Epidemiology and outcomes of renal replacement therapy: results from the ERA-EDTA registry

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Chapter 3

An update on renal replacement therapy in Europe ERA-EDTA Registry data from 1997 to 2006

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Summary

Background. Recent studies have indicated a stabilization in the incidence rates of renal replacement therapy (RRT) for end-stage renal disease (ESRD) in a number of European countries. The aim of this study was to provide an update on the incidence, prevalence and outcomes of RRT in Europe over the past decade.

Methods. Nineteen European national or regional renal registries with registry data from 1997 to 2006 participated in the study. Incidence and prevalence trends were analysed with Poisson and Joinpoint regression. Cox regression methods were used to examine patient survival.

Results. The total adjusted incidence rate of RRT for ESRD increased from 109.9 per million population (pmp) in 1997 to 119.7 pmp in 2000, i.e. an average annual percentage change (AAPC) of 2.9% (95% CI: 2.1-3.8%). Thereafter, the incidence increased at a much lower rate to 125.4 pmp in 2006 (AAPC 0.6% (95% CI: 0.3-0.8%)). This change in the trend of the incidence of RRT was largely due to a stabilisation in the incidence rates of RRT for females aged 65-74 years, males aged 75-84 years and patients receiving RRT for ESRD due to hypertension / renal vascular disease. The overall adjusted prevalence in Europe continued to increase linearly at 2.7% per year. Between the periods 1997-2001 and 2002-2006, the risk of death decreased for all treatment modalities, with the most substantial improvement in patients starting peritoneal dialysis (19% (95% CI: 15-22%)) and in patients receiving a kidney transplant (17% (95% CI: 11-23%)).

Conclusions. This European study shows that the annual rise of the overall incidence rate of RRT for ESRD has diminished and that in several age groups the incidence rates have now stabilized. The survival of dialysis patients and kidney transplant recipients has continued to improve.

Introduction

Since renal replacement therapy (RRT) of end-stage renal disease (ESRD) became widely available in the 1960s, the number of prevalent patients on RRT has continued to rise at an alarming rate. This has largely been due to an increased number of patients starting RRT and the improved survival of patients receiving dialysis or undergoing kidney transplantation [1-4]. Two ERA-EDTA Registry publications [5,6] based on relatively small databases earlier this decade outlined this almost linear increase of patient numbers as well as the substantial improvement in patient survival on RRT over time. However, more recent data seemed to indicate a stabilisation in the incidence rates of RRT in a number of European countries [7-9]. The aim of this study was therefore to provide an update on the incidence, prevalence and outcomes of RRT for ESRD in Europe over the past decade in the 19 European countries and regions that currently provide individual patient data to the ERA-EDTA Registry.

Subjects and Methods

Data collection

Nineteen national or regional renal registries participating in the ERA-EDTA Registry with individual patient data from January 1st, 1997 to December 31st, 2006, participated in the study. These included the national registries of Austria, Denmark, England / Wales (United Kingdom (UK)), Finland, Greece, Iceland, Norway, Scotland (UK), Sweden, The Netherlands, and the regional registries of Dutch- and French-speaking Belgium, Calabria (covering 4% of Italy), and Andalusia, Asturias, Basque country, Cantabria, Catalonia, Valencian region (together covering 53% of Spain). The data from Asturias (Spain), Cantabria (Spain), Dutch-speaking Belgium, England / Wales (UK), and French-speaking Belgium only comprised patients older than 20 years of age. The population covered by these registries rose from 106 million people in 1997 to 157 million in 2006, which was partly due to the increasing coverage of the renal registry in the UK (from 25% in 1997 to 90% in 2006). Details of the database and the methods used for data collection and data processing have been reported previously [6].

Data analysis

To avoid any effects of late reporting by renal centres over the period 1997-2006 the recent 2007 update of the ERA-EDTA Registry database was used for analysis of the data.

The incidence of RRT was defined as the number of patients starting RRT annually and the prevalence as the number of patients alive and receiving RRT on 31 December. Incidence rates and prevalence per million population (pmp), or per million age-related

population (Pmarp), were calculated by dividing the observed count by the mid-year population. Primary renal diseases were defined according to the ERA–EDTA coding system and classified into seven groups [6,10]. Adjusted rates were calculated by using the EU25 age and sex distribution [10]. Time trends were analysed with Poisson regression and Joinpoint regression. The slope of a trend was calculated using the observed rate as the outcome variable, and the year as the explanatory variable. The analysis was adjusted for changes in the age and sex distribution of the population. The average annual percent change (AAPC) was then computed by the formula AAPC = (exp(β)-1) x 100, where β denotes the regression coefficient representing the estimated effect of time on the rate. To examine whether trends were linear, Joinpoint regression software (version 3.3) provided by the Surveillance Research Program of the US National Cancer Institute [11] was used. Joinpoint regression allows the identification of points in time where a significant change in the linear slope of a trend occurs. The analysis starts with zero joinpoints (i.e. a straight line), and then tests whether one or more joinpoints are significantly different and must be added to the model [12]. The ten-year study period allowed identification of a maximum of two joinpoints.

Statistical analysis of unadjusted and adjusted survival was performed by the Kaplan-Meier method and by Cox proportional hazards regression. For the analysis of patient survival on RRT the date of onset of RRT was the starting point and death was the event studied. Censored observations were recovery of renal function, loss to follow-up and end of the follow-up period. For analysis of patient survival on dialysis (overall and separately for haemodialysis and peritoneal dialysis) the first day on dialysis was the starting point, the event studied was death and reasons for censoring were recovery of renal function, loss to follow-up, end of follow-up time and kidney transplantation. For analysis of patient and graft survival after transplantation the date of the first transplant was defined as the first day of follow-up. For the analysis of patient survival after transplantation, death was the event studied and for graft survival the events were graft failure and death. Reasons for censoring were loss to follow-up and end of the follow-up period. To study the trend in survival over time, the study patients were classified according to the date of onset of RRT, the onset of dialysis or the date of the first kidney transplant into two cohorts: 1997-2001 and 2002-2006. SAS 9.1 software was used for all statistical analyses.

Results

Trends in the overall incidence rate of RRT, 1997-2006

The unadjusted incidence rate of RRT for ESRD in the 19 countries/regions together increased from 107.4 pmp in 1997 to 119.5 pmp in 2000, by 3.4% (95% CI: 1.4;5.5) annually. After the year 2000, the unadjusted incidence increased more slowly (AAPC 1.1%

(95% CI: 0.5;2.3)), to 130.9 in 2006. Table 1 shows the age- and sex-adjusted incidence of RRT pmp, and the AAPC, between 1997 and 2006 for all countries/regions together, and for each country and region separately. The total adjusted incidence rate of RRT in the 19 participating registries increased from 109.9 pmp in 1997 to 119.7 pmp in 2000, i.e. an average increase of 2.9% (95% CI: 2.1;3.8) per year. Thereafter, the adjusted incidence rate increased more slowly (AAPC 0.6% (95% CI: 0.3;0.8)), to 125.4 pmp in 2006.

As shown, trends in the adjusted incidence rates of RRT varied widely across the countries/regions: in some the rates continued to increase (Andalusia (Spain), Austria, Dutch-speaking Belgium, England / Wales (UK), French-speaking Belgium, Norway, and The Netherlands) during the study period, whereas in other countries/regions the adjusted incidence rates stabilized (Asturias (Spain), Basque Country (Spain), Calabria (Italy), Cantabria (Spain), Catalonia (Spain), Finland, Greece, Iceland, Sweden, Scotland (UK), and Valencian region (Spain)), or even declined (Denmark) near the end of the study period.

Trends in the incidence rate of RRT by age, sex and primary renal disease, 1997-2006

Between 1997 and 2000, the age-adjusted incidence rate of RRT increased in both males (from 134.4 to 153.8, AAPC 3.3% (95% CI: 0.6;6.1)) and females (from 86.5 to 93.3, AAPC 2.8% (95% CI: 1.0;4.5)). However, after 2000 the rates increased at a much lower rate (AAPC males: 1.1% (95% CI: 0.6;1.6), AAPC females: 0.7% (95% CI: 0.1;1.3). Figures 1 and 2 show the trends in the unadjusted incidence rates of RRT by sex and age group. For both males and females in the age groups 0-19 and 20-44 years, and for males in the age group 45-64, the incidence rate of RRT remained unchanged during the study period, but among females in the age group 45-64 there was a slight decrease. In the age group 65 to 74 years, the incidence rate increased between 1997 and 2000 in both males and females (by 1.1 and 3.5% respectively). However, after 2000 it stabilized in females, whereas it continued to increase in males. In the older age groups there was a substantial increase in the incidence rates in both males and females during the early years of the decade but the increase was much smaller towards the end of the period. Among males aged 75-84 the incidence rate of RRT even stabilized after 2004.

As shown in Figure 3 the age- and sex-adjusted incidence rates of RRT for ESRD due to glomerulonephritis/sclerosis and pyelonephritis decreased during the study period, whereas that due to polycystic kidneys (adult type) remained stable. In 2004, after a long period of increase, the incidence rates of RRT for ESRD due to hypertension / renal vascular disease or miscellaneous causes started to stabilise, whereas those due to 'unknown/missing' causes continued to rise. In addition, the incidence of RRT for ESRD due to diabetes continued to increase after 2000, but at less than half the rate present before 2000. Subgroup analysis showed that the changes in the incidence rates of RRT for ESRD due to diabetes or hypertension / renal vascular disease were a consequence of changes of the incidence rates of RRT for ESRD due to these causes in patients aged 65-74 and 75-84

years. In addition, analysis of data from registries that used separate codes for nephropathy due to type 1 and type 2 diabetes showed that both the increase in the incidence of RRT for diabetic ESRD and the change in this trend, could be attributed to the age- and sex-adjusted trends in RRT for ESRD due to type 2 diabetes (AAPC 1997-2002: 8.3% (95% CI: 6.4;10.3) and 2002-2006: 3.2% (95%CI: 0.6;5.8)). In contrast, the adjusted incidence of RRT for ESRD due to type 1 diabetes decreased during the study period (AAPC -1.1% (95% CI: -2.0;-0.2)).

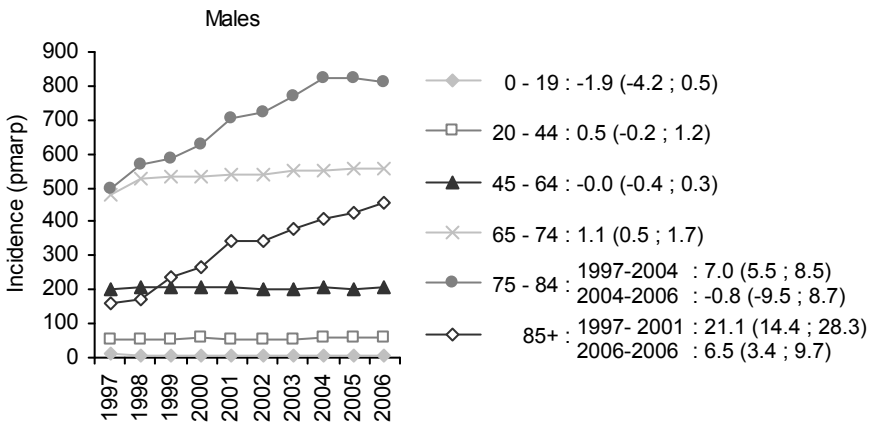

Figure 1. Trends in the unadjusted incidence of RRT per million population and average annual percent change (95%CI) during the period 1997-2006, by age groups, in males.

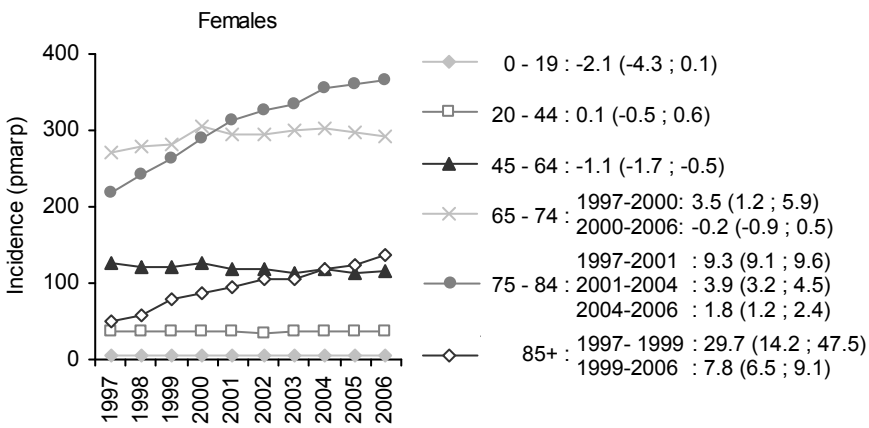

Figure 2. Trends in the unadjusted incidence of RRT per million population and average annual percent change (95%CI) during the period 1997-2006, by age groups, in females.

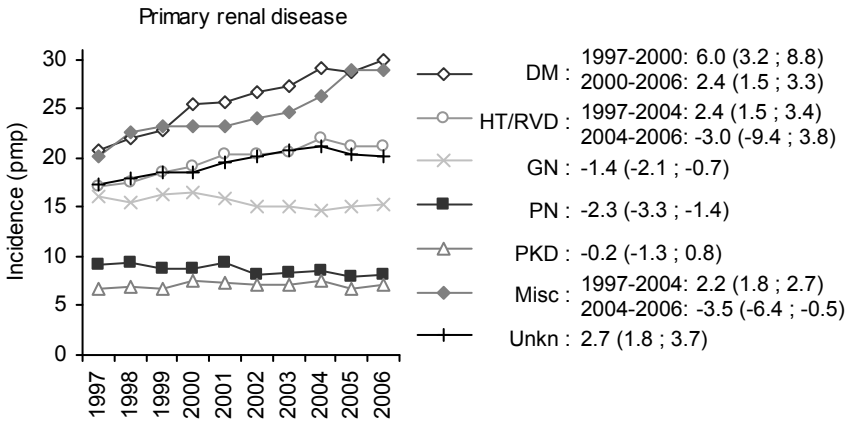

Figure 3. Trends in the incidence of RRT per million population, and average annual percent change (95%CI), during the period 1997-2006, by primary renal disease, adjusted for age and sex distribution. Abbreviations used: DM: diabetes mellitus; GN: glomerulonephritis/sclerosis; HT/RVD: hypertension / renal vascular disease; Misc: miscellaneous; PKD: polycystic kidneys, adult type; PN: pyelonephritis; Unkn: unknown/missing.

Trends in the overall prevalence of RRT, 1997-2006

Table 2 shows the age- and sex-adjusted prevalence of RRT pmp between 1997 and 2006 for each country and region. The overall prevalence increased from 642 pmp in 1997 to 816 pmp in 2006, with an average annual increase of 2.7% (95% CI: 2.7;2.9). While the prevalence of RRT continued to rise slowly in most countries, it appeared to have stabilized in Calabria (Italy), Catalonia (Spain), Denmark, and Valencian region (Spain).

Between 1997 and 2006, the adjusted prevalence of patients receiving haemodialysis increased from 301 to 376 pmp (AAPC 1997-2002: 1.9% (95% CI: 1.0;2.8) and 2002-2006: 3.7% (95% CI: 2.5;4.9)), and the prevalence of patients with a functioning kidney transplant increased from 275.6 to 362.5 pmp (AAPC 3.1% (95% CI: 3.0;3.3). The prevalence of patients on peritoneal dialysis increased from 59 to 70 pmp in 2000, and stabilized thereafter (AAPC 1997-2000: 5.5% (95% CI: 3.0;8.1) and 2000-2006: -0.4% (95% CI: -1.1;0.4)).

Trends in survival, 1997-2006

Table 3 shows the crude patient survival probabilities and crude and adjusted hazard ratios for all patients starting RRT (including all types) or dialysis between 1997 and 2001 and between 2002 and 2006 as well as the patient and graft survival and hazard ratios for kidney transplant recipients in the same cohorts.

Renal replacement therapy (including all types). Although the crude patient survival on RRT did not differ between the two cohorts (HR 0.98, 95% CI: 0.97-1.00), adjustment for age, sex,

Table 1. Incidence of RRT per million population during the period 1997-2006, adjusted for age and sex distribution.

	Incidence by year										Trend 1		Trend 2	
Country / region	1997 pmp	1998 pmp	1999 pmp	2000 pmp	2001 pmp	2002 pmp	2003 pmp	2004 pmp	2005 pmp	2006 pmp	period	AAPC % (95% CI)	period	AAPC % (95% CI)
Andalusia, Spain	110	128	117	133	129	138	137	138	141	140	1997-2006	↑ 2.2 (1.0;3.4)		
Asturias, Spain	83	101	91	110	112	114	108	132	101	102	1997-2006	~ 2.2 (-0.9;5.4)		
Austria	128	129	135	132	138	134	138	156	148	153	1997-2006	↑ 2.1 (1.2;3.0)		
Basque Country, Spain	98	106	94	114	109	92	128	112	107	99	1997-2006	~ 0.8 (-1.9;3.6)		
Calabria, Italy	116	137	115	127	111	133	130	137	127	121	1997-2006	~ 0.6 (-1.4;2.5)		
Cantabria, Spain	106	80	124	114	144	110	126	135	142	115	1997-2006	~ 2.8 (-1.0;6.7)		
Catalonia, Spain	131	131	144	139	136	140	144	132	141	126	1997-2006	~ -0.1 (-1.3;1.2)		
Denmark	106	111	126	134	141	133	133	131	119	117	1997-2001	↑ 7.6 (4.2;11.2)	2001-2006	↓-3.7 (-5.9;-1.5)
Dutch-speaking Belgium	131	137	144	141	150	161	160	163	163	169	1997-2006	↑ 2.8 (2.1;3.4)		
England/Wales, UK	97	97	96	95	100	97	99	105	108	112	1997-2006	↑ 1.6 (0.9;2.4)		
Finland	77	93	93	97	91	92	93	94	92	83	1997-2006	~ 0.3 (-1.5;2.1)		
French-speaking Belgium	118	136	158	153	173	169	156	179	172	181	1997-2006	↑ 3.5 (1.5;5.5)		
Greece	108	113	118	145	156	155	169	177	171	172	1997-2001	↑ 10.8 (4.1;18.1)	2001-2006	~ 2.5 (-1.4;6.6)
Iceland	68	95	44	77	94	92	83	87	81	79	1997-2006	~ 1.2 (-3.7;6.5)		
Norway	87	95	93	94	97	93	97	102	101	101	1997-2006	↑ 1.4 (0.8;2.1)		
Scotland, UK	105	111	116	113	103	110	119	112	121	112	1997-2006	~ 0.7 (-0.5;2.0)		
Sweden	116	120	118	123	119	119	113	113	110	117	1997-2006	~ -0.6 (-1.4;0.1)		
The Netherlands	104	101	103	102	105	108	108	110	109	114	1997-2006	↑ 1.2 (0.8;1.6)		
Valencian region, Spain	138	158	155	168	142	152	149	157	140	144	1997-2006	~ -0.5 (-2.1;1.2)		
All countries	110	114	116	120	120	120	122	126	124	125	1997-2000	↑ 2.9 (2.1;3.8)	2000-2006	↑ 0.6 (0.3;0.8)

Table 2. Prevalence of RRT per million population during the period 1997-2006, adjusted for age and sex distribution.

	Prevalence by year										Trend 1		Trend 2 / Trend 3	
Country / region	1997 pmp	1998 pmp	1999 pmp	2000 pmp	2001 pmp	2002 pmp	2003 pmp	2004 pmp	2005 pmp	2006 pmp	period	AAPC % (95% CI)	period	AAPC % (95% CI)
Andalusia, Spain	735	785	810	849	866	909	939	968	999	996	1997-2006	↑ 3.5 (3.0;3.9)		
Asturias, Spain	613	649	660	698	729	752	765	814	827	835	1997-2006	↑ 3.6 (3.1;4.0)		
Austria	653	674	697	716	750	769	794	829	854	875	1997-2006	↑ 3.4 (3.3;3.5)		
Basque Country, Spain	658	710	742	784	820	834	872	902	937	948	1997-2000	↑ 6.0 (3.8;8.3)	2000-2006	↑ 3.3 (2.6;4.0)
Calabria, Italy	783	818	837	858	860	876	897	906	909	913	1997-1999	↑ 3.4 (-1.3;8.3)	1999-2004 2004-2006	↑ 1.5 (0.1;3.0) ~ 0.3 (-4.0;4.8)
Cantabria, Spain	566	578	633	645	698	682	722	746	747	745	1997-2006	↑ 3.3 (2.4;4.1)		
Catalonia, Spain	884	915	936	959	975	989	1007	1037	1028	1028	1997-2004	↑ 2.1 (1.8;2.5)	2004-2006	~ -0.4(-2.9;2.2)
Denmark	540	567	607	640	679	704	730	751	760	768	1997-2001	↑ 6.0 (4.8;7.2)	2001-2004 2004-2006	↑ 3.4 (0.1;6.9) ~ 1.0 (-2.2;4.3)
Dutch-speaking Belgium	676	705	734	760	795	826	848	876	908	939	1997-2001	↑ 4.1 (3.8;4.5)	2001-2006	↑ 3.4 (3.1;3.6)
England/Wales, UK	559	540	556	561	577	578	596	649	690	712	1997-2006	↑ 3.1 (2.0;4.1)		
Finland	489	518	546	579	602	621	642	660	680	686	1997-2000	↑ 5.9 (5.2;6.6)	2000-2004 2004-2006	↑ 3.4 (2.8;4.0) ↑ 1.9 (0.7;3.1)
French-speaking Belgium	678	717	764	797	842	889	929	978	1010	1054	1997-2002	↑ 5.6 (5.0;6.1)	2002-2006	↑ 4.3 (3.7;5.0)
Greece	644	681	722	762	789	809	848	851	872	885	1997-2000	↑ 5.8 (4.7;6.9)	2000-2003 2003-2006	↑ 3.4 (1.4;5.4) ↑ 1.7 (0.7;2.6)
Iceland	368	417	383	408	457	490	535	532	527	526	1997-2006	↑ 4.5 (2.9;6.1)		
Norway	517	549	580	609	633	660	688	725	743	763	1997-1999	↑ 5.9 (5.4;6.5)	1999-2004 2004-2006	↑ 4.4 (4.3;4.6) ↑ 2.8 (2.4;3.3)
Scotland, UK	572	600	628	655	668	686	707	718	741	759	1997-2000	↑ 4.5 (3.7;5.2)	2000-2006	↑ 2.5 (2.3;2.7)
Sweden	644	668	686	706	724	744	753	772	783	804	1997-2001	↑ 3.0 (2.5;3.4)	2001-2006	↑ 2.0 (1.7;2.3)
The Netherlands	586	604	623	639	647	672	691	711	736	768	1997-2004	↑ 2.7 (2.4;3.0)	2004-2006	↑ 4.1 (2.1;6.0)
Valencian region, Spain	906	957	989	1032	1012	1028	1022	1058	1044	1047	1997-2000	↑ 3.8 (1.7;6.0)	2000-2006	~ 0.4 (-0.2;1.1)
All countries	642	656	679	700	713	726	744	774	798	816	1997-2006	↑ 2.7 (2.5;2.9)		

primary renal disease and country revealed a 12% improvement in survival in the 2002-2006 cohort compared to the 1997-2001 cohort.

Dialysis. The crude patient survival was very similar for patients who began dialysis between 1997 and 2001, and those who started between 2002 and 2006. However, adjustment for age, sex, primary renal disease and country showed that the risk of death among patients who started dialysis in 2000-2006 was reduced by 11% compared to those who started in the previous period. The improvement over time was more pronounced for peritoneal dialysis patients (19%) than for haemodialysis patients (10%). The trends in the 1-, 2-, 5- and 8-year survival of dialysis patients are shown in Figure 4.

Transplantation. In patients receiving their first kidney transplant both crude patient and graft survival improved (Table 3). After adjustment for age, sex, primary renal disease and country, the risk of death in the 2002-2006 cohort was reduced by 17% and the risk of graft failure by 11%. This improvement was more pronounced in living donor transplants (30% for patient survival and 9% for graft survival) than in deceased donor transplants (13% for patient survival and 8% for graft survival). The trends in the 1-, 2-, 5- and 8-year survival of kidney transplant recipients and kidney allografts are shown in Figures 5 and 6.

The pattern of improvement in survival was similar in all age, sex and primary renal disease groups.

Discussion

This European study shows a steady increase in the overall incidence of RRT for ESRD per million population during the period 1997-2000, followed by a much smaller increase of 0.6% per year thereafter. Although in some countries the prevalence of RRT stabilized in the more recent years, the overall prevalence in Europe continued to increase linearly at a rate of about 2.7% per year. In addition, we show that the survival of patients on RRT improved between the periods 1997-2001 and 2002-2006. The risk of death decreased for all treatment modalities, with the most substantial improvement in survival observed in peritoneal dialysis patients (19%) and kidney transplant recipients (17%) and a more moderate improvement in haemodialysis patients (10%).

After a steady rise in the overall incidence rate of RRT for ESRD in Europe, from 50 pmp in 1980 to 117 pmp in 1998-1999 [1,5], our results demonstrated a further increase to 125.4 pmp in 2006. However, starting from 2000 there was a trend towards stabilisation of the overall incidence rate, with an average annual increase of only 0.6%, albeit substantial differences existed between countries and regions in Europe. This is consistent with trends

Table 3. Crude patient survival probabilities and hazard ratios of all patients starting RRT (including all types) or dialysis in the periods 1997-2001 and 2002-2006 and crude patient and graft survival probabilities and crude and adjusted hazard ratios for all patients receiving their first kidney transplant in 1997-2001 or 2002-2006.

Survival type	Cohort	1 year Survival (95%CI)	2 year Survival (95%CI)	5 year Survival (95%CI)	crude HR (95% CI)	adjusted HR (95% CI)*
Patient survival on RRT	1997-2001	81.3 (81.1-81.6)	69.8 (69.6-70.1)	46.3 (46.2-46.5)	1 (ref)	1 (ref)
	2002-2006	81.3 (81.1-81.5)	70.0 (69.8-70.2)		0.98 (0.97-1.00)	0.88 (0.86-0.89)
Patient survival on dialysis	1997-2001	80.7 (80.4-80.9)	67.7 (67.5-68.0)	37.2 (37.1-37.4)	1 (ref)	1 (ref)
	2002-2006	80.6 (80.4-80.8)	68.1 (67.9-68.3)		0.97 (0.95-0.98)	0.89 (0.88-0.91)
Haemodialysis	1997-2001	78.8 (78.5-79.1)	65.8 (65.5-66.0)	35.9 (35.7-36.0)	1 (ref)	1 (ref)
	2002-2006	78.7 (78.4-78.9)	65.8 (65.5-66.0)		0.98 (0.96-0.99)	0.90 (0.89-0.92)
Peritoneal dialysis	1997-2001	88.4 (87.9-88.9)	75.9 (75.3-76.5)	43.1 (42.7-43.6)	1 (ref)	1 (ref)
	2002-2006	89.7 (89.3-90.2)	79.4 (78.8-80.0)		0.87 (0.83-0.90)	0.81 (0.78-0.85)
Patient survival after transplantation	1997-2001	95.8 (95.5-96.1)	94.0 (93.7-94.4)	87.8 (87.3-88.2)	1 (ref)	1 (ref)
	2002-2006	96.1 (95.8-96.4)	94.5 (94.2-94.8)		0.91 (0.85-0.98)	0.83 (0.77-0.89)
Living donor transplantation	1997-2001	97.2 (96.5-97.8)	96.6 (95.8-97.2)	93.3 (92.3-94.1)	1 (ref)	1 (ref)
	2002-2006	97.9 (97.4-98.3)	97.1 (96.5-97.6)		0.81 (0.65-1.01)	0.70 (0.56-0.88)
Deceased donor transplantation	1997-2001	95.4 (95.0-95.8)	93.4 (92.9-93.8)	86.2 (85.7-86.8)	1 (ref)	1 (ref)
	2002-2006	95.6 (95.2-95.9)	93.7 (93.3-94.1)		0.95 (0.88-1.02)	0.87 (0.80-0.94)
Graft survival after transplantation	1997-2001	89.9 (89.5-90.4)	87.1 (86.6-87.6)	78.1 (77.6-78.6)	1 (ref)	1 (ref)
	2002-2006	90.8 (90.4-91.2)	88.2 (87.8-88.6)		0.92 (0.88-0.97)	0.89 (0.85-0.94)
Living donor transplantation	1997-2001	94.2 (93.3-95.0)	92.5 (91.5-93.4)	85.6 (84.4-86.7)	1 (ref)	1 (ref)
	2002-2006	94.4 (93.7-95.0)	92.8 (92.0-93.5)		0.92 (0.79-1.06)	0.91 (0.78-1.05)
Deceased donor transplantation	1997-2001	89.4 (88.9-89.9)	86.3 (85.7-86.9)	76.7 (76.1-77.3)	1 (ref)	1 (ref)
	2002-2006	90.0 (89.5-90.4)	87.2 (86.7-87.7)		0.95 (0.90-1.01)	0.92 (0.87-0.98)

* Adjusted hazard ratios were adjusted for fixed values of age, sex, primary renal disease, and country to enable comparison of survival within current cohorts with previous and future cohorts. These values were determined by the means and distributions of these variables within the RRT (age 62.5 years, 61.4% males, 21.2% diabetes, 16.6% hypertension / renal vascular disease and 12.7% glomerulonephritis), dialysis (age 63.0, 61.4% males, 21.5% diabetes, 16.9% hypertension / renal vascular disease and 12.5% glomerulonephritis) and transplant patient populations (age 45.5, 63.1% males, 12.4% diabetes, 9.3% hypertension / renal vascular disease and 24.9% glomerulonephritis).

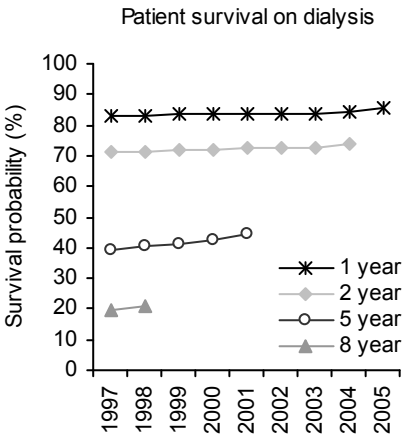

Figure 4. Change in patient survival of patients starting dialysis between 1997 and 2006. Survival probabilities were adjusted for age, sex, primary renal disease, and country.

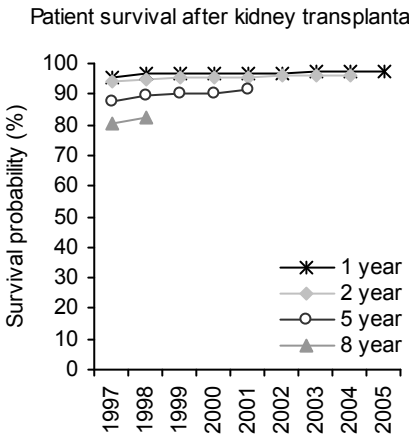

Figure 5. Change in patient survival of patients receiving a kidney transplant between 1997 and 2006. Survival probabilities were adjusted for age, sex, primary renal disease, and country.

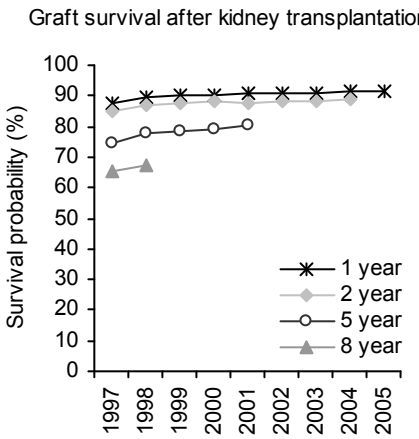

Figure 6. Change in graft survival of patients receiving a kidney transplant between 1997 and 2006. Survival probabilities were adjusted for age, sex, primary renal disease, and country.

in the United States [13,14], New Zealand [15,16] and Canada [17], where registry data also show a less steep increase in the more recent years.

The increase of the (unadjusted) overall incidence rate of RRT between 1997 and 2000 was primarily due to increasing rates in the three oldest age groups, 65 74 years, 75-84 years, and 85 years and older. There appears to be a relationship between the age at the onset of RRT and the period in which a stabilization of incidence rates occurred. Whereas the incidence rate in the age groups below 45 years has been stable for decades [5], that in the 45-64 age group became stable at the end of the 1990s [18]. The results of this study show that in males aged 65-74 years the incidence rate of RRT increased by only 1.1% annually, whereas it levelled of in females. Remarkably, also in males aged 75-84 years, rates have stabilized from 2004, and in females the AAPC decreased to 1.8% per year [5,19]. Nevertheless, the incidence rate among those aged 85 years and older continued to rise although this rise was much smaller towards the end of the study period. In line with our results, other large registries [13,15-17] have also found that the rate of increase in incidence among patients aged 65-74 and 75 years and older was much lower after 2000 than before. Only in Australia trends towards stabilisation in the older age groups are lacking [15,16].

Similar trends towards stabilisation were found in the incidence rates of RRT for ESRD due to hypertension / renal vascular disease (stable from 2004) and type 2 diabetes (a less steep increase starting from 2002), respectively, which appears to result primarily from the stabilising incidence rates of RRT for ESRD due to these primary renal diseases in the age groups 65-74 and 75-84 years. However, at the same time the incidence rate of RRT for ESRD due to unknown or missing causes increased and therefore our findings concerning the different primary renal disease categories should be interpreted with caution. Nevertheless, similar results were found by Foley et al. [14] who demonstrated that among whites aged 60-69 years in the United States the incidence rate of RRT for ESRD due to diabetes remained constant after 2000. Furthermore, these data suggested a flattening of the growth of the incidence of RRT for ESRD due to hypertension.

The recent decline in the annual growth of the incidence rate of RRT for ESRD in Europe could be explained by several factors: a stabilisation in the prevalence of underlying causes of ESRD, a slower progression of chronic kidney disease (CKD) to ESRD, as well as a higher mortality in the earlier stages of CKD. Despite a steady increase in the prevalence of diabetes [20] and hypertension [21] in the general population, our data showed a flattening of the incidence rates of RRT for ESRD due to these disorders within the older age groups. It has been suggested that this could be due to the increasing awareness of the growing burden of CKD [22-25], and the greater emphasis on early detection and prevention. Therapeutic interventions now available aim to reduce the rate of progression of CKD

[22,26] and the extent of co-morbid conditions and complications. Perhaps these primary and secondary prevention methods are now starting to bear fruit resulting in incidence rates of RRT that are increasing at a much lower pace.

Previous studies have shown that a considerable proportion of patients with CKD die before reaching ESRD [27-29], however, there are no indications for *increasing* death rates in CKD patients [13] that could explain the stabilizing incidence rates of RRT. Another potential cause of a slower rise in the incidence is reduced access to RRT due to non-referral or late referral to nephrologists. However, this seems to be unlikely as the incidence rate in the group that would be most likely be affected, i.e. the patients aged 85 years and older, has continued to increase.

On the other hand, a small but continuous increase in the incidence rate of RRT could be caused by a tendency towards starting dialysis earlier in the course of CKD, i.e. at higher levels of residual renal function [30,31]. In this perspective, it is of interest to note that USRDS data showed that almost the entire increase in the incidence counts during the period 1996-2005 occurred in patients who started RRT at higher levels of estimated glomerular filtration rate (> 10 ml/min/1.73m²) [32].

All medical (e.g. prevalence of diabetes mellitus in general population) and non-medical factors (e.g. non-referral to nephrologists) that influence the trends in the incidence rate of RRT may also explain international differences in the incidence rate trends.

We show that although the crude survival on RRT did not improve substantially, the adjusted survival of patients on dialysis and after transplantation, as well as graft survival after transplantation continued to improve during the last decade. Especially the patient survival on peritoneal dialysis has improved. This might be due to the more widespread use of biocompatible solutions, icodextrin and optimization of the length of the short dwell using automated peritoneal dialysis together resulting in a better preservation of the peritoneal membrane, a better preservation of the residual renal function, and a better control of fluid balance, especially in high transporters [33-41]. In addition, another selection of patients for this mode of treatment might have contributed to the improved patient survival on peritoneal dialysis. The survival after kidney transplantation has improved substantially, presumably partly due to slight increases in percentages of living donor kidney transplants and pre-emptive transplants, and also due to increased tailoring of immune suppression to the individual patient and avoidance of excessive toxic drug use [42,43]. The improvement in the survival on RRT might also be a consequence of the primary and secondary prevention methods leading to a better condition of patients starting RRT [44] (less complications) and more adequate medical and psychological preparation for RRT [45,46].

Conclusions

This European study shows that on average there is a decrease in the annual growth of the overall incidence rate of RRT for ESRD and a trend towards stabilisation. This is largely due to a stabilisation of the incidence among females aged 65-74 years, males aged 75-84 years and in patients receiving RRT for ESRD due to hypertension / renal vascular disease. Nevertheless, trends in the incidence rates of RRT differed widely across countries, ranging from steady increase to substantial decrease, potentially due to differences in the prevalence and progression of CKD and variable access to RRT. Therefore, international research in CKD patients using standardized methodology is necessary.

The survival of patients on dialysis, and even more, after kidney transplantation continued to improve between the periods 1997-2001 and 2002-2006. This might be due to technical improvements in RRT, but also to a better condition of patients starting RRT due to increased awareness of the importance to detect, and treat patients with CKD to delay its progression.

Our data suggest that nephrologists in Europe are making progress in their efforts to prevent the development of ESRD and to prolong the survival of those who, in spite of these efforts, will require RRT. These findings should stimulate further action to control the progression of CKD by implementation of effective renoprotective strategies.

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