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Original Article

Modelling treatment trajectories to optimize the organization of renal replacement therapy and public health decision-making

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ABSTRACT

Background. Nephrologists need to better understand the impact of their decisions about long-term treatment strategies. Healthcare planning requires the anticipation of demand. Indicators from ESRD registries are especially difficult to interpret when the underlying dynamic process is not well understood. Therefore, we have developed a statistical tool to study the course of incident ESRD patient cohorts over time and to quantify, by simulations, the impact of various expected changes or new strategies.

Methods. Based on the data from 67 258 ESRD adult patients, we first estimated transition rates between 10 different modalities of treatment ('compartments') with a multistate model. In a second step, we predicted the number of patients in each compartment at each time point for a cohort of 1000 patients for 180 months after the onset of renal replacement therapy (RRT). We tested two scenarios to illustrate the possibility of simulating policy changes.

Results. Increased use of non-assisted automated peritoneal dialysis (PD) (from 7.7 to 19.2% at RRT onset) will not substantially influence the proportion of total RRT time in PD for patients aged 18–44 without diabetes. Improving access to kidney transplants from cadaveric donors for patients aged 45–69 with diabetes will increase the 15-year restricted mean lifetime by 5 months and the time spent with a functioning graft (34 versus 23%).

Conclusions. A model based on patients' treatment trajectories can improve the description and understanding of RRT as a dynamic phenomenon. Its use for simulation may help professionals and decision-makers to optimize renal organization and care.

INTRODUCTION

End-stage renal disease (ESRD) is a chronic state that may last many years before death. During this time, patients may receive various modalities of renal replacement therapy (RRT), including in-centre haemodialysis (HD), out-of-centre HD, continuous ambulatory peritoneal dialysis (PD), automated PD, renal transplantation from a living donor or from a deceased donor etc. Among the many factors related to treatment choice are clinical condition (such as frailty and associated comorbidities), patient preference, health professionals' experience or beliefs and existing renal-care supply (e.g. availability of renal grafts, self-care HD units, financial aspects) [1–8].

Although only a few randomized trials have compared specific RRT modalities, many observational studies have done so, e.g. comparing HD versus PD or dialysis versus renal transplantation [9–17]. Their results are not consistent, unsurprisingly, given that indication and selection bias cannot be completely controlled in such observational studies [18]. We therefore lack persuasive data about treatment outcomes,

especially treatment courses combining various modalities. Standard approaches, such as the Cox proportional hazards model, may not be appropriate for comparing strategies with transfers between treatment modalities. More complex approaches, such as multistate models, even if they do not totally resolve indication bias, might well be more appropriate since they allow simulations and consider various treatments, outcomes (called states or compartments) and transitions.

ESRD patients require thorough and balanced information when they choose an RRT modality [19, 20]. Moreover, patients treatments may change during the course of their disease. These changes must be anticipated. Accordingly, information is needed about global long-term strategies that combine various complementary modalities. Similarly, healthcare planning requires anticipation of the necessary or available supply of these different modalities. Thus, our partners in the Ministry of Health and the health insurance funds also require information.

ESRD registries provide numerous essential indicators about RRT, such as point prevalence rates and patient counts by treatment modality [21, 22]. Nonetheless, these indicators are especially difficult to interpret when the underlying dynamic process is not well understood. Tools are necessary to assist both individual and public health decision-making and to answer various questions: How should renal-care supply be organized in the future? What strategies should be developed for which patient groups? What is the likely impact of various expected changes or new strategies?

To obtain this necessary dynamic vision of patient trajectories through RRT modalities, we are developing a statistical tool to simulate outcomes of an incident ESRD patient cohort and illustrate the course of their RRT over time. Our second aim is to simulate potential strategies, such as increasing the incidence of patients on PD or increasing access to transplantation to examine how these trends would change the distribution of patients through RRT modalities for 15 years after dialysis initiation.

METHODS

Population

The Renal Epidemiology and Information Network (Rein) registry includes all ESRD patients on RRT—either dialysis or transplantation—treated in France. The details of its organizational principles and quality control are described elsewhere [23]. The registry began in 2002 and grew progressively to include the entire country. At the start of the registry in a region, all (prevalent) dialysis patients in that region are registered. Patients with preemptive grafts and those living with a functioning graft are identified from the transplant database, which began in all regions in 1959 [24]. This study included all adult patients who received at least one RRT treatment between 2002 and 2010 in the regions for which the information system allows the linkage of dialysis treatments and transplantations, i.e. 19 regions corresponding to ~71% of the French population. For patients for whom ESRD onset occurred after the region's inclusion in the database (i.e. incident patients), each patient's follow-up began on the first day of treatment. For patients whose ESRD onset preceded the region's inclusion in the database (prevalent patients), follow-up started on the day of the region's inclusion (late entries, left truncation). The date of first RRT is known for each patient. Each patient was then followed until death or the study end point on 31 December 2010 (right truncation).

Basis of the model

The study considers seven types of events reported to the registry on occurrence: (i) RRT initiation, (ii) changes in the type of dialysis, (iii) renal transplantation, (iv) renal graft failure, (v) death, (vi) recovery of renal function and (vii) loss to follow-up (when patients move to a region or a country that does not participate in the registry). Ten modalities of treatment were defined: nurse-assisted automated PD (A-APD), non-assisted automated PD (nA-APD), nurse-assisted continuous ambulatory PD (A-CAPD), non-assisted continuous ambulatory PD (nA-CAPD), haemodialysis in a hospital-based in-centre unit (CHD), haemodialysis in a medical satellite unit (MUHD), haemodialysis in a self-care or nurse-assisted satellite unit (AHD), haemodialysis at home (HHD), renal graft from a cadaveric donor (CRT) and renal graft from a living donor (LDRT).

We defined the treatment course of a patient as the successive passage between different treatment modalities at various times, and the time spent in each modality, until death or study end point. Our model is based on the transitions between modalities and the volume of patients in each modality at each time point. Because the exact date of each event is known, the length of time in a given state and the time, since RRT began for each transition can be calculated, and we can apply a continuous-time approach. A simplified version of the model (considering only three treatment modalities) is described in the supplementary files (see Supplementary Figure S3).

Our estimates were performed in six groups, stratified for age at ESRD onset: [18–44], [45–69], [70 years and over] and diabetes (comorbidity present or absent at RRT initiation).

Statistical methods

All the treatment courses were split into 1-month periods. To take into account treatment changes that could occur within a month, each month was again split to assess the patient's exact contribution to the given modality.

In a first step, we estimated the parameters (transition rates between the 10 modalities and between each of these modalities and death) with a multistate model [25, 26]. We considered each modality separately for each age and diabetes status, estimating the transition rates from this modality to the others and to death. These estimations resulted from maximizing a Poisson likelihood based on the number of patient-months at risk and taking competing risks [27] into account (the possibility of transition into another compartment). We assumed that transition rates from one state to another do not depend on past transitions. The parameters of the model were estimated by using the first 180 months of follow-up (15 years). The transition rates were presumed constant within

seven time intervals: [0–6] months, [6–12] months, [12–18] months, [18–24] months, [24–36] months, [36–60] months and [60–180] months.

In a second step, we predicted the mean volume of each compartment at each time point for a cohort of 1000 patients during the 180 months after RRT began. The predicted changes in compartment volumes (i.e. in the number of patients in each compartment) between time t and time $t+1$ were estimated by resolving a system of differential equations (continuous-time deterministic structural model). We simulated the outcome of the cohort, based on the transition rate estimates in the first step and the initial distribution of the patients in the various modalities observed in REIN for each given age group and diabetes status. To check the validity of our model, we split our data set into two groups. In the first, we estimated our parameters. In the second, we compared the observed distribution of the patients in the various treatment modalities according to time since first RRT and the predicted distribution based on the estimation in the first group (see Supplementary Figure S2).

Representation of the results

The evolution of the simulated cohort is showed graphically by plotting aggregated patient distribution in the different compartments. The distribution in the death compartment was obtained from the estimator of actuarial survival. Distribution in the various other treatment compartments was based on the proportions observed for living patients.

The 15-year restricted mean lifetime for one patient was calculated considering the total months alive during the period for each simulation. Each simulation is conducted for a total of 180 months × 1000 patients = 180 000 months. Only the sum of the months alive are considered and then divided by 1000 to obtain the mean for one patient.

The feasibility of each scenario was approached by the number of transitions between RRT modalities (per 1000 patients) during the period. The role of each treatment modality was summarized by the mean time spent in each modality.

Stimulation of new strategies

We were able to simulate new strategies by changing some transition rates or the initial distribution of patients in the various treatment modalities. Each scenario was then compared with the unchanged baseline scenario, for a 15-year restricted mean lifetime, the number of transitions between RRT modalities (per 1000 patients) and mean time spent in each modality.

Two scenarios were tested to illustrate the possibility of simulating policy or population changes. The first scenario tested an increased use of non-assisted automated PD in patients aged 18–44 without diabetes. Because PD is a modality that is chosen mainly at RRT onset, this simulation successively applied an initial increase in the distribution of non-assisted automated PD from 7.7% (current practice) to 11.5, 15.4 and 19.2% and the percentage of in-centre HD decreased correspondingly. The transition rates between the compartments were left unchanged.

The second scenario tested improving access to kidney transplants from cadaveric donors for patients aged 45–69 with diabetes: this change implies more renal grafts available and a shorter time spent on the waiting list. This simulation multiplied the transition rates from all dialysis compartments by 2 and by 3 during the first 24 months. The initial treatment distribution was unchanged.

Sensitivity analyses

Increased transfers in a given compartment induced by envisioning some future scenarios could affect the behaviour of that compartment. If the increase concerns patients with

Table 1. Characteristics of the population at the study start

	Incident patients (n = 33 271)	Prevalent patients (n = 33 987)
Age at study start		
Mean ± SD (years)	67.3 ± 15.4	60.5 ± 15.7
18–44 years (%)	9.7	18.0
45–69 years (%)	37.6	49.4
≥70 years (%)	52.7	32.6
Diabetes (%)	36.2	20.3
Time since RRT onset		
Mean ± SD (years)	0.0	6.0 ± 6.3
Maximum (years)	0	39.5
Treatment at study start		
Assisted automated PD	1.4	0.7
Non-assisted automated PD	2.4	1.3
Assisted continuous PD	6.2	2.4
Non-assisted continuous PD	3.2	1.5
HD in-centre	77.3	41.9
HD medical satellite unit	2.3	2.8
HD self-care unit	4.5	15.3
HD home	0.1	1.1
Renal graft cadaveric donor	2.1	31.8
Renal graft living donor	0.4	1.1
Other[a]	0.3	0.1

[a]Other: lost to follow-up, recovery of renal function, unknown.

characteristics similar to those of the patients currently transferred into that compartment, we can suppose that the compartment behaviour will remain stable. But if the increase is based on new indications, transition rates will change. To simulate new behaviour, we performed sensitivity analysis on out-transfers by envisioning different transition rates. In our

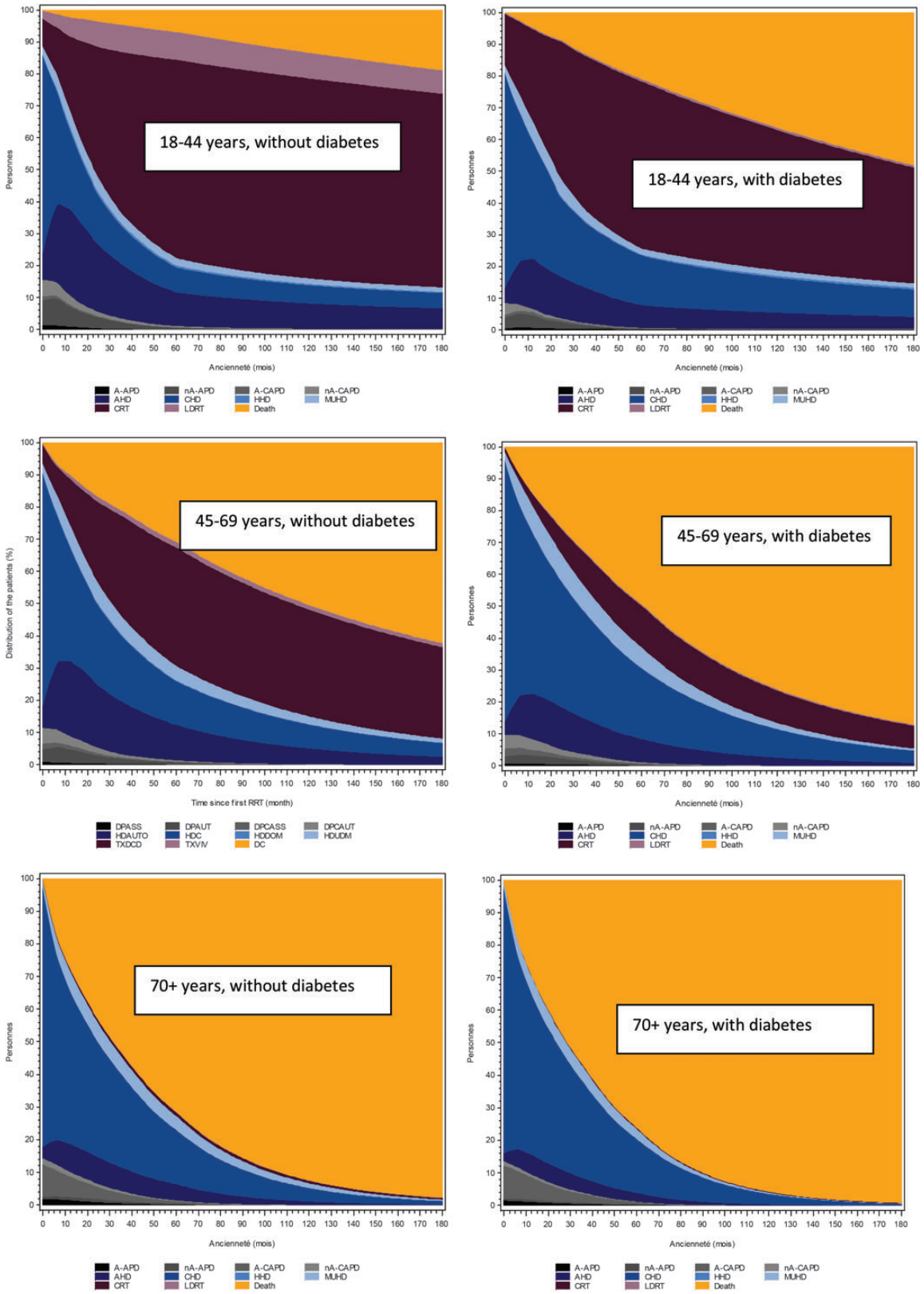

FIGURE 1: Simulated distribution of the patients in the various treatment modalities according to time since first RRT (in months), by age and diabetes status at RRT initiation.

Table 2. Distribution of the various treatment modalities at day 0 and at 2, 10 and 15 years after RRT initiation (row percentage), in a simulation covering a total of 180 months

	Months since RRT began	A-APD (%)	nA-APD (%)	A-CAPD (%)	nA-CAPD (%)	CHD (%)	MUHD (%)	AHD (%)	HHD (%)	CRT (%)	LDRT (%)	DC (%)
18–44 years without diabetes	0	1.5	7.7	1.2	5.2	61.7	2.5	8.7	0.3	8.5	2.7	0
	24	0.5	3.6	0.4	1.4	16	4.7	21.4	1	39.6	7.9	3.4
	120	0	0.2	0	0.1	5.7	1.7	7.9	0.5	62.6	8	13.3
	180	0	0.1	0	0.1	4.8	1.4	6.4	0.4	60.6	7.3	18.8
18–44 years with diabetes	0	0.6	3.5	1	3.6	67.4	2.3	5	0.2	16.1	0.4	0
	24	0.5	2.2	0.7	0.4	25.3	5.7	13.3	0.5	42.5	0.4	8.5
	120	0.3	0.1	0	0.2	11	1.7	5	0.6	44.1	0.8	36.2
	180	0.3	0	0	0.1	8.6	1.3	3.8	0.6	36.4	0.7	48.
45–69 years without diabetes	0	0.9	3.9	1.8	5	72.1	2.7	7	0.3	5.8	0.5	0.
	24	0.5	2.6	0.7	1.8	25.4	6.5	19.8	0.4	24.5	1.6	16.3
	120	0	0.1	0	0.1	7.4	2.5	4.9	0.1	33.1	1.4	50.3
	180	0	0	0	0	4.3	1.3	2.5	0.1	28.4	1.2	62.2
45–69 years with diabetes	0	0.7	2.3	2.5	4.4	81.7	2.7	4.3	0	1.4	0.1	0
	24	0.6	1.8	1.1	1.8	39.9	8.6	13.4	0.2	7.5	0.4	24.6
	120	0	0	0	0.1	8.9	2	2.5	0.1	10.1	0.4	75.9
	180	0	0	0	0	3.8	0.7	1	0	7.1	0.3	87
70+ years without diabetes	0	1.9	0.8	10	1.9	79.9	1.9	3.4	0	0.3	0	0
	24	1	0.9	3.9	1	35.9	5.9	8.2	0	0.9	0	42.1
	120	0	0	0.1	0	4.2	1.5	1.1	0	0.8	0.1	92.4
	180	0	0	0	0	1.1	0.4	0.2	0	0.5	0.1	97.7
70+ years with diabetes	0	1.6	0.6	10.3	1.3	81.9	1.9	2.4	0	0	0	0
	24	0.8	0.5	4.3	0.7	38.2	4.9	5.5	0.1	0.3	0	44.7
	120	0	0	0	0	3.2	0.4	0.3	0	0.2	0	95.8
	180	0	0	0	0	0.6	0.1	0	0	0.2	0	99.2

A-APD, nurse-assisted automated PD; nA-APD, non-assisted automated PD; A-CAPD, nurse-assisted continuous ambulatory PD; nA-CAPD, non-assisted continuous ambulatory PD; AHD, HD in a self-care or nurse- assisted satellite unit; CHD, HD in a hospital based in-centre unit; HHD, home HD; MUHD, HD in a medical satellite unit; CRT, renal transplantation from cadaveric donor; LDRT, renal transplantation for living donor; DC, death.

second example, because increasing transplantation in patients aged 45–69 with diabetes might well lead to more deaths after transplantation, we performed a sensitivity analysis, increasing the transition rates from the compartment 'renal transplantation with cadaveric donor' to the compartment 'death' starting from the current one and then increasing it progressively until reaching the observed value of the transfer rate from the 'in-centre HD' compartment to the 'death' compartment.

RESULTS

Outcomes of 67 258 adult patients, registered in the French REIN registry, were used for this study. At inclusion, 33 271 were incident (ESRD onset date after registry start) and 33 987 prevalent patients (ESRD onset before inclusion in the registry). Table 1 summarizes the characteristics of both populations. As expected, prevalent patients are younger and more often treated with a renal graft. Patient distribution in the 11 different compartments—each treatment modality and death—according to time since first RRT (in months) differed according to age at RRT initiation and diabetes status (see Supplementary Figure S1).

Figure 1 shows the simulated distribution of 1000 patients in these various compartments according to time since first RRT (in months), again, by age at RRT initiation and diabetes status. As expected, mortality increased with age and diabetes (Table 2). The role of transplantation decreased with age and with diabetes, a change mirrored by the increased role of in-centre HD. In all groups, PD accounted for only a small portion of the total time spent in RRT (Table 3).

Of the patients younger than 45 years and without diabetes, 15.6% started with PD and 11.2% with a preemptive graft (Table 2). After 2 years, 47.5% of the patients were living with a renal graft. Fifteen years after RRT onset, overall 67.9% were still alive and had a renal graft, and 18.8% had died. The 15-year restricted mean lifetime was 161.9 months (of a possible maximum of 180 months) (Table 3). Over the 15-year period, PD accounted for only 2.7% of the total RRT time, whereas transplantation accounted for 69.9%.

Of the younger patients with diabetes, 8.7% started with PD and 16.5% with a preemptive graft (Table 2). After 2 years, 42.9% of the patients were living with a renal graft. Fifteen years after RRT onset, only 37.1% were still alive and had a renal graft, and 48% were dead. The 15-year restricted mean lifetime was 130.8 months (Table 3). During the 15-year period, PD accounted for only 2.3% of the total RRT time and transplantation for 60.3%.

Table 3. Fifteen-year restricted mean lifetime (months) and the total distribution of the various treatment modalities during the 180-month simulation period (column percentage)

	18–44 years without diabetes	18–44 years with diabetes	45–69 years without diabetes	45–69 years with diabetes	70+ years without diabetes	70+ years with diabetes
15-year restricted mean lifetime (months)	161.9	130.8	110.4	75.24	45.24	39.62
Distribution of the time spent in various treatment modalities during the 15-year restricted mean lifetime (%)						
Assisted automated PD	0.2	0.6	0.3	0.4	1.4	1.4
Non-assisted automated PD	1.5	0.9	1.5	1.4	1.0	0.7
Assisted continuous PD	0.2	0.3	0.5	1.0	5.5	6.7
Non-assisted continuous PD	0.8	0.5	1.1	1.7	1.4	1.0
HD in-centre	11.3	23.4	23.6	48.2	62.3	71.4
HD medical satellite unit	2.7	3.4	5.9	9.9	11.5	8.8
HD self-care unit	12.8	9.9	15.1	13.6	13.3	8.8
HD home	0.7	0.7	0.3	0.3	0.1	0.2
Renal graft cadaveric donor	61.3	59.4	49.3	22.7	3.2	1.1
Renal graft living donor	8.6	0.9	2.3	0.9	0.2	0.0

Table 4. Scenario 1: increasing use of non-assisted automated PD in patients aged 18–44 without diabetes

Initial distribution of nA-APD (%)	7.7	11.5	15.4	19.2
15-year restricted mean lifetime (months)	161.9	162.2	162.4	162.7
Distribution of the time spent in various treatment modalities during the 15-year restricted mean lifetime (%)				
Assisted automated PD	0.2	0.2	0.2	0.2
Non-assisted automated PD	1.5	1.9	2.4	2.8
Assisted continuous PD	0.2	0.2	0.2	0.2
Non-assisted continuous PD	0.8	0.8	0.8	0.8
HD in-centre	11.3	11.0	10.7	10.4
HD medical satellite unit	2.7	2.6	2.6	2.5
HD self-care unit	12.8	12.4	12.1	11.8
HD home	0.7	0.6	0.6	0.6
Renal graft cadaveric donor	61.3	61.5	61.7	61.9
Renal graft living donor	8.6	8.7	8.8	8.9

Based on a simulation covering a total of 180 months, impact on the 15-year restricted mean lifetime (months) and the total distribution of the various treatment modalities (column percentage).

In the intermediate age group (45–69 years) without diabetes, 11.6% of the patients started with PD and 6.3% with a preemptive graft (Table 2). After 2 years, only 26.1% of the patients were living with a renal graft. Fifteen years after RRT onset, only 29.6% were still alive with a renal graft, and 62.2% had died. The 15-year restricted mean lifetime was 110.4 months (Table 3). Over the 15-year period, PD accounted for only 3.4% of the RRT time and transplantation for 51.6%.

Of those aged 45–69 with diabetes, 9.9% started with PD and 1.5% with a preemptive graft (Table 2). After 2 years, only 7.9% of the patients were living with a renal graft. Fifteen years after RRT onset, 87% were dead. The 15-year restricted mean lifetime was 75.2 months, less than half the potential 180 months (Table 3). Over the 15-year period, PD accounted for only 4.5% of the RRT time and transplantation for 23.6%.

Of those older than 70 years without diabetes, 14.6% started with PD (Table 2). After 2 years, only 6.8% were still on PD. Fifteen years after RRT onset, 97.7% had died. The 15-year restricted mean lifetime was 45.2 months (Table 3). Over the 15-year period, PD accounted for 9.3% of the RRT time.

Of those in the oldest group who also had diabetes, 13.8% started with PD (Table 2). After 2 years, only 6.3% of the patients were still on PD. Fifteen years after RRT began, 99.2% were dead. The 15-year restricted mean lifetime was 39.6 months (Table 3). PD accounted for 9.8% of the RRT time over the 15-year period.

Two scenarios were tested to illustrate the possibility of simulating policy or population changes. The first scenario tested an increased use of non-assisted automated PD in patients aged 18–44 without diabetes. Because PD is a modality that is nearly always chosen only at RRT onset, this simulation successively applied an initial increase in the distribution of non-assisted automated PD from 7.7 to 11.5, 15.4 and 19.2%, and the percentage of in-centre HD decreased correspondingly. The transition rates between the compartments

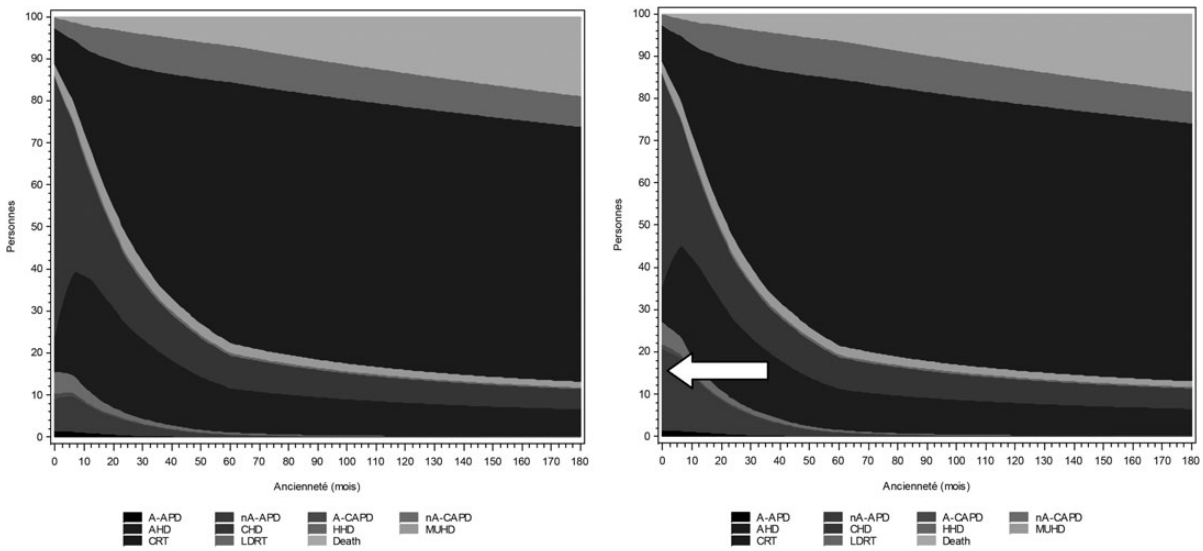

FIGURE 2: Scenario 1: increasing use of non-assisted automated PD in patients of 18–44 years without diabetes. Impact on the distribution of patients in the different compartments from RRT initiation through the 180-month simulation period. The large white arrow points out the nA-APD compartment.

Table 5. Scenario 2: improving access to renal transplantation from cadaveric donor organs for patients aged 45–69 with diabetes

Transition rates to transplantation with a deceased cadaveric donor graft during the first 24 months	Unchanged	Multiplied by 2		Multiplied by 3	
Sensitivity analysis of transitions rates from transplantation with a cadaveric donor graft to death	Unchanged	Unchanged	Transitions observed for in-centre HD[a]	Unchanged	Transitions observed for in-centre HD[a]
15-year restricted mean lifetime (months)	75.24	78.12	77.43	80.74	79.84
Number of renal transplants from a deceased donor performed during the period	186	239	239	287	287
Number of deaths for patients with a renal graft from a cadaveric donor during the period	30	41	46	51	58
Distribution of the time spent in various treatment modalities during the 15-year restricted mean lifetime (%)					
Assisted automated PD	0.4	0.4	0.4	0.4	0.4
Non-assisted automated PD	1.4	1.2	1.2	1.0	1.0
Assisted continuous PD	1.0	0.9	0.9	0.9	0.9
Non-assisted continuous PD	1.7	1.6	1.6	1.4	1.5
HD in-centre	48.2	44.9	45.2	42.1	42.5
HD medical satellite unit	9.9	8.9	9.0	8.1	8.2
HD self-care unit	13.6	12.0	12.1	10.7	10.8
HD home	0.3	0.2	0.2	0.2	0.2
Renal graft cadaveric donor	22.7	29.0	28.5	34.4	33.8
Renal graft living donor	0.9	0.9	0.9	0.8	0.8

Impact on the 15-year restricted mean lifetime (months), the total number of renal transplantations performed and the total distribution of the various treatment modalities (column percentage) during the 180-month simulation period.

[a]Because increasing transplantation in this group might well lead to more deaths after transplantation, we performed a sensitivity analysis, increasing the transition rates from the compartment 'renal transplantation with cadaveric donor' to the compartment 'death' starting from the current one to the observed value of the transfer rate from the 'in-centre HD' compartment to the 'death' compartment.

were left unchanged. Table 4 and Figure 2 present the result of this scenario, compared with the unchanged basic scenario. As shown, even such a major change in medical practice will not have an important impact on PD's proportion of total RRT time in young patients, because of the high transition rate to transplantation. Multiplying the initial percentage of patients starting with non-assisted automated PD by 2.5 will increase the total time spent in this modality by only 1.3%, i.e. 2 months, on average, for a restricted mean lifetime of 162 months.

The second scenario tested improving access to kidney transplants from cadaveric donors for patients 45–69 years with diabetes: this change would imply greater availability of renal grafts and a shorter time spent on the waiting list. This simulation multiplied the transition rates from all dialysis compartments by 2 and by 3 during the first 24 months. The initial treatment distribution was unchanged. Because increasing transplantation in this group at potential risk could increase the risk of death, we performed a sensitivity analysis, increasing the transition rates from the compartment 'renal transplantation with cadaveric donor' to the compartment 'death' to the level observed from the compartment of in-centre HD (extreme scenario). The results of this scenario and the sensitivity analysis are presented in Table 5 and Figure 3. As expected, increasing the renal transplantation rate had a major impact on the number of transplantations performed, on the 15-year restricted mean lifetime and on the proportion of transplantation in the total RRT time. Increasing the risk of death from this compartment slightly reduced the impact of this strategy.

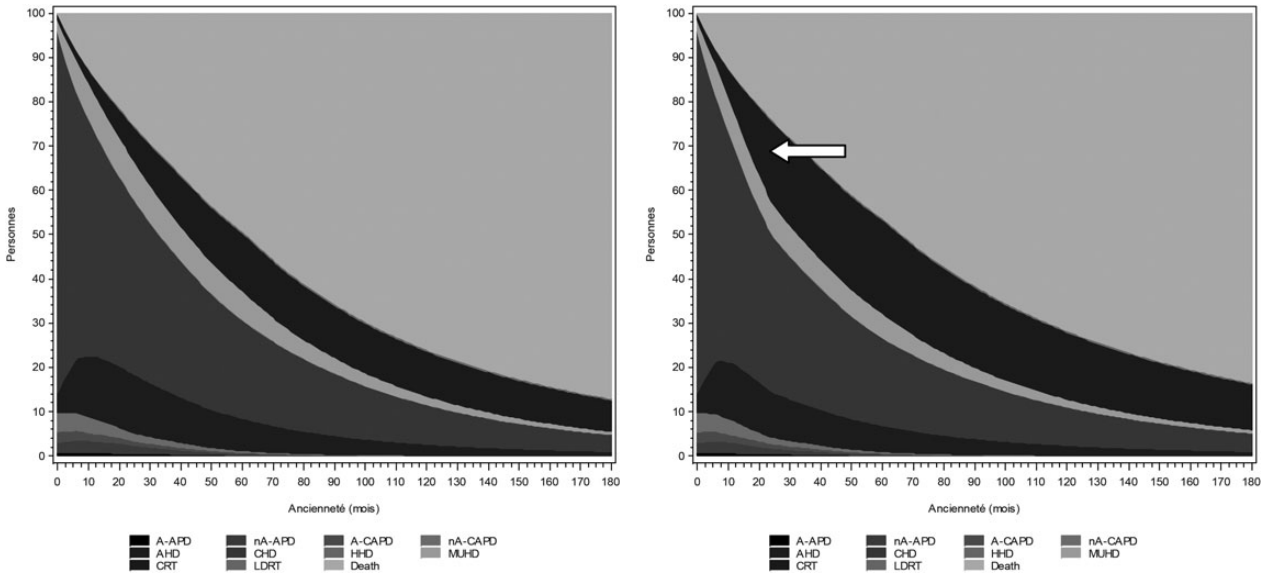

FIGURE 3: Scenario 2: improving access to renal transplantation from a cadaveric donor graft for patients aged 45–69 with diabetes. Impact on the distribution of patients in the different compartments from RRT initiation through the 180-month simulation period. The large white arrow points out the CRT compartment.

DISCUSSION

The high burden of ESRD has led many registries to develop tools to predict numbers of RRT patients at different points in the future. These tools can be divided into two categories. The first comprises multistate transition models, either deterministic or probabilistic. Their calculations are based on the observation of transitions between three treatment states—HD, PD and transplantation—and one absorbing state—death [28–31]. One study also included status on renal transplantation waiting list registration [29]. This type of study starts with the current number of prevalent patients and an estimation of future incident patients. These tools are useful for predicting future demand. They can also be used to simulate various scenarios of trends or changes in techniques or populations, such as more grafts [30], increasing ESRD incidence [29, 31], an increase in the percentage of patients with diabetes [29, 31], better survival [29, 31] or different balances between HD and PD [29]. The second category of model uses historical data from time-series for forecasting [32]. They allow the number of ESRD patients in the future to be estimated, but they require long periods of historical data and cannot be used for simulations.

Models have also been developed to provide cost-effectiveness analyses for ESRD. Some use multistate transition models [30, 33–36] to simulate the use of more preemptive grafts [36], more transplants from living donors [34] or increasing use of PD [33, 35]. Some are based on individual simulations of a cohort of incident patients and generate random patient profiles and medical histories for each patient [25].

Because most of these models aimed to predict future prevalence counts, they have simulated prevalent patient cohorts mixed with incoming new patients on a calendar time axis. The vision of the underlying process is less clear than in our model, where the time axis is time since RRT began. In France, at least three treatment states are insufficient to illustrate the various therapies available. For this reason, our model includes 10 different treatments. Further compartments may be added in the future to take the development of new strategies into consideration, such as daily home HD, or out-centre dialysis supervised by telemedicine.

Some of the previous tools did take age and diabetes status into account but presented their final results as a whole for the entire population. We chose to stratify our cohort because, as our results illustrate, the course of the cohort differs substantially from one group to another, and future trend scenarios are also likely to vary in their effects according to age and diabetes status. It also improves the clarity of the results. But the main reason for choosing a stratification approach is that it allows the simulation of different scenarios according to the patients' age and diabetes. Healthcare planners, for example, are more likely to want to simulate more renal transplantations or more autonomous modalities in younger patients, and more assisted modalities among elderly patients. Our model makes it possible to differentiate scenarios according to the patient characteristics.

The strength of our model is that it allows a simulation of the treatment course of the patients in the context of various strategies and the quantification of the impact of various changes. Previously published models have not described current practices graphically nor did they illustrate the underlying dynamic phenomena. We think that the visual output we propose is a strong point of this paper, since it provides a simple description of a complex dynamic process.

The principal limitation of our model is that the transition rates are estimated from current practices and only at the national level. Past analyses suggest that substantial heterogeneity exists from one region to another or even from one centre to another. Moreover, increasing transfers in some

compartments may change the global behaviour of this compartment and modify the transition rates toward other compartments. We conducted some sensitivity analysis to simulate some such resulting changes in transition rates, but the 'true' future behaviour is not known. The sensitivity analysis was based upon expert opinion.

A second limitation of our model was to consider, for technical reasons, that the rates were constant within seven separate time intervals. The initial description of our data showed that this simplification is acceptable, because most transitions occurred in the first 3 years (data not shown). We chose to use age and diabetes to characterize our patients, but introducing other risk factors for estimating particular transition rates would be likely to improve this tool.

In conclusion, a model based on patient treatment trajectories can usefully improve descriptions and understanding of the dynamic phenomenon of RRT. It should help nephrologists and patients as well as the Ministry of Health and the health insurance funds to optimize the organization of renal care and public health decision-making. It may also be a tool to facilitate evidence-based public health decisions by evaluating the performance of the organization of renal care, before and after modification, under different useful configurations and over long periods of time. Such a tool might also help to evaluate the benefit of various strategies. As many factors are related to treatment choice and in view of the lack of randomized clinical trials, simulations may be a way to promote translational research in public health and clinical medicine.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

No author has any conflict of interest to declare.

REFERENCES

1. Stack AG. Determinants of modality selection among incident US dialysis patients: results from a national study. J Am Soc Nephrol 2002; 13: 1279–1287
2. Mignon F, Michel C, Viron B. Why so much disparity of PD in Europe? Nephrol Dial Transplant 1998; 13: 1114–1117
3. Jassal SV, Krishna G, Mallick NP *et al.* Attitudes of British Isles nephrologists towards dialysis modality selection: a questionnaire study. Nephrol Dial Transplant 2002; 17: 474–477
4. Jung B, Blake PG, Mehta RL *et al.* Attitudes of Canadian nephrologists toward dialysis modality selection. Perit Dial Int 1999; 19: 263–268
5. Couchoud C, Savoye E, Frimat L *et al.* Variability in case mix and peritoneal dialysis selection in fifty-nine French districts. Perit Dial Int 2008; 28: 509–517
6. van de Luijtgaarden MW, Noordzij M, Stel VS *et al.* Effects of comorbid and demographic factors on dialysis modality choice and related patient survival in Europe. Nephrol Dial Transplant 2011; 26: 2940–2947
7. Jager KJ, Korevaar JC, Dekker FW *et al.* The effect of contraindications and patient preference on dialysis modality selection in ESRD patients in The Netherlands. Am J Kidney Dis 2004; 43: 891–899
8. Mendelssohn DC, Mullaney SR, Jung B *et al.* What do American nephologists think about dialysis modality selection? Am J Kidney Dis 2001; 37: 22–29
9. Ross S, Dong E, Gordon M *et al.* Meta-analysis of outcome studies in end-stage renal disease. Kidney Int 2000; 57: S-28–S-38
10. Mehrotra R, Chiu YW, Kalantar-Zadeh K *et al.* The outcomes of continuous ambulatory and automated peritoneal dialysis are similar. Kidney Int 2009; 76: 97–107
11. Wolfe RA, Ashby VB, Milford EL *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341: 1725–1730
12. Xue JL, Everson SE, Constantini EG *et al.* Peritoneal and hemodialysis: II. Mortality risk associated with initial patient characteristics. Kidney Int 2002; 61: 741–746
13. Fenton SS, Schaubel DE, Desmeules M *et al.* Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. Am J Kidney Dis 1997; 30: 334–342
14. Frimat L, Durand PY, Loos-Ayav C *et al.* Impact of first dialysis modality on outcome of patients contraindicated for kidney transplant. Perit Dial Int 2006; 26: 231–239
15. Schaubel DE, Morrison HI, Fenton SS. Comparing mortality rates on CAPD/CCPD and hemodialysis. The Canadian experience: fact or fiction? Perit Dial Int 1998; 18: 478–484
16. Vonesh EF, Snyder JJ, Foley RN *et al.* Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? Kidney Int Suppl 2006; 103: S3–S11
17. Sens F, Schott-Pethelaz AM, Labeeuw M *et al.* Survival advantage of hemodialysis relative to peritoneal dialysis in patients with

end-stage renal disease and congestive heart failure. Kidney Int 2011; 80: 970–977
18. Jaar BG. The Achilles heel of mortality risk by dialysis modality is selection bias. J Am Soc Nephrol 2011; 22: 1398–1400
19. Moss AH. Shared decision-making in dialysis: the new RPA/ASN guideline on appropriate initiation and withdrawal of treatment. Am J Kidney Dis 2001; 37: 1081–1091
20. Covic A, Bammens B, Lobbedez T *et al.* Educating end-stage renal disease patients on dialysis modality selection: clinical advice from the European Renal Best Practice (ERBP) Advisory Board. Nephrol Dial Transplant 2010; 25: 1757–1759
21. Stel VS, van de Luijtgaarden MW, Wanner C *et al.* The 2008 ERA-EDTA Registry Annual Report-a precis. NDT Plus 2011; 4: 1–13
22. U S Renal Data System. USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases. 2011
23. Couchoud C, Stengel B, Landais P *et al.* The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. Nephrol Dial Transplant 2006; 21: 411–418
24. Strang WN, Tuppin P, Atinault A *et al.* The French organ transplant data system. Stud Health Technol Inform 2005; 116: 77–82
25. Lee CP, Chertow GM, Zenios SA. A simulation model to estimate the cost and effectiveness of alternative dialysis initiation strategies. Med Decis Making 2006; 26: 535–549
26. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York: Wiley, 2002
27. Kay R. A Markov model for analysing cancer markers and disease states in survival studies. Biometrics 1986; 42: 855–865
28. Schaubel DE, Morrison HI, Desmeules M *et al.* End-stage renal disease in Canada: prevalence projections to 2005. CMAJ 1999; 160: 1557–1563
29. Roderick P, Davies R, Jones C *et al.* Simulation model of renal replacement therapy: predicting future demand in England. Nephrol Dial Transplant 2004; 19: 692–701
30. Rodina-Theocharaki A, Bliznakova K, Pallikarakis N. Markov Chain Monte Carlo simulation for projection of end stage renal disease patients in Greece. Comput Methods Programs Biomed 2012; 107: 90–96
31. Gilbertson DT, Liu J, Xue JL *et al.* Projecting the number of patients with end-stage renal disease in the United States to the year 2015. J Am Soc Nephrol 2005; 16: 3736–3741
32. Xue JL, Ma JZ, Louis TA *et al.* Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. J Am Soc Nephrol 2001; 12: 2753–2758
33. Weijnen TJ, van Hamersvelt HW, Just PM *et al.* Economic impact of extended time on peritoneal dialysis as a result of using polyglucose: the application of a Markov chain model to forecast changes in the development of the ESRD programme over time. Nephrol Dial Transplant 2003; 18: 390–396
34. Haller M, Gutjahr G, Kramar R *et al.* Cost-effectiveness analysis of renal replacement therapy in Austria. Nephrol Dial Transplant 2011; 26: 2988–2995
35. Teerawattananon Y, Mugford M, Tangcharoensathien V. Economic evaluation of palliative management versus peritoneal dialysis and hemodialysis for end-stage renal disease: evidence for coverage decisions in Thailand. Value Health 2007; 10: 61–72
36. Liem YS, Wong JB, Winkelmayer WC *et al.* Quantifying the benefit of early living-donor renal transplantation with a simulation model of the Dutch renal replacement therapy population. Nephrol Dial Transplant 2012; 27: 429–434

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