangolquí near Quito. In September 2003, she started the PhD project described in this thesis with Prof.dr. M.G.M. Hunink and Dr. J.L. Bosch for which she obtained an AGIKO stipend from ZonMw. In 2005, she spent five months in Boston, USA, continuing her research project under the supervision of Prof.dr. J.B. Wong of the Division of Clinical Decision Making, Informatics and Telemedicine at Tufts Medical Center and Dr. W.C. Winkelmayer of the Division of Pharmacoepidemiology and Pharmacoeconomics and Renal Division at the Brigham and Women's Hospital. During this period, she also worked as a teaching assistant for Prof.dr. K.M. Kuntz at the Department of Health Policy and Management at the Harvard School of Public Health. In October 2007, she won the First Prize of the Lee Lusted Student Prizes at the Annual Meeting of the Society for Medical Decision Making in Pittsburgh, USA, presenting work described in this thesis. Currently, she is continuing her residency in Internal Medicine (supervisors: Dr. J.L.C.M. van Saase, Erasmus MC University Medical Center Rotterdam and Dr. E. Maartense, Reinier de Graaf hospital Delft).

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everything will be okay
in the end.

if it's not okay,
it's not the end.

(unknown)